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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

SCHEDULE 14A

Proxy Statement Pursuant to Section 14(a) of
the Securities Exchange Act of 1934 (Amendment No.)

Filed by the Registrant

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.
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ISIS PHARMACEUTICALS, INC.

**1896 Rutherford Road
Carlsbad, CA 92008**

**NOTICE OF
2005 ANNUAL MEETING OF STOCKHOLDERS
AND PROXY STATEMENT**

Dear Stockholders,

I am pleased to invite you to Isis Pharmaceuticals' 2005 Annual Meeting of Stockholders. We will host the meeting at our offices in Carlsbad, California on Thursday, May 26, 2005 at 9:30 a.m. Pacific Time. In addition to covering the formal items on the agenda, we will review the major developments of the past year and answer your questions. Please note if you wish to attend the meeting in person that, although we have moved our corporate headquarters, we will hold the Annual Meeting in the same place as previous years.

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.

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 unable to attend, please note that a web cast and copy of the slides presented will be available at www.isispharm.com.⁽¹⁾

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 through 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

(1) 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.

ISIS PHARMACEUTICALS, INC.

1896 Rutherford Road
Carlsbad, CA 92008

NOTICE OF 2005 ANNUAL MEETING OF STOCKHOLDERS

Date: Thursday, May 26, 2005
Time: 9:30 a.m., Pacific Time
Place: Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008

Dear Stockholders,

At our 2005 Annual Meeting, we will ask you to:

- elect three Directors to serve for a three-year term each and one Director to serve for a one year term;
- ratify the Audit Committee of the Board of Directors' selection of Ernst & Young LLP as independent auditors for our fiscal year ending December 31, 2005; and
- transact any other business that may be properly 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 28, 2005 you may vote at the Annual Meeting.

By order of the Board of Directors,

B. Lynne Parshall
Secretary

Carlsbad, California
April 19, 2005

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.

1896 Rutherford Road
Carlsbad, CA 92008

PROXY STATEMENT INFORMATION ABOUT THE 2005 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 2005 Annual Meeting of Stockholders to be held on Thursday, May 26, 2005, at 9:30 a.m. Pacific Time, or at any adjournment or postponement of the meeting, for the purposes stated in this document. The Annual Meeting will be held at 1896 Rutherford Road, 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 19, 2005 to all stockholders who are entitled to vote. Only stockholders who owned our common stock at the close of business on March 28, 2005 are entitled to vote at the Annual Meeting. On this record date, we had 57,527,999 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 at the meeting in person 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. The inspector of election will count votes for the meeting, and will separately count "For" and "Against" votes, abstentions and broker non-votes. 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 broker holds your shares 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. Discretionary items are proposals considered routine under the rules of the New York Stock Exchange on which a broker may vote shares held in street name in the absence of your voting instructions. On non-discretionary items for which you do not give your broker instructions, the shares will be treated as broker non-votes. Proposals 1 and 2 are considered discretionary items.

You may vote in one of the following ways:

- attend the 2005 Annual Meeting and vote in person;
 - complete, sign, date and return the enclosed proxy card; or
 - vote by phone or through 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 2005.

Solicitation

We will bear the entire cost of soliciting proxies, including preparing, assembling, printing and mailing 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. We will not pay our Directors and employees any additional compensation for soliciting proxies.

General Information for all Shares Voted by Phone or Through the Internet

Votes submitted by phone or through the Internet must be received by 11:59 p.m., Eastern Time, on May 25, 2005. Submitting your proxy by phone or through the Internet 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 or 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 through 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 from our proxy card.

A number of brokers and banks are participating in an ADP Investor Communications program which 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 by phone or through the Internet (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 at the Annual Meeting. You may revoke your proxy by any one of the following four ways:

- you may mail another proxy marked with a later date;
- you may revoke it through 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 included in our proxy statement and form of proxy for, or to be presented at, the 2006 Annual Meeting of Stockholders, you must send the proposal to Isis by no later than December 20, 2005. 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, 2006 and no later than the close of business on February 25, 2006. 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 of one third of our total number of Directors. Presently, the Board has nine members with each class consisting of three Directors. Each class serves a three-year term and we hold elections each year at the Annual Meeting to elect the Directors whose terms are expiring.

The Board represents the interests of our stockholders by overseeing the Chief Executive Officer and other senior management in the operation of the Company. The Board's goal is to optimize long-term value by providing the Company guidance and strategic oversight on our stockholders' behalf. Therefore, on April 16, 2004, the Board adopted membership standards and believes that the Board members should meet the minimum membership requirements listed below. In addition to these minimum standards, the Board will consider a member or nominee's diversity, maturity and such other factors as the Board deems appropriate based on its current needs.

The minimum membership requirements are as follows:

- members must be able to read and understand basic financial statements;
- members must demonstrate high personal integrity and ethics;
- members cannot serve as a director on the board of more than seven other publicly traded companies;
- members cannot serve more than ten consecutive terms on the Board; and
- members cannot run for re-election or serve on the Board once they have reached the age of 80 years old.

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. However, the Board believes it is important for our stockholders to ratify any member of the Board who has been appointed by the Board. As a result, whenever the Board appoints a new member, such as Dr. DiMarchi, the Board will submit such new member's directorship for approval at the next regularly scheduled Annual Meeting of stockholders. If elected by the stockholders, such Board member will serve the remaining term of the class of Directors to which he or she was elected.

Information about the 2005 Elections

The Board has nominated four Directors for election at the 2005 Annual Meeting. Each of the nominees currently serves as one of our Directors and, except for Drs. DiMarchi and Berthelsen, each was previously elected by our stockholders. Based on the recommendation of our Chief Executive Officer and the unanimous nomination of our Nominating, Governance and Review Committee, Dr. DiMarchi and Dr. Berthelsen were appointed to the Board by the then current members of the Board in December 2004 and May 2002, respectively. If re-elected, three of the nominees, Dr. Berthelsen, Ms. Parshall and Mr. Wender, will serve until the 2008 Annual Meeting and Dr. DiMarchi will serve until the 2006 Annual Meeting or, in each case, until his or her successor is elected and has qualified, or in the case of their death, resignation or removal.

Our stockholders elect Directors by a plurality of the votes of the shares present in person or represented by proxy at the meeting and entitled to vote in the election of Directors. Shares represented by executed proxies will be voted for the election of the four 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.

Biographies of Nominees for Election for a Three-year Term Expiring at the 2008 Annual Meeting

Spencer R. Berthelsen, M.D., age 53, 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 and Medical Director, and has been 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 50, 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 Trustees of the Bishops School and is also a member of the American, California and San Diego bar associations.

Joseph H. Wender, age 60, 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.

Biography of Nominee for Election for a One-Year Term Expiring at the 2006 Annual Meeting

Dr. DiMarchi, appointed on December 14, 2004 by our Board of Directors, is a Class III Director in the class whose term expires upon the 2006 Annual Meeting. However, in accordance with our membership requirements, as set forth on page 4 above, he is nominated for election this year.

Richard D. DiMarchi, Ph.D., age 52, has served as a Director of Isis since December 2004. Dr. DiMarchi is a professor and the Jack and Linda Gill Distinguished Chair in Biomolecular Science at Indiana University, Bloomington, Indiana. Prior to joining Indiana University, Dr. DiMarchi worked for 22 years at Eli Lilly and Company in several senior management positions, including Group Vice President, Biotechnology and Product Development, from 1996 to 2003, and Vice President, Endocrine Research and Clinical Investigation, from 1992 to 1996. He is a co-founder and Chairman of Ambrx, Inc., a biotechnology company started in 2003, which focuses on protein therapeutics.

THE BOARD OF DIRECTORS RECOMMENDS THAT YOU VOTE IN FAVOR OF THE ELECTION OF EACH OF THE ABOVE NOMINEES

Biographies of additional Directors Whose Terms Expire at the 2007 Annual Meeting

Stanley T. Crooke, M.D., Ph.D., age 60, was a founder of Isis and has been Chief Executive Officer and a Director since January 1989. He was elected Chairman of the Board in February 1991. Prior to founding Isis from 1980 until January 1989, Dr. Crooke was employed by SmithKline Beckman Corporation, a pharmaceutical company, 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, and EPIX Pharmaceuticals, Inc., a developer of magnetic resonance imaging contrast agents.

John C. Reed, M.D., Ph.D., age 46, 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 the Deputy Director of the Cancer Center beginning in 1994, as Scientific Director of the Institute beginning in 1995, and as Cancer Center Director in 2002. He also currently serves as adjunct professor in the University of California, San Diego's (UCSD) Department of Molecular Pathology and in San Diego State University's Biology department. In addition, Dr. Reed is an associate member of UCSD's Cancer Center. Prior to these positions, from 1989 to 1992, Dr. Reed worked as Assistant Director, Laboratory of Molecular Diagnosis at the hospital of the University of Pennsylvania and Assistant Professor, Department of Pathology and Laboratory Medicine at the University of Pennsylvania School of Medicine. In June 2004, Dr. Reed joined the Board of Stratagene, Inc., a biopharmaceutical company. In December 2004, Dr. Reed was appointed to the Independent Citizen's Oversight Committee of the California Institute for Regenerative Medicine.

Mark B. Skaletsky, age 56, has served as a Director of Isis since January 1989. Mr. Skaletsky has been the Chairman, Chief Executive Officer and President of Trine Pharmaceuticals, Inc., a biopharmaceutical company, formerly known as Essential Therapeutics since March 2001. 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. Mr. Skaletsky is also a Director of ImmunoGen, Inc. and Alkermes Inc., both biopharmaceutical companies. He is a Director and past Chairman of the Biotechnology Industry Organization.

Biographies of Directors Whose Terms Expire at the 2006 Annual Meeting

Christopher F.O. Gabrieli, age 45, 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 partner 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 51, 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 Godward's San Diego office and serves as the partner in charge of that office. Mr. Muto also serves on that firm's firmwide management committee.

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 the 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, our Chief Executive Officer and Executive Vice President, 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., 1896 Rutherford Road, 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 has three committees: an Audit Committee, a Compensation Committee, and a Nominating, Governance and Review Committee. Below is a description of each committee of our Board. 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 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

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

In 2004, the Audit Committee met seven times and its members were Mr. Wender (Chairman), Dr. Berthelsen and Mr. Skaletsky. For 2005, the Audit Committee is composed of Mr. Wender (Chairman), Dr. Berthelsen and Mr. Gabrieli.

Our Audit Committee charter requires that each member must be independent. We consider the members to be 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 all of the other 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. Our Board has determined that the Audit Committee's financial expert is Mr. Wender based on, among other things, his over 30 years of experience as an investment banker with Goldman, Sachs & Co. We provide the Audit Committee with the funding it needs to perform its duties.

In 2004, 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. Our Audit 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.

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 for our Directors and reviews and approves the compensation and other terms of employment of our 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.

In 2004, three Directors comprised the Compensation Committee: Mr. Skaletsky (Chairman), Dr. Reed and Mr. Wender. For 2005, the members are Mr. Wender (Chairman), Drs. Berthelsen and Reed. 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 one time in 2004 and acted by unanimous written consent fifteen times. Our Compensation 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.

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.

Two Directors currently comprise the Nominating, Governance and Review Committee: Dr. Berthelsen and Mr. Gabrieli. Mr. Muto serves as counsel to the Committee. 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 met once during 2004. In addition, the Nominating, Governance and Review Committee met in March 2005 to recommend to the Board the candidates for election at the 2005 Annual 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 represent rigorously 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, the minimum membership requirements discussed on page 4, 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 the 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. In December 2004, the Nominating, Governance and Review Committee met and reviewed the appointment of Dr. DiMarchi who was identified by Dr. Crooke and determined it was in the best interest of the Company and its stockholders to appoint Dr. DiMarchi to the Board.

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: 1896 Rutherford Road, Carlsbad, CA 92008, by December 20, 2005. 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.

Meetings and Attendance

The Board of Directors met four times in 2004, all at regularly scheduled meetings, and acted by unanimous written consent five times. During 2004, all Directors attended at least 80% of the meetings of the Board and the committees on which they served. We encourage each member of the Board to attend the Annual Meeting of Stockholders. Mr. Muto, Dr. Berthelsen and Dr. Reed attended our 2004 Annual Meeting of Stockholders.

The following table provides membership and meeting information for fiscal 2004 for each of the Board committees:

Name	Audit	Compensation	Nominating, Governance and Review	
Dr. Spencer R. Berthelsen	X		X	
Dr. Stanley T. Crooke				
Dr. Richard D. DiMarchi				
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 2004	7	1	**	1

* Committee Chairperson

** Acted by written consent 15 times as well

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, or individual Directors, may do so by sending written communications addressed to the Secretary of Isis at 1896 Rutherford Road, Carlsbad, CA 92008. 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. The Nominating, Governance and Review Committee is drafting a formal process for stockholder communications with the Board and, if adopted, we 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.

PROPOSAL 2

RATIFICATION OF SELECTION OF INDEPENDENT AUDITORS

The Audit Committee of the Board of Directors has selected Ernst & Young LLP as our independent registered public accounting firm for the fiscal year ending December 31, 2005, 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 2005 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 registered public accounting firm, 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 Isis.

We require 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 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, 2004, 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 registered public accounting firm, 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 registered public accounting firm 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, 2004 and 2003, 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 were \$290,970 and \$134,647, respectively. \$161,068 of the fees billed during fiscal 2004 were primarily for services related to Sarbanes-Oxley 404 internal controls test work.

Audit Related Fees

During the fiscal years ended December 31, 2004 and 2003, 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 \$24,904 and \$17,140, respectively. The fees billed during such fiscal years were primarily for services related to Ernst & Young LLP's consultations related to accounting for a number of our business transactions.

Tax Fees:

During the fiscal years ended December 31, 2004 and 2003, the aggregate fees billed by Ernst & Young LLP for professional services rendered for tax compliance, tax advice and tax planning were \$6,800 and \$31,905, respectively. These fees were for services related to the preparation of our tax returns and other filings we made with the Internal Revenue Service for 2003 and consultations regarding the application of various provisions of the Internal Revenue Code (the "Code") for each year. In 2004, we utilized Deloitte & Touche LLP for the majority of our tax services.

Financial Information Systems Design and Implementation Fees:

During the fiscal years ended December 31, 2004 and 2003, there were no fees billed by Ernst & Young LLP for information technology consulting.

All Other Fees:

During the fiscal years ended December 31, 2004 and 2003, all other fees billed by Ernst & Young LLP were \$790 and \$1,616, 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, 2004, none of the total hours expended on our financial audit by Ernst & Young LLP were provided by persons other than Ernst & Young LLP's full-time permanent employees.

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

SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

This table outlines the ownership of our common stock as of February 28, 2005 by:

- each Director and nominee for Director;
- each executive officer named in the Summary Compensation Table under "Executive Compensation—Compensation of Executive Officers";
- all Directors and executive officers as a group; and
- every entity that we know beneficially owns more than five percent of our common stock.

Beneficial Owner	Beneficial Ownership(1)	
	Number of Shares	Percent of Total(2)
Citigroup Inc.(3) 399 Park Avenue New York, NY 10043	5,385,335	9.4
Eli Lilly and Company(4) Lilly Corporate Center Indianapolis, IN 46285	4,166,167	7.2
Federated Investors, Inc.(5) Federated Investors Tower Pittsburgh, PA 15222-3779	4,029,478	7.0
Mazama Capital Management, Inc.(6) One S. W. Columbia, Suite 1500 Portland, Oregon 97258	4,372,702	7.6
Spencer R. Berthelsen(7)	46,870	*
Stanley T. Crooke(8)	1,456,487	2.5
Richard D. DiMarchi	0	*
Christopher F. O. Gabrieli(9)	201,671	*
Frederick T. Muto(10)	30,000	*
B. Lynne Parshall(11)	346,565	*
John C. Reed(12)	32,500	*
Mark B. Skaletsky(13)	67,500	*
Joseph H. Wender(14)	76,500	*
C. Frank Bennett(15)	163,912	*
Richard K. Brown(16)	54,004	*
David J. Ecker(17)	192,998	*
All Directors and executive officers as a group (16 persons)(18)	3,002,119	5.1

* 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 57,527,898 shares of common stock outstanding on February 28, 2005, adjusted as required by rules promulgated by the SEC.

- (3) Includes 3,546,264 shares held by Citigroup Global Markets Inc. ("CGM"), 3,546,264 shares held by Citigroup Financial Products Inc. ("CFP"), 5,322,818 shares held by Citigroup Global Markets Holdings Inc. ("CGM Holdings") and 5,385,335 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 of the foregoing, the holdings reported for CGM Holdings and Citigroup Inc. include the shares held by their respective wholly-owned subsidiaries.
- (4) Includes 3,541,875 with sole voting and dispositive power, and 624,791 shares with shared voting and dispositive power. Based on information contained in their Schedule 13G, Amendment 1.
- (5) Federated Investors, Inc. (the "Parent") is the parent holding company of Federated Equity Management Company of Pennsylvania and Federated Global Investment Management Corp. (the "Investment Advisers"), which act as investment advisers to registered investment companies and separate accounts that own shares of our common stock. The Investment Advisers are wholly owned subsidiaries of FII Holdings, Inc., which is a wholly owned subsidiary of the Parent. All of the Parent's outstanding voting stock is held in the Voting Shares Irrevocable Trust (the "Trust") for which John F. Donahue, Rhodora J. Donahue and J. Christopher Donahue act as trustees. Based on information contained in their Schedule 13G.
- (6) Mazama Capital Management, Inc. has sole voting authority over 2,466,150 shares and sole dispositive power over 4,372,702 shares.
- (7) Includes 70 shares owned by Dr. Berthelsen's daughter for which he disclaims beneficial ownership. Includes 17,500 shares of common stock issuable upon exercise of options held by Dr. Berthelsen that are exercisable on or before April 29, 2005.
- (8) Includes 508,625 shares of common stock issuable upon exercise of options held by Dr. Crooke that are exercisable on or before April 29, 2005. Also includes 24,571 shares of common stock issuable upon exercise of options held by Rosanne Crooke, Dr. Crooke's wife, that are exercisable on or before April 29, 2005, 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.
- (9) 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 45,500 shares of common stock issuable upon exercise of options held by Mr. Gabrieli that are exercisable on or before April 29, 2005.
- (10) Includes 1,500 shares of common stock indirectly beneficially owned through the Cooley Godward LLP Salary Deferral and Profit Sharing Plan and 28,500 shares of common stock issuable upon exercise of options held by Mr. Muto that are exercisable on or before April 29, 2005.
- (11) Includes 276,321 shares of common stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before April 29, 2005, and an aggregate of 60,090 shares of common stock issuable upon exercise of options which Ms. Parshall transferred to her two daughters that are exercisable on or before April 29, 2005.
- (12) Includes 32,500 shares of common stock issuable upon exercise of options held by Dr. Reed that are exercisable on or before April 29, 2005.
- (13) Includes 45,500 shares of common stock issuable upon exercise of options held by Mr. Skaletsky that are exercisable on or before April 29, 2005.
- (14) Includes 45,500 shares of common stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before April 29, 2005.

- (15) Includes 162,854 shares of common stock issuable upon exercise of options held by Dr. Bennett that are exercisable on or before April 29, 2005.
- (16) Includes 51,656 shares of common stock issuable upon exercise of options held by Dr. Brown that are exercisable on or before April 29, 2005.
- (17) Includes 37,493 shares of common stock held by the Ecker Family Revocable Trust in which Dr. Ecker is a trustee. Also includes 155,505 shares of common stock issuable upon exercise of options held by Dr. Ecker that are exercisable on or before April 29, 2005.
- (18) Includes an aggregate of 1,785,210 shares issuable upon exercise of options held by all current Directors and executive officers as a group that are exercisable on or before April 29, 2005.

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, 2004, all Section 16(a) filing requirements applicable to our officers, Directors and greater than ten percent beneficial owners were complied with except Dr. Arthur A. Levin, who was four days late reporting shares sold under a Rule 10b5-1 Plan because the broker administering his plan failed to notify Dr. Levin within the two-day reporting requirement of the trade.

EXECUTIVE COMPENSATION

Compensation of Directors

We pay our non-employee Directors a fee of \$25,000 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, 2004, we paid total fees of \$18,750 to each of our non-employee Directors plus an additional payment of \$6,250 paid in December 2003, excluding Dr. DiMarchi who was elected in December 2004.

In 2004, each non-employee Director also received automatic stock option grants under our 2002 Non-Employee Directors' Stock Option Plan. On July 1, 2004, 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 \$5.72 per share, 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. In December 2004, in connection with his appointment to the Board, Dr. DiMarchi received an option to purchase 20,000 shares of our common stock, at an exercise price of \$6.09 the fair market value on the date of grant. 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, 2004, 2003, and 2002.

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. Crooke Chairman, CEO and President	2004	539,499	122,651	—	80,000	—
	2003	510,300	191,363	—	117,333(3)	—
	2002	486,000	205,286	—	55,000	—
B. Lynne Parshall Director, Executive VP & Chief Financial Officer	2004	422,305	84,989	—	38,400	—
	2003	405,089	127,603	—	81,466(4)	—
	2002	385,799	136,650	—	35,000	—
C. Frank Bennett Vice President, Antisense Research	2004	287,311	49,561	—	28,800	—
	2003	274,939	77,327	—	46,099(5)	—
	2002	261,847	76,040	—	19,000	—
Richard K. Brown Vice President, Business Development	2004	317,710	33,360	—	18,000	—
	2003	305,490	72,172	—	65,500(6)	—
	2002	290,943	49,926	—	12,000	—
David J. Ecker Vice President, and Scientific Head of Ibis Division	2004	317,805	51,119	—	32,640	—
	2003	271,765	79,491	—	92,865(7)	—
	2002	257,597	81,607	—	23,200(8)	—

- (1) Bonuses are included here in the years they were earned, not in the year in which they were paid. Bonuses represent compensation for achievements and are not necessarily paid in the year they are earned; i.e., bonuses for 2004 were paid in January 2005.
- (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) 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.
- (8) Includes 10,000 options granted to Dr. Ecker in January 2002 in association with his promotion.

Stock Option Grants and Exercises

Executive officers are granted stock options under our 2000 Broad-Based Equity Incentive Plan (the "2000 Plan") and our 1989 Stock Option Plan (the "1989 Plan"). During 2004, options to purchase a total of 498,850 shares and 1,583,641 shares of our common stock had been granted under the 2000 Plan and 1989 Plan, respectively.

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 in 2002. When there is no material non-public information available, Rule 10b5-1 allows corporate insiders to establish plans that permit prearranged future sales of their securities. With respect to our insiders who participate in our 10b5-1 trading program, we do not allow them to buy or sell our stock outside of the 10b5-1 trading program. All of our executive officers who have vested stock options and/or own shares of our stock currently participate in our 10b5-1 trading program.

The following tables show certain information regarding options granted to, exercised by, and held at December 31, 2004 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	80,000	3.84	6.81	1/1/14	\$ 342,503	\$ 867,902
B. Lynne Parshall	38,400	1.84	6.81	1/1/14	\$ 164,402	\$ 416,593
C. Frank Bennett	28,800	1.38	6.81	1/1/14	\$ 123,301	\$ 312,445
Richard K. Brown	18,000	.86	6.81	1/1/14	\$ 77,063	\$ 195,278
David J. Ecker	32,640	1.57	6.81	1/1/14	\$ 139,741	\$ 354,104

(1) All options granted in 2004 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 2,082,491 shares granted in 2004 to employees only under our 2000 Plan and 1989 Plan. This is not necessarily indicative of the number of options that will be granted in the future.

(3) The potential realizable value is calculated based on the term of the option at its time of grant, based on the assumption that the market value of the underlying stock increases at the stated values, compounded annually. Actual gains, if any, on stock option exercises are dependent on the future performance of the common stock, overall market conditions and the option holders continued employment through the vesting periods. The amounts reflected in this table may not necessarily be achieved.

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)
			Exercisable/ Unexercisable	Exercisable/ Unexercisable
Stanley T. Crooke	50,000	\$ 70,890	470,934/131,399	\$32,264/\$18,236
B. Lynne Parshall	—	—	315,470/72,396(3)	\$27,056/\$15,293(3)
C. Frank Bennett	—	—	147,051/52,848	\$16,578/\$ 9,371
Richard K. Brown	—	—	39,211/44,289	\$23,479/\$13,271
David J. Ecker	12,150	\$ 59,261	134,958/68,547	\$38,508/\$21,766

- (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, 2004 (\$5.90) 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 60,090 options transferred to Ms. Parshall's two daughters.

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, 2004.

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	3,863,000(a) \$	8.92	5,108,000(c)
Equity compensation plans not approved by stockholders	4,804,000(b) \$	7.88	792,000
Total	8,667,000 \$	8.34	5,900,000

(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, 72,993 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 nine 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 28, 2005, there were 5,592,286 shares reserved for issuance under the 2000 Plan, options to purchase an aggregate of 4,711,468 shares had been granted and were outstanding under the 2000 Plan, options to purchase an aggregate of 397,714 shares had been exercised under the 2000 Plan, and 880,818 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 for 36 months 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, 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, 2004, approximately 4,803,647 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 nine 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 on or before December 31, 2005 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.

Compensation Committee Interlocks and Insider Participation

As noted above, during the fiscal year ended December 31, 2004, our Compensation Committee was composed of Mr. Skaletsky, Dr. Reed and Mr. 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.

Compensation Committee Report(2)

In 2004, 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 Isis' executive officers;
- evaluating and recommending to the Board the compensation plans and programs advisable for Isis, as well as modifying or terminating existing plans and programs;
- establishing policies with respect to equity compensation arrangements;
- reviewing and approving compensation arrangements for Isis' executive officers, including its Chief Executive Officer;
- reviewing and approving compensation arrangements for Isis' Directors;
- administering Isis' 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.

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. The Compensation Committee approves the total compensation for each of the executive officers.

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

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 different from 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 in comparable companies. 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 similar size in similar industries. We structure our management bonus program around both the individual's and Isis' performance. The Compensation Committee assesses Isis' achievement against our key corporate objectives, and determines the corporate bonus guideline for all participants in the bonus program. Individual bonus guidelines are determined by an individual's manager and approved by the CEO. The Compensation Committee reviews all bonus grants and approves all executive officer bonuses.

We use our stock option program to give all employees, including Isis' executive officers, an economic interest in the long-term appreciation of our common stock. We grant existing employees new options on an annual basis to provide a continuing financial incentive. The size of the individual annual option grant is related to the employee's position and performance in the previous year. For 2004, the Compensation Committee did not consider the number of options held by executive officers when awarding new grants.

Taxes

Under Section 162(m) of the Code, we can only deduct up to \$1 million of compensation we pay to certain executive officers each taxable year. However, we may deduct compensation above \$1 million if it is "performance based compensation" within the meaning of the Internal Revenue Code. The Compensation Committee has determined that stock options granted under the 1989 Plan and the 2000 Plan with an exercise price at least equal to the fair market value of our common stock on the date of grant is performance-based compensation.

Assessment of 2004

We set very challenging objectives for 2004. In achieving most of those objectives, we made significant progress in the areas discussed below. However, 2004 had its disappointments. Most notably, the results of Isis' Phase III clinical trials of alicaforsen in patients with Crohn's disease that did not demonstrate statistically significant induction of clinical remission compared to placebo. Further, the price of Isis' stock suffered a significant decline over the year. We also failed to achieve some of our partnering objectives. Therefore, in addition to the substantial reduction in force which the Board approved, the Compensation Committee recommended to the Board a corporate performance bonus guideline of 50%, with the guideline for a year in which all objectives were achieved by the Company being 100%, and a reduction of salary increase guideline from 4% to 3% for all employees at director level or above, including Isis' executive officers.

Advanced Isis' Drugs in Development with Focus on Second-Generation Drugs

Inflammatory Disease:

- *Ulcerative Colitis (ISIS 2302)*—In December 2004, Isis released results of three Phase II studies of alicaforsen (ISIS 2302) enema to treat patients with ulcerative colitis. In the trials, alicaforsen enema produced significant and long-lasting disease improvement, as measured by changes in the Disease Activity Index and out-performed both placebo and the enema standard of care. Isis

plans to find a strong commercial partner for alicaforsen enema, while planning a Phase III program for the drug.

Cardiovascular Diseases:

- *ISIS 301012* is a second-generation compound which targets apoB-100. Isis initiated a Phase I study in late 2003 in volunteers with borderline elevated cholesterol. In 2004, Isis announced data from this trial, which demonstrated that ISIS 301012 produced dose-dependent, rapid and prolonged reductions of its target, in LDL and VLDL, and in total cholesterol levels. Isis has also demonstrated that an oral formulation of ISIS 301012 reduces cholesterol in animals.

Metabolic Diseases:

- *ISIS 113715*—In May 2003, Isis initiated a Phase I clinical trial in healthy volunteers. In September 2003, Isis reported results from this Phase I study in which ISIS 113715 increased insulin sensitivity in normal volunteers. In addition, subjects treated with ISIS 113715 did not experience hypoglycemia or excessively low blood sugar. A Phase II study was initiated in 2004. Isis intends to report the results from this trial mid-2005.

Cancer:

- *ISIS 345794* emerged from Isis' internal oncology research program and is in preclinical development for cancer. This second generation drug targets Signal Transducer and Activator of Transcription 3, or STAT-3, a protein that regulates cell division and growth and prevents cell death. In preclinical studies, Isis has demonstrated that antisense inhibition of STAT-3 significantly delayed tumor growth and increased the rate of cancer cell death in multiple cell and animal models of cancer.

Recently Discontinued Products:

- *alicaforsen (ISIS 2302) for Crohn's Disease*—administered intravenously (IV) did not demonstrate statistically significant induction of clinical remissions in patients with Crohn's disease compared to placebo in two Phase 3 clinical trials. As a result of these trials, Isis will not invest further in the development of alicaforsen for Crohn's disease.
- *Affinitak™ (ISIS 3521, LY900003)*—in combination with Gemzar® (gemcitabine HCl) and cisplatin did not demonstrate statistically significant improvement in median survival in patients with non-small cell lung cancer in a Phase III study sponsored by Eli Lilly and Co ("Lilly"). As a result of these trials, neither Lilly nor Isis will invest further in the development of Affinitak.
- *ISIS 104838*—produced positive disease responses in patients with rheumatoid arthritis, according to results of two Phase II studies. While Isis was encouraged by the performance of this drug, in light of the strong competition in this market and the significant investment required to bring the first oral anti-TNF product to market, Isis elected to discontinue development of this drug, and focus its resources on its two most promising second generation products ISIS 301012 and ISIS 113715.
- *ISIS 14803*—is a first generation antisense drug to treat Hepatitis C which Isis will not continue to develop.

Isis' Partnered Second-Generation Development Pipeline Continued to Expand

- *LY2181308*, the first drug from the Isis-Lilly drug discovery alliance to advance to the clinic, entered Phase 1 clinical trials in patients with cancer in November 2004. The compound targets survivin, which plays a role in cancer cell death, or apoptosis. For the accomplishment of this milestone, Isis earned a \$1.5 million payment from Lilly.

- *LY2275796* was licensed to Lilly in September 2004. Isis earned a \$750,000 payment from Lilly for the license. This second-generation antisense drug targets eukaryotic initiation factor 4E, or eIF-4E, a protein involved in tumor progression, angiogenesis and metastasis. *LY2275796* ended the year in preclinical studies and is the second antisense anti-cancer drug to emerge from the Isis-Lilly collaboration.
- *OGX-011*, formerly called ISIS 112989, is a second generation antisense inhibitor of clusterin, which Isis is co-developing and commercializing *OGX-011* with OncoGenex, a Canadian oncology-focused research and development company. In June 2004, the partnership reported results of a Phase I study of *OGX-011* in prostate cancer. Results from the trial demonstrated *OGX-011* was well-tolerated, achieved excellent drug concentration in its target tissue, the prostate, and produced up to a 91 percent dose-dependent reduction of its target. This drug ended the year in the process of completing a second Phase I clinical trial.
- *ATL1102* entered into a Phase IIa clinical trial in patients with multiple sclerosis (MS) in December 2004. Results of a dose-escalating Phase I study of the second-generation antisense drug showed that six mg/kg/week of *ATL1102* appeared well-tolerated. In March 2005, ATL announced that, although it and the trial investigators are confident that the current *ATL 1102* Phase II trial is safe, in light of the recently announced safety issues associated with one other VLA-4 inhibitor that works through a different mechanism, ATL decided to halt the current trial and convene an advisory group to consider the potential development path for *ATL 1102* which may include restarting a Phase II trial program in multiple sclerosis and exploring *ATL 1102* as an inhaled asthma treatment.
- *ATL1101* entered a Phase I study in patients with mild to moderate psoriasis. The drug is designed to block the synthesis of the IGF-1 receptor, a protein involved in the regulation of cell overgrowth in psoriasis.

Furthered TIGER Biosensor Program

- Entered into a two-year contract providing up to \$19.5 million to further the development of Isis' TIGER biosensor system to identify infectious agents in potential biological warfare attacks.
- Received three new government contracts valued at up to \$10 million for the continued development of its TIGER biosensor technology.
- Hired an experienced business head for Ibis Technologies to help lead it to commercialization.
- Isis did not complete a commercial transaction for the TIGER biosensor system that was a source of revenue in 2004.

Advanced Antisense Research Programs

- Reported positive data from multiple preclinical studies that demonstrated the utility of four second-generation antisense inhibitors in identifying new diabetes and related metabolic disease targets for drug discovery and as potential innovative treatments for these conditions.
- Announced positive data from preclinical studies evaluating an antisense drug that suppressed the production of the mutant protein Cu/Zn superoxide dismutase (SOD1), a molecule associated with an aggressive form of amyotrophic lateral sclerosis (ALS).

Other Business Developments

- Formed a strategic alliance with Alnylam to accelerate the development and commercialization of RNAi therapeutics. Isis earned a \$5.0 million technology access fee and a \$500,000 payment from Isis' participation in Alnylam's partnering program.

- Earned \$4.0 million in milestone payments from Eyetech associated with Eyetech's filing of an NDA for Macugen® and receipt of marketing clearance for the drug. Isis also sold a portion of its royalty rights in Macugen to Drug Royalty USA, Inc. in exchange for aggregate payments of \$24.0 million over the next three years.
- Jointly developed a new high performance solid support for the manufacture of oligonucleotides with Nitto Denko Corporation of Osaka, Japan. The new solid support has the potential to decrease manufacturing costs of oligonucleotide-based drugs, including antisense.
- Extended its anti-cancer antisense drug discovery collaboration with Lilly.
- Acquired Elan Corporation plc's minority interest in Orasense and HepaSense, joint ventures arising out of prior collaborations between Isis and Elan, and eliminated all future royalty obligations to Elan related to the oral delivery platform developed within the Orasense collaboration and to ISIS 14803.
- Failed to achieve its objective to outlicense at least one of the drugs in its development pipeline.

Patents and Proprietary Rights

Isis expanded its strong intellectual property position in RNA-based drug discovery by licensing core intellectual property regarding all therapeutic uses of miRNA from the Max Planck Society.

Overall Accomplishment of Objectives

As a result of the foregoing factors and based on a combination of the accomplishment of major research and drug development objectives and the success of alicaforsen enema in Phase II trials for ulcerative colitis, the failure of alicaforsen in patients with Crohn's disease to demonstrate statistically significant induction of clinical remission compared to placebo, and the significant decline in the price of Isis' stock in 2004, the Compensation Committee recommended to the Board a corporate performance bonus guideline of 50%, with the guideline for a year in which all objectives were achieved by the Company being 100%, which, together with individual performance, formed the basis for cash bonus awards for 2004. Individual executive officer base salary increases were based on individual executive officer performance; however, merit salary increases for executive officers were reduced by 25% as a result of the significant disappointments for the year.

Compensation for Isis' 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 chief executive officers in comparable biotechnology companies and assessed Dr. Crooke's performance in light of Isis' objectives achieved and not achieved, as discussed above. As a result, the Compensation Committee recommended that Dr. Crooke receive a base salary increase of 3%, to \$549,262 for 2005. Dr. Crooke received a base salary increase in 2004 of 4.5% and an increase of 5% in 2003. In January 2005, Dr. Crooke received a bonus of \$122,651 for accomplishments in 2004, likewise based on the assessment of corporate objectives achieved and not achieved. On January 2, 2004, the Committee approved an option grant of 80,000 shares of common stock for performance in 2003 for Dr. Crooke, pursuant to Isis' 1989 Plan, at an exercise price of \$6.81 per share, the fair market value on the date of grant. In January 2005, the Committee approved an option grant of 75,720 shares of common stock for performance in 2004 for Dr. Crooke, pursuant to Isis' 1989 Plan, at an exercise price of \$5.80 per share, the fair market value on the date of grant. The options vest over a four-year period; 25% after the first year and 2.08% per month for the remaining 36 months.

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

AUDIT COMMITTEE REPORT(3)

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, 2004 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 principles. 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.

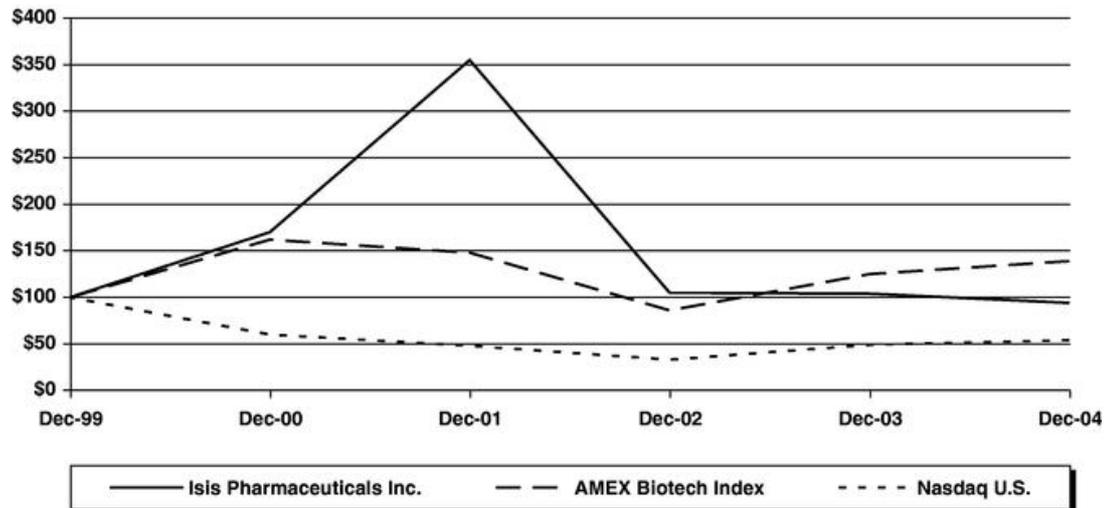
The Audit Committee discussed with our independent auditors the overall scope and plans for their audit. The Audit Committee met with the independent auditors, with and without management present, to discuss the results of their examinations, their evaluations of our internal controls, and the overall 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 our Annual Report on Form 10-K for the fiscal year ended December 31, 2004 for filing with the SEC. The Audit Committee and the Board have also recommended, subject to stockholder approval, the selection of Ernst & Young LLP as our independent auditors.

Joseph H. Wender, Chairman
Spencer R. Berthelsen
Christopher F. O. Gabrieli

(3) 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.

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



	Dec-99	Dec-00	Dec-01	Dec-02	Dec-03	Dec-04
Isis Pharmaceuticals Inc.	\$ 100	\$ 170	\$ 355	\$ 105	\$ 104	\$ 94
AMEX Biotech Index	\$ 100	\$ 162	\$ 148	\$ 86	\$ 125	\$ 139
Nasdaq U.S.	\$ 100	\$ 60	\$ 48	\$ 33	\$ 49	\$ 54

The above table and chart assume \$100 invested on December 31, 1999 in our common stock, the NASDAQ Composite Index (Total Return) and the AMEX Biotech Index. Total return assumes reinvestment of dividends.

(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.

Certain Relationships and Related Transactions

Rosanne Crooke, the wife of Dr. Crooke, our Chairman and Chief Executive Officer, is a non-executive employee of Isis and earns more than \$60,000 per year in compensation. However, Mrs. Crooke's compensation is commensurate with the compensation with that of other employees at the same level at Isis.

One of our Directors, Mr. 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 2004 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 each of our executive officers and Directors and certain non-executive officers 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 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, 1896 Rutherford Road, 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, Inc., please request a copy of our Annual Report. The report includes our Form 10-K for the year ended December 31, 2004 that we filed with the SEC, and is available free of charge. Please send written requests to:

B. Lynne Parshall, Secretary
Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008

You may also visit the Company's website (www.isispharm.com) to view our 2004 Annual Report. 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.

By Order of the Board of Directors

B. Lynne Parshall
Secretary

April 19, 2005

ANNUAL MEETING OF STOCKHOLDERS OF

ISIS PHARMACEUTICALS, INC.

May 26, 2005

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

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

THE BOARD OF DIRECTORS RECOMMENDS A VOTE "FOR" THE ELECTION OF DIRECTORS AND "FOR" PROPOSAL 2.

PLEASE SIGN, DATE AND RETURN PROMPTLY IN THE ENCLOSED ENVELOPE. PLEASE MARK YOUR VOTE IN BLUE OR BLACK INK AS SHOWN HERE ☒

- | | FOR | AGAINST | ABSTAIN |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|---------|---------|
| 1. To elect three directors to hold office until the 2008 Annual Meeting of Stockholders and elect Dr. DiMarchi to hold office until the 2006 Annual Meeting of Stockholders. | o | o | o |
| 2. To ratify the selection of Ernst & Young LLP as independent auditors of the Company for its fiscal year ending December 31, 2005 | | | |

NOMINEES:

- FOR ALL NOMINEES
 - Spencer R. Berthelsen
 - Richard D. DiMarchi
- WITHHOLD AUTHORITY FOR ALL NOMINEES
 - B. Lynne Parshall
 - Joseph H. Wender
- FOR ALL EXCEPT (See instructions below)

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

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: o

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, 2005

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 1896 Rutherford Road, Carlsbad, California 92008 on Thursday, May 26, 2005 at 9:30 a.m. PT, and at any and all continuations and adjournments thereof, with all powers that the undersigned would possess if personally present, upon and in respect of the following matters and in accordance with the following instructions, with discretionary authority as to any and all other matters that may properly come before the meeting.

UNLESS A CONTRARY DIRECTION IS INDICATED, THIS PROXY WILL BE VOTED FOR PROPOSALS 1 AND 2 AS MORE SPECIFICALLY DESCRIBED IN THE PROXY STATEMENT. IF SPECIFIC INSTRUCTIONS ARE INDICATED, THIS PROXY WILL BE VOTED IN ACCORDANCE THEREWITH.

(Continued and to be signed on the reverse side)

ANNUAL MEETING OF STOCKHOLDERS OF

ISIS PHARMACEUTICALS, INC.

May 26, 2005

PROXY VOTING INSTRUCTIONS

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

—OR—

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

COMPANY NUMBER

—OR—

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

ACCOUNT NUMBER

You may enter your voting instructions at 1-800-PROXIES or www.voteproxy.com up until 11:59 PM Eastern Time the day before the cut-off or meeting date.

V Please detach along perforated line and mail in the envelope provided IF you are not voting via telephone or the Internet. V

THE BOARD OF DIRECTORS RECOMMENDS A VOTE "FOR" THE ELECTION OF DIRECTORS AND "FOR" PROPOSAL 2.

PLEASE SIGN, DATE AND RETURN PROMPTLY IN THE ENCLOSED ENVELOPE. PLEASE MARK YOUR VOTE IN BLUE OR BLACK INK AS SHOWN HERE

- 1. To elect three directors to hold office until the 2008 Annual Meeting of Stockholders and elect Dr. DiMarchi to hold office until the 2006 Annual Meeting of Stockholders.
2. To ratify the selection of Ernst & Young LLP as independent auditors of the Company for its fiscal year ending December 31, 2005

NOMINEES:

- FOR ALL NOMINEES
WITHHOLD AUTHORITY FOR ALL NOMINEES
FOR ALL EXCEPT (See instructions below)

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

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: o

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.

DEAR STOCKHOLDERS,

ISIS AND OUR GROWING LIST OF PARTNERS HAVE LED IN THE ADVANCEMENT OF ALL AREAS OF ANTISENSE DRUG DEVELOPMENT, FROM BASIC RESEARCH TO DRUG DISCOVERY TO CLINICAL DEVELOPMENT TO COMMERCIAL- SCALE MANUFACTURING.

THESE ADVANCES ARE EVIDENCED BY THE:

- Number of antisense drugs in development;
- Number of companies participating in development of these drugs;
- Range of diseases in which we are studying antisense drugs;
- Significant reductions in the cost to deliver antisense drugs;
- Invention of improved second-generation chemistries, and
- Development of many routes of administration for antisense drugs, including the potential for oral and aerosol delivery.

Through our investment, innovation and passion, we have created antisense technology; a technology that allows us to efficiently generate drugs for ourselves and our partners. Our second-generation drugs represent the future of Isis and the technology. We are committed to broadening the applications for antisense, while taking advantage of the technology's productivity and capitalizing on the drug assets that arise from our drug discovery and development programs.

Our business strategy is designed to take advantage of our knowledge and expertise in RNA-based drug development and the strengths of our technology, patent position, employees and management team to advance multiple drug candidates toward the market. We plan to execute this strategy by licensing our drugs as early in the clinical development process as we can on the best terms possible. This strategy allows us to participate in the progress of many drugs as they move through the clinic, while decreasing our investment in any one product. Further, by increasing the number of antisense drugs in development, we significantly increase the probability of multiple commercial successes.

As we enter 2005, we have all the elements in place to continue to implement this strategy. We have an exciting pipeline, excellent partners, and more than 1,500 issued or exclusively licensed patents, all of which provide us with a sound leadership position in oligonucleotide-based therapeutics. We have built the infrastructure necessary to efficiently and effectively discover and develop antisense drugs. And, along the way, we have advanced our TIGER biosensor system to an important stage in its development. We are optimistic about the prospects of the Company and the therapeutic and commercial potential of each one of our products in development. What remains is for us to execute our 2005-2006 plan by achieving the following objectives:

FIRST, WE MUST FIND A STRONG PARTNER FOR ALICAFORSEN ENEMA, AND AGGRESSIVELY MOVE THIS NEAR-TERM PRODUCT OPPORTUNITY TOWARDS THE MARKET.

In late 2004, we announced data from three Phase 2 clinical trials of alicaforsen enema involving more than 300 patients with ulcerative colitis (UC). These trials demonstrate the drug improves signs and symptoms of UC and is well-tolerated. In the Phase 2 studies, alicaforsen enema outperformed both placebo and the enema standard-of-care. As a result, we now have the information we need to plan a Phase 3 development program. We believe alicaforsen enema represents an attractive commercial opportunity for Isis. If the activity, durability and safety results demonstrated in the Phase 2 trials are replicated in late-stage trials, we believe alicaforsen enema will be an important new drug for patients with this disease.

Our goal in 2005 is to meet with the U.S. Food and Drug Administration to discuss Phase 3 clinical trial plans for alicaforsen enema, identify the best marketing partner with late-stage development and commercial expertise, and work with that partner to develop and implement a successful Phase 3 program. This strategy should allow us to benefit from a partner's clinical trial

experience and knowledge, and avoid the significant costs associated with late-stage development. In turn, we will focus our resources and unique strengths on advancing our second-generation drugs.

SECOND, WE PLAN TO ADVANCE OUR TWO KEY SECOND-GENERATION DRUGS, ISIS 301012 AND ISIS 113715, TO CLINICAL PROOF-OF-VALUE.

ISIS 301012, a drug that inhibits apoB-100 for the treatment of high cholesterol, is an important asset. *ISIS 301012* administered subcutaneously is completing Phase 1 studies. Last year, we reported data from this Phase 1 trial that showed *ISIS 301012* produces dose-dependent, rapid and prolonged reductions of its target, and in LDL, VLDL and total cholesterol levels in volunteers with borderline elevated cholesterol. Further, these data demonstrate that *ISIS 301012* is working as designed; it inhibits and reduces its intended target, resulting in the predicted therapeutic pharmacological outcome, the lowering of cholesterol. Importantly, we have also demonstrated that an oral form of the drug reduces cholesterol in animals. These results gave us the confidence to initiate a Phase 1 trial of the oral formulation of *ISIS 301012* in March 2005.

In 2005-2006, through our development of both the subcutaneous injection and oral formulations of *ISIS 301012*, we plan to:

- define the optimal dose and schedule for *ISIS 301012* as a single agent;
- prepare for the initiation of combination studies with oral lipid-lowering drugs;
- define the oral bioavailability of *ISIS 301012* and demonstrate reduction of apoB-100 and cholesterol in man;
- advance *ISIS 301012* into additional clinical trials to evaluate longer-term dosing, and
- explore other indications, such as therapeutic apheresis, that may offer shortened routes to commercialization.

Consistent with these goals, we plan to:

- report final results from the ongoing Phase 1 single agent study in normal volunteers with borderline elevated cholesterol;
- initiate a Phase 2 trial to evaluate dose and dose schedule in patients with high cholesterol;
- initiate a pharmacokinetic study to evaluate the addition of *ISIS 301012* to statin therapy, and
- initiate a Phase 2 study in patients with high cholesterol who are also taking statins.

ISIS 113715, a drug that inhibits PTP-1B for the treatment of type 2 diabetes, represents another significant product opportunity. This drug is in Phase 2 clinical trials. In a Phase 1 study, *ISIS 113715* increased insulin sensitivity in normal volunteers. Subjects treated with *ISIS 113715* did not experience hypoglycemia, or excessively low blood sugar, which is an adverse effect observed with many currently available type 2 diabetes treatments.

The goals of our *ISIS 113715* development program in 2005-2006 are to:

- demonstrate the safety of the drug as a single agent in patients with type 2 diabetes to support longer-term dosing;
- define the optimal dose and schedule to support future clinical trials;
- advance *ISIS 113715* into additional clinical trials to evaluate longer-term dosing, and
- explore the drug in patients who are also taking oral anti-diabetic therapies.

In line with these goals, we plan to:

- report results from the ongoing Phase 2 single agent trial in patients with type 2 diabetes;
 - report results following 12 weeks of dosing in patients with this disease, and
-

- initiate dosing in patients with type 2 diabetes who are also taking oral anti-diabetic therapy.

THIRD, WE INTEND TO CAPTURE VALUE FROM OUR PORTFOLIO OF SECOND-GENERATION ANTISENSE PRODUCT OPPORTUNITIES AND CONTINUE OUR ADVANCEMENT OF THE TECHNOLOGY.

In our internal development initiatives, we plan to focus our drug discovery efforts on molecular targets that give us early clinical proof-of-value and have the potential to be exciting new drugs that address numerous therapeutic areas with major market potential. Specific areas we are concentrating on include inflammatory, metabolic and cardiovascular diseases, and cancer. In 2005-2006, we intend to advance at least two new drug candidates from our drug discovery programs into development.

FOURTH, WE PLAN TO EXPAND OUR PARTNERS' DEVELOPMENT PIPELINES AND SUPPORT THE CONTINUED ADVANCEMENT OF CURRENTLY PARTNERED SECOND-GENERATION DRUGS.

We are pleased with the progress made within our current collaborations and our achievements in establishing new ones. Our overall goal in working with partners is to participate in advancing their products through the clinical development process and toward the market.

In 2004, we extended our anti-cancer drug discovery collaboration with Eli Lilly and Company and reported continued progress within our alliance throughout the year. Lilly initiated a Phase 1 trial of LY2181308 in patients with cancer. LY2181308 is the first drug from our alliance to enter the clinic. This second-generation antisense drug targets survivin, a molecule that allows cells that would normally undergo programmed cell death to survive. We also licensed LY2275796 to Lilly in September 2004, the second antisense anti-cancer drug to emerge from the Isis-Lilly collaboration. LY2275796 targets eukaryotic initiation factor-4E, a protein involved in the growth and progression of tumors. This drug is in preclinical development. For these accomplishments we earned \$2.25 million in milestone payments from Lilly.

In 2005-2006, our goal is to support the continuation of Lilly's anti-cancer antisense research and development programs. Further, we are optimistic we will add new antisense drug candidates to Lilly's oncology franchise, and plan to continue to discover and advance additional compounds for licensing consideration by Lilly.

We have also successfully engaged in other strategic drug discovery and development collaborations, which we call our satellite company partnerships. Satellite companies allow us to benefit from our partners' expertise and highly focused research efforts. In turn, partners gain from our experience and expertise in RNA-based drug discovery and development and access to our proprietary antisense chemistries and leading intellectual property. We currently work with high-quality life sciences companies such as OncoGenex Technologies, Inc., Antisense Therapeutics Limited (ATL), Alnylam Pharmaceuticals, Inc., Santaris Pharma A/S and Sarissa, Inc.

OncoGenex has been a partner since 2001. This collaboration combines OncoGenex's proprietary antisense position in inhibitors to the cancer target clusterin, with our proprietary second-generation antisense chemistry. The lead drug in this collaboration is OGX-011 which targets clusterin, a cell survival protein that when overproduced, prevents cancer cell death and counters the effectiveness of standard anti-tumor treatments. Currently, we are supporting OncoGenex's OGX-011 development initiatives. In June 2004, the partnership reported that OGX-011 was well-tolerated, achieved excellent drug concentration in its target tissue, the prostate, and produced up to a 91% dose-dependent reduction of its target in a Phase 1 trial.

In 2003, we expanded our partnership with OncoGenex to include the development of OGX-225, the first bi-specific antisense inhibitor to enter development. A bi-specific inhibitor is a single-stranded antisense drug designed to inhibit the production of two proteins simultaneously. OGX-225 targets both insulin-like growth factor binding protein-5 and insulin-like growth factor binding protein-2, two molecules involved in the development of metastatic disease in hormone-regulated tumors. OGX-225 is

in the research phase of development. Recently, we again expanded our collaboration with OncoGenex to allow for the development of two additional second-generation antisense drug candidates for cancer.

In 2005-2006, we will support OncoGenex's expansion of OGX-011 development into additional cancer therapeutic areas through the completion of a second Phase 1 trial evaluating OGX-011 in combination with TAXOTERE® in solid tumors, and the initiation of Phase 2 clinical trials of the drug in patients with lung, breast and prostate cancers.

ATL is an Australian-based antisense company we helped found in 2001. We are supporting ATL's development efforts to determine the potential of ATL 1102 as an effective treatment for multiple sclerosis (MS). ATL 1102 is an antisense inhibitor of VLA-4. ATL 1102 entered a Phase 2a clinical trial in patients with MS after positive findings from an earlier trial. In March 2005, ATL announced that, although it and the trial investigators are confident that the current ATL 1102 Phase 2a trial is safe, in light of recently announced safety issues associated with another VLA-4 inhibitor that works through a different mechanism, ATL decided to halt the current trial. ATL plans to convene an advisory group to consider the potential development path for ATL 1102.

In 2004, ATL also initiated a proof-of-concept study to explore the activity of ATL 1101 in patients with psoriasis. ATL 1101 is a second-generation antisense drug designed to block the synthesis of the insulin-like growth factor-1 receptor, a protein involved in the regulation of cell growth in psoriasis.

In 2005-2006, we will support ATL's ongoing development efforts to determine the potential of ATL 1102 for MS and to explore the activity of ATL 1101 in psoriasis.

Alnylam is a partnership focused on a particular antisense mechanism of action called RNAi or siRNA. Alnylam is widely considered to be the center of excellence for RNAi research and therapeutic development. In 2004, we formed a strategic alliance with Alnylam to accelerate the development and commercialization of RNAi therapeutics. This alliance combines our expertise in antisense drug development, antisense mechanisms of action and oligonucleotide chemistry with Alnylam's expertise in RNAi therapeutics.

In this transaction, we licensed to Alnylam our patent estate relating to antisense mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a \$5 million technology access fee, participation in fees from Alnylam's partnering programs and downstream milestone and royalty payments. We have already realized value from this alliance through the receipt of a \$500,000 license fee from Alnylam related to Alnylam's partnership with Merck to develop and commercialize RNAi therapeutics for ocular diseases. Recently, we and Alnylam expanded our strong patent positions in RNA-based drug discovery by licensing core intellectual property regarding all therapeutic uses of microRNA.

Sarissa, a Canadian biotechnology company emerging from the University of Western Ontario, is our most recent satellite company relationship. In February 2005, we licensed an anti-cancer antisense drug to Sarissa. The licensed drug is an antisense inhibitor of thymidylate synthase, a well-known drug target that protects cancer cells from the effects of several chemotherapy treatments. In preclinical studies, antisense inhibition of thymidylate synthase suppressed human tumor cell growth and overcame tumor cell resistance to marketed thymidylate synthase-targeted drugs. This drug is in the research phase of development.

We will support Sarissa's development efforts by providing them with access to our RNA-based drug discovery and development expertise. This partnership, similar to the one we have with OncoGenex, combines our second-generation chemistry and experience in antisense discovery and development with Sarissa's deep understanding of the biological role of thymidylate synthase and oncology expertise.

FIFTH, OUR GOAL IS TO CONTINUE THE DEVELOPMENT OF OUR TIGER BIOSENSOR SYSTEM, AND IMPLEMENT A BUSINESS PLAN TO TAKE ADVANTAGE OF THE MANY COMMERCIAL PRODUCT OPPORTUNITIES AVAILABLE FOR TIGER.

We have continued to make excellent progress in advancing core TIGER (Triangulation Identification Genetic Evaluation of Risks) technology, and in creating new applications for the TIGER biosensor system.

During 2004, the TIGER team made remarkable technology and system engineering advances that strengthened the potential commercial opportunities for this system. Our scientists added application development for epidemiological surveillance and biological products screening, and continued to expand our microbial agent database to support broader uses of the TIGER biosensor system. The bioweapons defense, epidemiological surveillance and biological products screening applications of our TIGER technology represent the first of many we plan to develop for the TIGER system to enhance its commercial value and opportunity in the government, research, and medical and diagnostic markets.

Our goals for the TIGER program in 2005-2006 are to continue to:

- secure government contracts;
- deploy TIGER biosensor systems to our government partners, and
- execute a business plan to successfully market TIGER's products and services to both government and non-government commercial customers.

SIXTH, WE PLAN TO CONTINUE TO CAPITALIZE ON OUR INTELLECTUAL PROPERTY ESTATE.

The most important aspect of our patent estate is that it protects our drugs in development, while supporting substantial long-term control of oligonucleotide-based therapeutics. We have been very successful in licensing our patent estate and have used it wisely to enter into a number of strategic relationships. To date, we have generated nearly \$70 million from licensings, which helps fund our drug discovery and clinical development programs. Our highly productive oligonucleotide chemistry program and patents arising from it should continue to provide significant licensing opportunities in the future.

In conclusion, we have created the right chemistry for success. The ideal mix of:

- exciting drugs in various stages of development with significant commercial potential;
- a sustainable portfolio of new product opportunities waiting to be developed;
- a strong blend of partnerships that encompass all areas of our business and are dedicated to increasing the use of our technologies in the marketplace;
- deep antisense drug discovery and development expertise;
- a strong management team, and
- a leadership position in RNA-based technology development that is unmatched.

The ongoing advancement of a technology that could significantly improve the efficiency of drug discovery and development and yield fundamentally different, improved drugs for patients is a substantial challenge. We have made great progress, but we have more to do. As we achieve our goals in the coming year, we will be significantly closer to bringing RNA-based products to market. We thank you for your continued interest in Isis and your support of our endeavors.

In an additional effort to contain costs, we are providing this letter along with our Annual Report on Form 10-K as a simplified version of our 2004 Annual Report. An on-line version of the Isis 2004 Annual Report is available on our web site at www.isispharm.com. The online version of our Annual Report is an interactive, multimedia discussion of the Company and its businesses. I hope you enjoy reading it.

You may also contact our Investor Relations and Corporate Communications Department at 760-603-2331, or by email at info@isisph.com, to request the Isis 2004 Annual Report, either on a CD-Rom or in hard copy, be sent to you free of charge. Please send written requests to:

B. Lynne Parshall, Secretary
Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008

Sincerely,

Stanley T. Crooke, M.D., Ph.D.
Chairman and CEO

FORWARD-LOOKING STATEMENT

This annual report contains forward-looking statements regarding our business, the financial position of Isis Pharmaceuticals, and the therapeutic and commercial potential of our technologies and products in development. Any statement describing our goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' clinical goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, in developing and commercializing technology and systems used to identify infectious agents, and in the endeavor of building a business around such products and services. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements can only be based on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. Factors that could cause or contribute to such differences include but are not limited to, those discussed in Isis' Annual Report on Form 10-K for the year ended December 31, 2004, which is on file with the U.S. Securities and Exchange Commission, and available from the company.

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MICHAEL TREBLE

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