

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

2006 ANNUAL MEETING OF STOCKHOLDERS

AND PROXY STATEMENT

Dear Stockholders,

I am pleased to invite you to Isis Pharmaceuticals' 2006 Annual Meeting of Stockholders. We will host the meeting at our offices in Carlsbad, California on Wednesday, May 3, 2006 at 9:00 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 our plans for 2006, and answer your questions.

This booklet includes the agenda for this year's Annual Meeting and the Proxy Statement. The Proxy Statement explains the matters we will discuss in the meeting and provides additional 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 webcast 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 2006 ANNUAL MEETING OF STOCKHOLDERS

Date: Wednesday, May 3, 2006
Time: 9:00 a.m., Pacific Time
Place: Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008

Dear Stockholders,

At our 2006 Annual Meeting, we will ask you to:

- elect three Directors each to serve for a three-year term and one Director to serve for a one year term;
- approve an amendment to our Restated Certificate of Incorporation to increase the authorized number of shares of Common Stock from 100,000,000 to 200,000,000 shares;
- approve an Amendment to the 2002 Non-Employee Directors' Stock Option Plan to (i) increase the total number of shares reserved for issuance under the Directors' Plan from 600,000 shares to 850,000 shares, and (ii) increase the annual non-discretionary stock option grant for our non-employee directors from 10,000 shares to 12,500 shares;
- ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2006 fiscal year; 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 7, 2006 you may vote at the Annual Meeting.

By order of the Board of Directors,

B. Lynne Parshall
Secretary

Carlsbad, California
March 22, 2006

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 2006 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 2006 Annual Meeting of Stockholders to be held on Wednesday, May 3, 2006, at 9:00 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 the Company's offices at 1896 Rutherford Road, Carlsbad, California. This Proxy Statement summarizes the information you will need 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 March 22, 2006 to all stockholders who are entitled to vote. Only stockholders who owned our common stock at the close of business on March 7, 2006 are entitled to vote at the Annual Meeting. On this record date, we had 72,521,087 shares of our common stock outstanding.

A quorum of stockholders is necessary to hold a valid meeting. A quorum will be present at the meeting if at least a majority of the outstanding shares are represented 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" 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, except that for Proposal 2 broker non-votes will have the same effect as negative votes.

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. This year, Proposal 3 regarding the amendment to our 2002 Non-Employee Directors' Stock Option Plan is a non-discretionary item, which means that if you do not instruct the broker on how to vote on this proposal, your broker will not have the authority to vote your shares.

You may vote in one of the following ways:

- attend the 2006 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 2006.

Solicitation

The Board of Directors of Isis is soliciting your proxy to vote at the Annual Meeting. Isis 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, electronic mail 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, but we expect to pay Georgeson Shareholder Communications Inc. its customary fee, estimated to be about \$10,000, for rendering solicitation services.

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 2, 2006. 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 your 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 Communication Services 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 by having the voting form in hand and calling the number or going to the website indicated on the form and following 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.

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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 2007 Annual Meeting of Stockholders, you must send the proposal to Isis by no later than November 22, 2006. 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 3, 2007 and no later than the close of business on February 2, 2007. Stockholders are also advised to review our Bylaws, which contain additional requirements with respect to advance notice of stockholder proposals and director nominations.

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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 members of 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 Joseph Klein, III, 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, the Board member will serve the remaining term of the class of Directors to which he or she was elected.

Information about the 2006 Elections

The Board has nominated four Directors for election at the 2006 Annual Meeting. Each of the nominees currently serves as one of our Directors and, except for Mr. Klein, was previously elected by our stockholders. Based on the unanimous nomination of our Nominating, Governance and Review Committee, Mr. Klein was appointed to the Board by the then-current members of the Board in December 2005. If re-elected, three of the nominees, Dr. DiMarchi, Mr. Gabrieli and Mr. Muto, will serve until the 2009 Annual Meeting and Mr. Klein will serve until the 2007 Annual Meeting or, in each case, until his successor is elected and has qualified, or until his death, resignation or removal.

Our stockholders elect Directors by a plurality of the votes of the shares represented in person or 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.

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Biographies of Nominees for Election for a Three-year Term Expiring at the 2009 Annual Meeting

Richard D. DiMarchi, Ph.D., age 53, has served as a Director of Isis since December 2004. Dr. DiMarchi has been a professor and the Jack and Linda Gill Distinguished Chair in Biomolecular Science at Indiana University, Bloomington, Indiana since August, 2003. 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.

Christopher F.O. Gabrieli, age 46, 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. Mr. Gabrieli is also Chairman of the Board of EPIX Medical, Inc., a developer of magnetic resonance imaging contrast agents.

Frederick T. Muto, age 52, 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 management committee.

Biography of Nominee for Election for a One-Year Term Expiring at the 2007 Annual Meeting

Mr. Klein, appointed to the Board on December 13, 2005, is a Director in the class whose term expires at the 2007 Annual Meeting. However, in accordance with our membership requirements, as set forth on page 4 above, he is nominated for election this year.

Joseph Klein, III, age 45, has served as a Director of Isis since December 2005. Mr. Klein is currently Managing Director of Gauss Capital Advisors, LLC, a financial consulting and investment advisory firm focused on biopharmaceuticals, which he founded in March 1998. In addition to his investment advisory and financial consulting activities, Mr. Klein currently serves as a Venture Partner of Red Abbey Venture Partners, LP, a life sciences private equity fund. From September 2001 to September 2002, Mr. Klein was a Venture Partner of MPM Capital, a healthcare venture capital firm. From June 1999 to September 2000 when it merged with WebMD Corporation, Mr. Klein served as Vice President, Strategy for Medical Manager Corporation, a leading developer of physician office management information systems. Mr. Klein serves on the board of directors of three publicly held biotechnology companies: BioMarin since June 2005; Clinical Data, Inc. since October 2005 and NPS Pharmaceuticals, Inc. since 1998.

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.

John C. Reed, M.D., Ph.D., age 47, 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 thirteen 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

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serves as an 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 June 2005, Dr. Reed joined the Board of Pharmion, a publicly-traded specialty pharmaceutical company focused on oncology. In December 2004, Dr. Reed was appointed to the Independent Citizen's Oversight Committee of the California Institute for Regenerative Medicine.

Biographies of Directors Whose Terms Expire at the 2008 Annual Meeting

Spencer R. Berthelsen, M.D., age 54, 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. He has been Chairman of the Board of Directors since October 2001 and Managing Director since August 2005. 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 from 1999 through 2005.

B. Lynne Parshall, age 51, 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. Ms. Parshall has served on the Boards of Corautus Genetics Inc. since May 2005 and CardioDynamics International Corporation since June 2005, both biopharmaceutical companies.

Joseph H. Wender, age 61, has served as a Director of Isis since January 1994. Mr. Wender joined GSC Partners in 2005 where he is a Senior Managing Director and Chairman of the Finance Committee. He is a former member of the GSC Advisory Board. Prior to this, he began with Goldman, Sachs & Co. in 1971 and became a General Partner of that firm in 1982, where he headed the Financial Institutions Group for over a decade. He sits on the Board of First Coastal Bancshares, a bank holding company, Affinity Financial, an Internet financial institution, Neurome, a biopharmaceutical company, and Vintrust, a wine management company. He also is Chairman of the Board of GSC Capital Corporation, a Real Estate Investment Trust (REIT). Mr. Wender is also a Director of a number of not-for-profit institutions, including COPIA, the St. Helena Hospital, The Joffrey Ballet and the Actors' Fund.

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," including but not limited to, Rule 4200(a)15 of the Nasdaq listing standards;
- is not an officer or employee of the Company; and
- is free of any relationship that would interfere with his or her individual exercise of independent judgment with regard to Isis.

Meetings and Attendance; Committee Members

The Board of Directors met five times in 2005, four regularly scheduled meetings and one special meeting, and acted by unanimous written consent six times. During 2005, all Directors attended at least 80% of the meetings of the Board and the committees on which they served, except Mr. Gabrieli who attended only 33% of the Audit Committee meetings due to personal schedule conflicts. We encourage each member of the Board to attend the Annual Meeting of Stockholders. None of our Board members, other than Dr. Crooke and Ms. Parshall, attended our 2005 Annual Meeting of Stockholders.

The following table provides membership and meeting information for fiscal 2005 for each of the Board committees:

Name	Audit	Compensation	Nominating, Governance and Review
Dr. Spencer R. Berthelsen	X	X	X

Dr. Stanley T. Crooke			
Dr. Richard D. DiMarchi			
Mr. Christopher F. O. Gabrieli	X		X*
Mr. Joseph "Skip" Klein			
Mr. Frederick T. Muto(3)			
Ms. B. Lynne Parshall			
Dr. John C. Reed		X	
Mr. Joseph H. Wender	X*	X*	
Total meetings in fiscal year 2005	6(1)	1(2)	2

- * Committee Chairperson
(1) Acted by written consent one time as well
(2) Acted by written consent 13 times as well
(3) Mr. Muto served as counsel to the Nominating, Governance and Review Committee

The following table provides membership information for fiscal 2006 for each of the Board committees:

Name	Audit	Compensation	Nominating, Governance and Review
Dr. Spencer R. Berthelsen	X	X*	X*
Dr. Stanley T. Crooke			
Dr. Richard D. DiMarchi		X	
Mr. Christopher F. O. Gabrieli			
Mr. Joseph "Skip" Klein	X		
Mr. Frederick T. Muto**			
Ms. B. Lynne Parshall			
Dr. John C. Reed		X	X
Mr. Joseph H. Wender	X*	X	

- * Committee Chairperson
** Mr. Muto serves as counsel to the Nominating, Governance and Review Committee

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 has the following 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.

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 2005, the Audit Committee met six times and acted by unanimous written consent once. Our Audit Committee charter is attached to this Proxy Statement as Appendix A and can be found on our corporate website at www.isispharm.com. (2) Each member meets the membership criteria set forth in the Audit Committee charter.

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 members of 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 in accordance with guidelines adopted by the Compensation Committee, which consists of one member, Dr. Crooke.

The Compensation Committee met one time in 2005 and acted by unanimous written consent thirteen times. Our Compensation Committee charter can be found on our corporate website at www.isispharm.com.(2)

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.

The Nominating, Governance and Review Committee met twice during 2005. You can find our Nominating, Governance and Review Committee charter on our corporate website at www.isispharm.com.(2)

(2) 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 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 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 2005, the Nominating, Governance and Review Committee met and reviewed the appointment of Mr. Klein who was identified by Dr. Crooke and determined it was in the best interest of the Company and its stockholders to recommend that the Board appoint Mr. Klein 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 November 22, 2006. Submissions must include the full name of the proposed nominee, a description of the proposed nominee's business experience for at least the previous five years, complete biographical information, a description of the proposed nominee's

qualifications as a Director and a representation that the nominating stockholder is a beneficial or record owner of our stock. Any such submission must be accompanied by the written consent of the proposed nominee to be named as a nominee and to serve as a Director if elected.

Stockholder Communications with the Board of Directors

We make every effort to ensure that the views of stockholders are heard by the Board or individual Directors, as applicable, and that appropriate responses are provided to stockholders in a timely manner. Stockholders who wish to communicate with the Board, 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.⁽³⁾

(3) 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

APPROVAL OF INCREASE IN NUMBER OF AUTHORIZED SHARES OF COMMON STOCK

The Board of Directors has adopted, subject to stockholder approval, an amendment to Isis' Restated Certificate of Incorporation to increase the authorized number of shares of our Common Stock from 100,000,000 shares to 200,000,000 shares.

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

In addition to the 72,290,387 shares of Common Stock outstanding at February 14, 2006, there were 9,394,924 shares of Common Stock issuable upon exercise of outstanding options granted under our stock option plans and 4,953,294 shares of Common Stock available for future option grants under our equity plans. Isis has also issued warrants and convertible debt which, on February 14, 2006, would have been exercisable and convertible into an aggregate of 10,525,104 shares of Common Stock. In addition, on December 22, 2005 we filed a Form S-3 shelf registration statement with the Securities and Exchange Commission (the "SEC") to register up to \$200,000,000 worth of Common Stock for possible issuance.

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

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

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

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

PROPOSAL 3

APPROVAL OF THE AMENDMENT TO THE 2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN

Stockholders are requested in this Proposal 3 to approve an amendment to the 2002 Non-Employee Directors' Stock Option Plan (the "Directors' Plan") which was adopted by the Board of Directors on February 28, 2006 subject to stockholder approval. The amendment to the Directors' Plan is to:

- increase the total number of shares reserved for issuance under the Directors' Plan from 600,000 shares to 850,000 shares; and
- increase the annual non-discretionary stock option grant for our non-employee Directors from 10,000 shares to 12,500 shares.

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 2006 Annual Meeting will be required to approve the amendment to the Directors' Plan.

The following description of the Directors' Plan is qualified in all respects by the specific terms of the Directors' Plan, a copy of which was filed with this Proxy Statement.

Purpose

The purpose of the Directors' Plan is to assist in retaining the services of persons now serving as our non-employee directors, to attract and retain the services of persons capable of serving on the Board of Directors and to provide incentives for such persons to exert maximum efforts to promote our success.

Administration

Our Board of Directors administers the Directors' Plan. Our Board of Directors may not delegate administration of the Directors' Plan to a committee. The Board of Directors has the power to construe and interpret the Directors' Plan and options granted under it, and to establish, amend and revoke rules and regulations for its administration.

Stock Subject To The Directors' Plan

Subject to stockholder approval of this Proposal 3, an aggregate of 850,000 shares of Common Stock were reserved for issuance under the Directors' Plan. As of February 14, 2006, and assuming stockholder approval of this Proposal 3, 381,000 shares of Common Stock were available for future grant under the Directors' Plan. As of February 14, 2006, there were options to purchase 360,000 shares of Common Stock issued and outstanding under the Directors' Plan and directors had exercised options to purchase 109,000. On February 14, 2006, the last reported sales price of our Common Stock on the Nasdaq National Market was \$7.26 per share. If our stockholders do not approve this Proposal 3, the total number of shares of Common Stock reserved for issuance under the Directors' Plan will remain at 600,000 shares and 131,000 shares of Common Stock will be available for future grant under the Director's Plan.

If options granted under the Directors' Plan expire or otherwise terminate without being exercised, the shares of Common Stock not acquired pursuant to such options again become available for issuance under the Directors' Plan.

Eligibility, Option Grants

The Directors' Plan provides that options may be granted only to a non-employee director. A "non-employee director" is defined in the Directors' Plan as a director of Isis or one of our affiliates who is not otherwise an

employee of Isis or any affiliate. Seven of our nine current directors, all except Dr. Crooke and Ms. Parshall, are eligible to participate in the Directors' Plan.

Options granted under the Directors' Plan are nonstatutory stock options, meaning that they are not intended to qualify as incentive stock options within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended (the "Code"). Option grants under the Directors' Plan are non-discretionary. The Directors' Plan provides for (i) an initial grant of an option to purchase 20,000 shares of Common Stock to each person when he or she first becomes a non-employee director of Isis, and (ii) an annual grant, on July 1 or the next business day should such date be a Saturday, Sunday or holiday, of an option to purchase 12,500 shares of Common Stock, if this Proposal 3 is approved, to each non-employee director, commencing July 1, 2006. Prior to the proposed amendment, the annual grant was an option to purchase 10,000 shares.

Terms of Options

Each option under the Directors' Plan is subject to the following terms and conditions.

Option Exercise. Options granted under the Directors' Plan become exercisable in four equal annual installments beginning on the first anniversary of the grant of the option. Vesting is conditioned upon continued service as a director or as an employee or consultant of Isis or one of our affiliates.

The Board has the power to accelerate the time during which an option may vest or be exercised. Options granted under the Directors' Plan do not permit exercise prior to vesting.

An option granted under the Directors' Plan may be exercised by giving written notice of exercise to Isis, specifying the number of full shares of Common Stock to be purchased accompanied by payment of the purchase price.

Exercise Price; Payment. The exercise price of options granted under the Directors' Plan is equal to 100% of the fair market value of the Common Stock on the date granted; however, an option may be granted with a lower exercise price if the option is granted pursuant to an assumption or substitution for another option in a manner which satisfies the provision of Section 424(a) of the Code. The exercise price of options granted under the Directors' Plan must be paid in cash. To the extent provided by the terms of an option, an optionholder may satisfy any federal, state or local tax withholding obligation relating to the exercise of such option by:

- a cash payment upon exercise;
- authorizing Isis to withhold a portion of the stock otherwise issuable to the optionholder;
- delivering already-owned shares of our Common Stock; or,
- a combination of these means.

Transferability; Term. Under the Directors' Plan, an option may not be transferred by the optionholder except as determined by the Board and as set forth in the option agreement. Currently, the Board has determined, and director option agreements provide, that in addition to the ability to transfer an option by will or the laws of descent and distribution, a director may transfer part or all of an option to any of the following:

(i) an optionholders' spouse, children (by birth or adoption), stepchildren, grandchildren, or parents;

(ii) a trust or other entity established solely for the optionholders' benefit or the benefit of the optionholders' spouse, children (by birth or adoption), stepchildren, grandchildren, or parents for estate planning purposes; or

(iii) an organization which is exempt from taxation under Section 501(c)(3) of the Code or to which tax-deductible charitable contributions may be made under Section 170 of the Code.

Furthermore, an optionholder may, by delivering written notice to Isis, in a form satisfactory to Isis, designate a third party who, in the event of the optionholder's death, will thereafter be entitled to exercise the option.

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No option granted under the Directors' Plan is exercisable by any person after the expiration of 10 years from the date the option is granted.

Other Provisions. The option agreement may contain such other terms, provisions and conditions not inconsistent with the Directors' Plan as may be determined by the Board.

Adjustment Provisions

If any change is made in, or other event occurs with respect to, the Common Stock subject to the Directors' Plan, or subject to any option under the Directors' Plan, without the receipt of consideration by Isis (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 Isis each, a "Capitalization Adjustment"), the Directors' Plan will be appropriately adjusted in the class(es) and maximum number of securities subject to the Directors' Plan and issuable pursuant to option grants under the Directors' Plan, and any outstanding options will be appropriately adjusted in the class(es) and number of securities and exercise price per share of the securities subject to such outstanding options. The Board of Directors will make such adjustments, and its determination will be final, binding and conclusive. The conversion of any convertible securities of Isis will not be treated as a transaction "without receipt of consideration" by Isis.

In the event of (i) the sale or other disposition of all or substantially all of our assets, (ii) the sale or other disposition of at least 90% of our outstanding securities, or (iii) certain specified types of merger, consolidation or similar transactions (each, a "Corporate Transaction" as defined more specifically in the Directors' Plan), any surviving or acquiring corporation may assume options outstanding under the Directors' Plan or may substitute similar options. If any surviving or acquiring corporation does not assume the options or substitute similar options, then with respect to options held by optionholders whose service with Isis or an affiliate of Isis has not terminated as of the effective date of the Corporate Transaction, the vesting of such options (and, if applicable, the time during which such options may be exercised) will be accelerated in full and the options will terminate if not exercised (if applicable) at or prior to such effective date. With respect to options outstanding under the Directors' Plan that have been neither assumed nor substituted and that are held by optionholders whose continuous service has terminated prior to the effective time of the Corporate Transaction, the vesting of the options, and, if applicable, the time at which such options may be exercised will not be accelerated unless otherwise provided in a written agreement between Isis or any affiliate and the holder of the option, and such options shall terminate if not exercised prior to the effective time of the Corporate Transaction.

In the event of a dissolution or liquidation of Isis, then all outstanding options under the Directors' Plan will terminate immediately prior to the completion of the dissolution or liquidation.

In the event of (i) a qualifying merger or consolidation, as described in the Directors' Plan, or similar transaction whereby following such transaction the stockholders of Isis immediately prior to such transaction do not own outstanding voting securities representing more than 50% of the combined voting power of the entity (or parent of the entity) surviving such transaction, (ii) a qualifying sale, lease, license or other disposition of all or substantially all of our assets, (iii) certain entities reporting under Section 13(d) or 14(d) of the Securities Exchange Act of 1934 (the "Exchange Act") acquire more than 50% of our voting power under certain qualifying circumstances, or (iv) a majority of our Board of Directors is replaced by individuals who are not nominated by members of our current Board of Directors or members nominated by our current Board of Directors or their nominees (each such event, a "Change of Control" for purposes of the Directors' Plan), the vesting of any outstanding options under the Directors' Plan held by persons whose continuous service with Isis or an affiliate of Isis has not terminated prior to the effective date of the Change of Control will accelerate in full, and the options will terminate on the earlier of 12 months following the date of the Change of Control or the expiration date set forth in the option grant.

The acceleration of an option in the event of a Corporate Transaction or a Change in Control event may be viewed as an anti-takeover provision, which may have the effect of discouraging a proposal to acquire or otherwise obtain control of Isis.

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Duration, Amendment and Termination

The Board at any time, and from time to time, may amend the Directors' Plan. However, except as relating to Capitalization Adjustments (described above), no amendment will be effective unless approved by Isis' stockholders to the extent stockholder approval is necessary to satisfy the requirements of Rule 16b-3 or any Nasdaq or securities exchange listing requirements. The Board, in its sole discretion, may submit any other amendment to the Directors' Plan for stockholder approval. Rights under any outstanding option granted before amendment of the Directors' Plan will not be impaired by any amendment of the Directors' Plan unless Isis requests the consent of the optionholder and the optionholder consents in writing.

Unless sooner terminated, the Directors' Plan will terminate on May 30, 2012.

Federal Income Tax Information

Nonstatutory stock options granted under the Directors' Plan generally have the following federal income tax consequences.

There are no tax consequences to the optionholder or Isis by reason of the grant of a nonstatutory stock option. Upon exercise of a nonstatutory stock option, the optionholder normally will recognize taxable ordinary income equal to the excess of the stock's fair market value on the date of exercise over the option exercise price. In the unlikely event the optionholder becomes an employee, we are required to withhold from regular wages or supplemental wage payments an amount based on the ordinary income recognized. Subject to the requirement of reasonableness and the satisfaction of a tax reporting obligation, we will generally be entitled to a business expense deduction equal to the taxable ordinary income realized by the optionholder.

Upon disposition of the stock, the optionholder will recognize a capital gain or loss equal to the difference between the selling price and the sum of the amount paid for such stock plus any amount recognized as ordinary income upon exercise of the option (or vesting of the stock). Such gain or loss will be long-term or short-term depending on whether the stock was held for more than one year. Slightly different rules may apply to optionholders who are subject to Section 16(b) of the Exchange Act.

New Plan Benefits Table

The following table presents certain information with respect to options we expect to grant under the Directors' Plan for the fiscal year ending December 31, 2006 to our non-employee directors, assuming stockholder approval of this Proposal 3. This table assumes that each non-employee director continues as one of our directors throughout the year and that we do not elect any additional non-employee directors. This information is for illustration only and may not be indicative of grants that are made in the future under the Directors' Plan.

NEW PLAN BENEFITS 2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN

Name of Non-Employee Director	Number of Option Shares
Spencer R. Berthelsen	12,500
Richard D. DiMarchi	12,500
Christopher F. O. Gabrieli	12,500
Joseph Klein, III	12,500
Frederick T. Muto	12,500
John C. Reed	12,500
Joseph H. Wender	12,500
Non-Employee Directors as a Group	87,500

THE BOARD OF DIRECTORS RECOMMENDS A VOTE IN FAVOR OF PROPOSAL 3

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PROPOSAL 4

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 our 2006 fiscal year, 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 2006 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, 2005, 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, 2005 and 2004, the aggregate fees billed by Ernst & Young LLP related to the integrated audit of our financial statements for such fiscal years and for the reviews of our interim financial statements were \$367,000 and \$290,970, respectively.

Audit Related Fees:

During the fiscal years ended December 31, 2005 and 2004, 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 \$0 and \$24,904, respectively. The fees billed during 2004 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, 2005 and 2004, the aggregate fees billed by Ernst & Young LLP for professional services rendered for tax compliance, tax advice and tax planning were \$23,894 and \$6,800, respectively. The fees for 2004 were for services related to the preparation of our tax returns and other filings we made with the Internal Revenue Service for 2005 and consultations regarding the application of various provisions of the Internal Revenue Code (the "Code") for each year. The fees for 2005 were for services related to the preparation of information requested in connection with a Franchise Tax Board audit. In 2004 and 2005, 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, 2005 and 2004, there were no fees billed by Ernst & Young LLP for information technology consulting.

All Other Fees:

During the fiscal years ended December 31, 2005 and 2004, all other fees billed by Ernst & Young LLP were \$1,765 and \$790, 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, 2005, 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 4

SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

This table outlines the ownership of our common stock as of February 14, 2006 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)
Federated Investors, Inc. (3) Federated Investors Tower Pittsburgh, PA 15222-3779	11,156,600	15.2
CAM North America, LLC (4) 399 Park Avenue New York, NY 10022	4,370,902	6.0
Farallon Partners, L.L.C. (5)	3,696,828	5.1

Spencer R. Berthelsen (6)	59,370	*
Stanley T. Croke (7)	1,535,170	2.1
Richard D. DiMarchi (8)	5,000	*
Christopher F. O. Gabrieli (9)	205,171	*
Joseph Klein, III (10)	8,100	*
Frederick T. Muto (11)	38,500	*
B. Lynne Parshall (12)	376,670	*
John C. Reed (13)	45,000	*
Joseph H. Wender (14)	80,000	*
Richard K. Brown (15)	83,285	*
Michael J. Treble (16)	30,000	*
Mark K. Wedel (17)	58,876	*
All Directors and executive officers as a group (15 persons)(18)	3,090,867	4.2

* Less than one percent.

(1) This table is based upon information supplied by officers, Directors, principal stockholders and Form 3s, 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 72,290,387 shares of common stock outstanding on February 14, 2006, adjusted as required by rules promulgated by the SEC.
- (3) 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 for which John F. Donahue, Rhodora J. Donahue and J. Christopher Donahue act as trustees. Based on information contained in their Schedule 13G, Federated Kaufmann Fund, a portfolio of Federated Equity Funds, holds 4,705,882 shares and 1,176,470 Warrants issued pursuant to the August 2005 Private Placement which are included in the beneficial ownership.
- (4) Includes CAM North America, L.L.C., with shared voting power over 2,050,505 shares and shared dispositive power over 2,707,361 shares; Salomon Brothers Asset Management Inc. with shared voting and dispositive power over 8,200 shares, Smith Barney Fund Management L.L.C. with shared voting and dispositive power over 1,499,750 shares, and TIMCO Asset Management Inc. with shared voting and dispositive power over 155,591 shares.
- (5) Includes an aggregate of 2,967,049 shares and Warrants exercisable for 729,779 shares, each Warrant being currently exercisable at an exercise price of \$5.2395 per shares (subject to adjustments pursuant to the terms of the Warrants). As the general partner of Farallon Capital Partners, L.P., Farallon Capital Institutional Partners, L.P., Farallon Capital Institutional Partners II, L.P., Farallon Capital Institutional Partners III, L.P., Farallon Special Situation Partners II, L.P.; Farallon Partners, L.L.C. may, for purposes of Rule 13d-3 under the Exchange Act, be deemed to own beneficially the shares held by such Farallon partnerships. As the managing members of Farallon Partners, L.L.C., each of Chun R. Ding, Joseph F. Downes, William F. Duhamel, Charles E. Ellwein, Richard B. Fried, Monica R. Landry, William F. Mellin, Stephen L. Millham, Rajiv A. Patel, Derek C. Schrier, Thomas F. Steyer and Mark C. Wehrly may each, for purposes of Rule 13d-3 under the Exchange Act, be deemed to own beneficially the shares held by such Farallon partnerships. Each of Farallon Partners, L.L.C. and each of its managing members disclaims any beneficial ownership of such shares. All of the above-mentioned entities and persons disclaim group attribution.
- (6) Includes 70 shares owned by Dr. Berthelsen's daughter for which he disclaims beneficial ownership. Includes 30,000 shares of common stock issuable upon exercise of options held by Dr. Berthelsen that are exercisable on or before April 15, 2006.
- (7) Includes 581,620 shares of common stock issuable upon exercise of options held by Dr. Croke that are exercisable on or before April 15, 2006. Also includes 30,259 shares of common stock issuable upon exercise of options held by Rosanne Croke, Dr. Croke's wife, that are exercisable on or before April 15, 2006, and 1,050 shares owned by her. Dr. Croke disclaims beneficial ownership of the shares of common stock owned and issuable upon exercise of options held by his wife.

- (8) Includes 5,000 shares of common stock issuable upon exercise of options held by Dr. DiMarchi that are exercisable on or before April 15, 2006.
- (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 49,000 shares of common stock issuable upon exercise of options held by Mr. Gabrieli that are exercisable on or before April 15, 2006.
- (10) Includes 100 shares of common stock indirectly beneficially owned by Mr. Klein’s son.

- (11) Includes 1,500 shares of common stock indirectly beneficially owned through the Cooley Godward LLP Salary Deferral and Profit Sharing Plan and 37,000 shares of common stock issuable upon exercise of options held by Mr. Muto that are exercisable on or before April 15, 2006.
- (12) Includes 315,745 shares of common stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before April 15, 2006, 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 15, 2006.
- (13) Includes 45,000 shares of common stock issuable upon exercise of options held by Dr. Reed that are exercisable on or before April 15, 2006.
- (14) Includes 49,000 shares of common stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before April 15, 2006.
- (15) Includes 80,937 shares of common stock issuable upon exercise of options held by Dr. Brown that are exercisable on or before April 15, 2006.
- (16) Includes 30,000 shares of common stock issuable upon exercise of options held by Mr. Treble that are exercisable on or before April 15, 2006.
- (17) Includes 50,422 shares of common stock issuable upon exercise of options held by Dr. Wedel that are exercisable on or before April 15, 2006.
- (18) Includes an aggregate of 1,886,796 shares issuable upon exercise of options held by all current Directors and executive officers as a group that are exercisable on or before April 15, 2006.

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, 2005, all Section 16(a) filing requirements applicable to our officers, Directors and greater than ten percent beneficial owners were complied with.

Employment, Severance and Change of Control Agreements

In February 2006, we amended agreements with Stanley T. Crooke and B. Lynne Parshall to continue their April 2003 retention agreements. Specifically, we agreed to continue to provide the following severance benefits:

- Dr. Crooke will be eligible to receive a severance payment equal to 36 months of his then-current base salary in the event his employment is terminated as a result of a Change of Control; and
- Ms. Parshall will be eligible to receive a severance payment equal to (i) 18 months of her then-current base salary in the event that her employment is terminated without cause and (ii) 30 months of her then-current base salary in the event that her employment is terminated as a result of a Change of Control.

These agreements will remain in effect as long as each individual continues to be employed by Isis.

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, 2005, we paid total fees of \$25,000 to each of our non-employee Directors, excluding Mr. Klein who was elected in December 2005.

In 2005, each non-employee Director also received automatic stock option grants under our 2002 Non-Employee Directors’ Stock Option Plan. On July 1, 2005, under the 2002 Non-Employee Directors’ Stock Option Plan, each of our non-employee Directors serving at that time received an option to purchase 10,000 shares of our common stock, at an exercise price of \$3.95 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 2005, in connection with his appointment to the Board, Mr. Klein received an automatic grant of an option to purchase 20,000 shares of our common stock under the 2002 Non-Employee Directors’ Stock Option Plan, at an exercise price of \$5.17 per share, 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, 2005, 2004, and 2003.

Summary Compensation Table

Name and Principal Position	Year	Annual Compensation			Long-Term Compensation Awards Securities Underlying Options (#)	All Other Compensation (\$)
		Salary (\$)	Bonus (\$)(1)	Other Annual Compensation (\$)(2)		
Stanley T. Crooke Chairman, CEO and President	2005	549,262	219,705	—	75,720	—
	2004	539,499	122,651	—	80,000	—
	2003	510,300	191,363	—	117,333(3)	—
B. Lynne Parshall Director, Executive VP & Chief Financial Officer	2005	434,974	146,151	—	30,263	—
	2004	422,305	84,989	—	38,400	—
	2003	405,089	127,603	—	81,466(4)	—
Richard K. Brown Vice President, Business Development	2005	327,241	66,757	—	26,900	—
	2004	317,710	33,360	—	18,000	—
	2003	305,490	72,172	—	65,500(5)	—
Michael J. Treble Vice President, President of the Ibis Division	2005	325,000	85,800	—	—(6)	99,589(7)
	2004	23,542	—	—	90,000(6)	—
Mark K. Wedel Senior Vice President, Clinical Research and Chief Medical Officer	2005	308,256	92,477	—	30,848	—
	2004	296,400	44,460	—	16,781	—
	2003	279,710	64,125	—	40,000(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 2005 were paid in January 2006.
- (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 49,000 options issued in a stock exchange offered to all employees in which 102,000 options previously granted to Dr. Brown were cancelled.
- (6) Mr. Treble commenced employment on December 6, 2004. As part of his hire, Mr. Treble received an initial grant of 90,000 stock options.
- (7) Relocation expense.
- (8) Includes 10,500 options issued in a stock exchange offered to all employees in which 26,500 options previously granted to Dr. Wedel were cancelled.

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"). In 2005, the Board granted options to purchase a total of 1,491,432 shares of our Common Stock to employees under the 1989 Plan. In 2005, we did not grant any options under our 2000 Plan.

In 2002, we implemented a stock trading program for our Board of Directors, corporate executive officers and other insiders, under Rule 10b5-1 of the Exchange Act. When there is no material non-public information available, Rule 10b5-1 allows corporate insiders to establish plans that permit prearranged future sales of 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, except Michael Treble, currently participate in our 10b5-1 trading program.

The following table shows certain information regarding options granted to, exercised by, and held at December 31, 2005 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	75,720	5.08	5.80	1/2/12	\$ 178,706	\$ 416,430
B. Lynne Parshall	30,263	2.03	5.80	1/2/12	\$ 71,423	\$ 166,435
Richard K. Brown	26,900	1.80	5.80	1/2/12	\$ 63,486	\$ 147,939
Michael J. Treble	—	—	—	—	—	—
Mark K. Wedel	20,848	1.40	5.80	1/2/12	\$ 49,203	\$ 114,656
	10,000(4)	0.67	3.94	5/24/12	\$ 16,040	\$ 37,379

- (1) All options granted in 2005 vest over a four-year period: 25% after the first year and 2.08% per month thereafter.
- (2) Based on options to purchase an aggregate of 1,491,432 shares granted in 2005 to employees under our 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 optionholders continued employment through the vesting periods. The amounts reflected in this table may not necessarily be achieved.
- (4) Granted to Dr. Wedel for a promotion in May 2005.

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Aggregated Option Exercises in Last Fiscal Year and FY-End Option Values

Name	Shares Acquired on Exercise	Value Realized (1)	Number of Securities Underlying Unexercised Options at Fiscal Year End		Value of Unexercised In-the-Money Options at Fiscal Year End (2)	
			Exercisable/Unexercisable		Exercisable/Unexercisable	
Stanley T. Crooke	—	—	545,253/132,800		\$5,891.58/\$168.39	
B. Lynne Parshall	—	—	(3)359,526/58,603		\$4,940.73/\$141.21	
Richard K. Brown	—	—	68,294/42,106		\$4,287.42/\$122.58	
Michael J. Treble	—	—	22,500/67,500		\$-/\$-	
Mark K. Wedel	—	—	39,759/47,870		\$918.72/\$13,026.28	

- (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, 2005 (\$5.24) 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, which Ms. Parshall transferred equally to her 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, 2005.

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 (c)
Equity compensation plans approved by stockholders(a)	4,392,000	\$ 7.88	4,304,000
Equity compensation plans not approved by stockholders(b)	3,588,000	\$ 7.84	1,976,000

Total	7,980,000	\$	7.86	6,280,000
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- (a) Consists of three Isis plans: the 1989 Plan, the 2002 Non-Employee Directors' Stock Option Plan and the 2000 Employee Stock Purchase Plan.
- (b) Consists of the 2000 Broad-Based Equity Incentive Plan only.
- (c) Of these shares, 50,944 remain available for purchase under the 2000 Employee Stock Purchase Plan as of December 31, 2005. 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 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 14, 2006, there were 5,990,000 shares authorized for issuance under the 2000 Plan, options to purchase an aggregate of 3,473,229 shares had been granted and were outstanding under the 2000 Plan, options to purchase an aggregate of 468,797 shares had been exercised under the 2000 Plan, and 2,047,974 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 under this plan 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, 2005, approximately 3,587,567 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.

Compensation Committee Interlocks and Insider Participation

As noted above, during the fiscal year ended December 31, 2005, our Compensation Committee was composed of Drs. Berthelsen and 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(4)

In 2005, the Compensation Committee of the Board of Directors consisted of Joseph Wender (Chairman), Spencer Berthelsen, and John Reed, 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.

(4) 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.

We structure our management bonus and salary increase program around both the individual's and Isis' performance. The Compensation Committee assesses Isis' achievements against our key corporate objectives, and determines the corporate bonus and salary increase guideline for all employees at director level or above, including Isis' executive officers. Individual bonus guidelines are determined by an individual's manager and approved by the CEO. The Compensation Committee reviews and approves all compensation for our executive officers, including annual bonus stock option grants, cash bonuses and base salary. In addition to company and individual performance, 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 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. At the end of each year, the Compensation Committee sets the maximum number of shares we can grant to our employees as a whole as part of the annual stock option grants. This overall maximum, plus each employee's position and performance in the previous year ultimately determines the size of the individual annual option grant. For 2005, 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 2005

2005 presented a number of challenges for Isis' management. In the face of these challenges, management achieved most of its objectives and made significant progress in the areas discussed below. However, 2005 had its disappointments. Most notably, Isis did not meet its partnering objectives for the year. Further, the price of Isis' stock did not appreciably increase from the previous year. Therefore, the Compensation Committee recommended to the Board a corporate performance bonus guideline of 80%, with the guideline for a year in which most objectives were achieved by the Company being 100%, and a salary increase guideline of 4.5% for all employees, including Isis' executive officers. The 2005 accomplishments included:

Advanced Development of Second-generation Antisense Drugs

The Company continued to advance its most promising drugs to treat cardiovascular, metabolic and inflammatory diseases.

ISIS 301012 (Targeting apoB-100 for the treatment of high cholesterol)

- Reported positive results from Phase 1 studies of ISIS 301012 in normal volunteers with borderline elevated cholesterol. ISIS 301012 produced rapid, dose-dependent and prolonged reductions of its target, apoB-100, with concomitant reductions in LDL-C, VLDL, and total cholesterol levels. ISIS 301012 also significantly reduced triglycerides.
- Initiated Phase 2 development program of ISIS 301012:
 - Initiated a Phase 2 study to optimize dose and frequency of dosing, and to further evaluate the safety and efficacy of ISIS 301012, in patients with high cholesterol.
 - Initiated a Phase 2 combination study to evaluate the safety and efficacy of ISIS 301012 in combination with simvastatin, in patients with high cholesterol.

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- Initiated, Phase 1 study of an oral capsule formulation of ISIS 301012. In 2006, ISIS 301012 demonstrated oral bioavailability and reduced apoB-100 and LDL-C.

ISIS 113715 (Targeting PTP1-B for the treatment of type 2 diabetes)

- Reported data from a Phase 2 study in diabetic patients. ISIS 113715 reduced HbA1C and plasma glucose in patients with type 2 diabetes, did not cause hypoglycemia and was well tolerated.

Added Two New Drugs to the Company's Development Pipeline

ISIS 369645 (Targeting IL4R-alpha for the treatment of asthma)

- Initiated development activities of ISIS 369645 for the treatment of asthma and related pulmonary diseases.

ISIS 353512 (Targeting CRP for the treatment of cardiovascular & inflammatory diseases)

- Initiated development activities of ISIS 353512, a generation 2.2 antisense drug, for the treatment of cardiovascular disease and inflammatory diseases.

Supported Advancement of Partners' Pipelines and Expanded Licensing and Partnerships

The Company continued to expand its drug discovery and development programs and capitalized on its patent estate through a combination of corporate partnerships, satellite company relationships and licensing transactions.

Collaborations

Lilly

- Extended the four-year drug discovery collaboration with Lilly to continue to advance the two anti-cancer antisense drugs, LY2181308 and LY2275796, identified during the initial collaboration and to continue their efforts to develop and refine antisense technologies.
- Lilly continued to conduct Phase 1 clinical trials of LY2181308 in cancer patients.

Pfizer

- Isis earned \$2.2 million in upfront fees and milestone payments in connection with a multi-year drug discovery collaboration with Pfizer to identify second-generation antisense drugs for the treatment of ophthalmic disease.

Satellite Company Relationships

OncoGenex Technologies, Inc.

OGX-011 (Targeting Clusterin for the treatment of breast, prostate and lung cancers)

- OncoGenex initiated four Phase 2 studies of OGX-011 for the treatment of prostate, non-small cell lung and breast cancers.
- Expanded antisense drug discovery and development collaboration in cancer for the development of two additional second-generation antisense anti-cancer drug candidates.

Antisense Therapeutics Ltd. (ATL)

ATL1101 (Targeting IGF-1R for the treatment of psoriasis)

- ATL reported results from a study of ATL1101 in patients with psoriasis. ATL1101 demonstrated activity in psoriasis patients and was well tolerated.

ATL-1102 (Targeting VLA4 for the treatment of multiple sclerosis)

- ATL received approval to restart the Phase 2 trial of ATL1102 for patients with relapsing-remitting multiple sclerosis.

Alnylam Pharmaceuticals, Inc.

- The Company received nearly \$4 million from Alnylam because of Alnylam's recent collaboration with Novartis for the development of RNAi therapeutics.

New Satellite Company Relationships

iCo Therapeutics

iCo 007 (Targeting c-raf kinase for the treatment of eye diseases)

- Licensed iCo 007 (ISIS 13650) to iCo for the treatment of various eye diseases such as age-related macular degeneration (AMD) and diabetic retinopathy. iCo is a company developing pre-existing drugs for a range of new conditions affecting isolated biological environments in areas such as the eye, spinal cord or joints.

Sarissa, Inc.

- Licensed an antisense inhibitor of thymidylate synthase (TS), a drug target that protects cancer cells from the effects of several chemotherapy treatments to Sarissa.

Licensing Transactions

Drug Royalty Corporation

- Received \$7 million from Drug Royalty USA, Inc. (DRC) as a partial payment for the acquisition of part of Isis' royalty rights in Macugen®.

Ibis Division Executes Commercialization Plans for TIGER Biosensor System

The Ibis division met major business milestones and continued to develop applications with government funding.

- Michael Treble, president of the Ibis division presented commercialization plans for the TIGER biosensor system.
- Executed commercialization plans by delivering first two TIGER biosensor systems to the Department of Homeland Security's National Bioforensic Analysis Center for use in microbial forensics and to the United States Army Medical Research Institute for Infectious Disease for use in biowarfare defense.
- Continued to increase revenues from government contracts and received additional government contracts and grants in 2005 for approximately \$11.2 million from several government agencies to support the initial operations of the TIGER biosensor system and continue advancing application development.
- Further validated the TIGER system in infectious disease surveillance as evidenced by studies published in the *Proceedings of the National Academy of Sciences* (PNAS), *Emerging Infectious Diseases*, and the *International Journal of Mass Spectrometry*.
- Received two prestigious industry awards, the "R&D 100" award, which recognizes the 100 most technology significant products introduced into the marketplace over the past year, and the Innovation Award for the Year from the Association for Laboratory Automation.

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, the successful completion of the approximately \$51 million private equity financing, the implementation of a corporate restructuring and related reduction in operating costs, the failure to meet partnering goals, and the lack of appreciable increase in the price of Isis' stock in 2005, the Compensation Committee recommended to the Board a corporate performance bonus guideline of 80%, with the guideline for a year in which all objectives were achieved by the Company being 100%. Together with individual performance, these guidelines formed the basis for cash bonus awards for 2005. Individual executive officer base salary increases were based on individual executive officer performance.

Compensation for Isis' CEO

Dr. Crooke's compensation is determined in accordance with the criteria described above for all executive officers. The Compensation Committee assessed Dr. Crooke's performance in light of Isis' objectives achieved and not achieved, as discussed above, and reviewed published salary survey data for chief executive officers in comparable biotechnology companies. As a result, the Compensation Committee recommended that Dr. Crooke receive a base salary increase of 6%, to \$582,218 for 2006. Dr. Crooke received a base salary increase in 2005 of 3% and an increase of 4.5% in 2004. In January 2006, Dr. Crooke received a bonus of \$219,705 for accomplishments in 2005, likewise based on the assessment of corporate objectives achieved. In January 2006, the

Committee approved an option grant of 128,924 shares of common stock for performance in 2005 for Dr. Crooke, pursuant to Isis' 1989 Plan, at an exercise price of \$5.25 per share, the fair market value on the date of grant. In comparison, for Dr. Crooke's performance over 2004, the Committee granted him an option to purchase 75,720 shares of common stock. The options vest over a four-year period; 25% after the first year and 2.08% per month for the remaining 36 months.

Joseph H. Wender, Chairman
Spencer R. Berthelsen
John C. Reed

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AUDIT COMMITTEE REPORT(5)

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, 2005 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, 2005 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

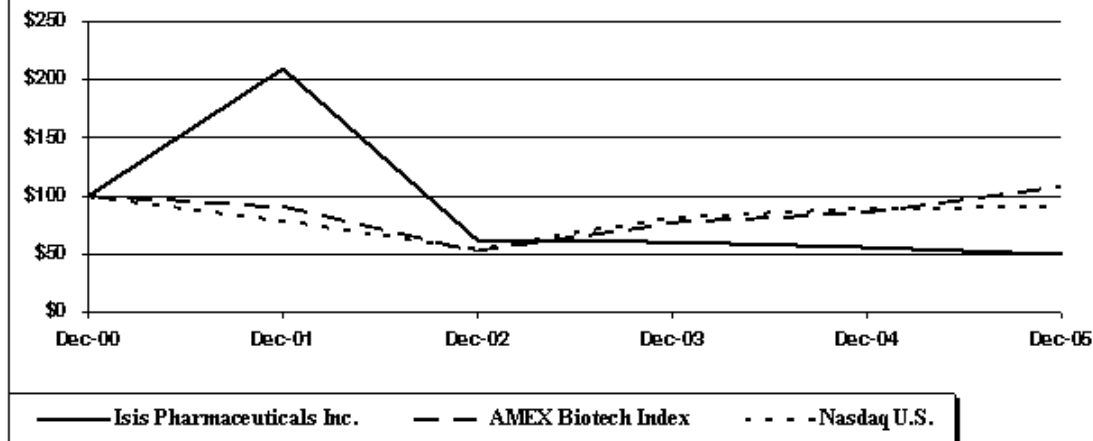
(5) This Section is not "soliciting material," is not deemed filed with the SEC and is not to be incorporated by reference in any filing of Isis under the 1933 Act or the Exchange Act.

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Performance Measurement Comparison(6)

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

CUMULATIVE TOTAL RETURN
Based upon an initial investment of \$100 on December 31, 2000
with dividends reinvested



SOURCE: GEORGE SON SHAREHOLDER COMMUNICATIONS INC.

	Dec-00	Dec-01	Dec-02	Dec-03	Dec-04	Dec-05
Isis Pharmaceuticals Inc.	\$ 100	\$ 209	\$ 62	\$ 61	\$ 56	\$ 49
AMEX Biotech Index	\$ 100	\$ 92	\$ 53	\$ 77	\$ 86	\$ 107
Nasdaq U.S.	\$ 100	\$ 79	\$ 55	\$ 82	\$ 89	\$ 91

The above table and chart assume \$100 invested on December 31, 2000 in our common stock, the NASDAQ Composite Index (Total Return) and the AMEX Biotech Index. Total return assumes reinvestment of dividends.

(6) 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, Dr. Rosanne Crooke’s compensation is commensurate with the compensation 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 2005 fiscal year.

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 and 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; and we will promptly provide you a separate proxy

statement. 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, 2005 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 2005 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

March 22, 2006

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APPENDIX A CHARTER OF THE AUDIT COMMITTEE OF THE BOARD OF DIRECTORS

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

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

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

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

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

APPENDIX B
CERTIFICATE OF AMENDMENT TO THE RESTATED CERTIFICATE OF INCORPORATION

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

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

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

THIRD: The Board of Directors of the Corporation, acting in accordance with the provisions of Sections 141 and 242 of the General Corporation Law of the State of Delaware, adopted resolutions at a meeting held on December 13, 2005 to amend Article V of the Restated Certificate of Incorporation of the Corporation to read in its entirety as follows:

The Corporation is authorized to issue two classes of shares designated respectively "Common Stock" and "Preferred Stock." The total number of shares of all classes of stock which the Corporation has authority to issue is 215,000,000 shares, consisting of 200,000,000 shares of Common Stock, each having a par value of \$.001, and 15,000,000 shares of Preferred Stock, each having a par value of \$.001. The Preferred Stock may be issued in one or more series. The Board of Directors is authorized to fix the number of shares of any such series of Preferred Stock and to determine the designation of any such series (a "Preferred Stock Designation"), subject to (a) such stockholder approvals as may be provided for herein and (b) the number of shares of Preferred Stock authorized at that time by this Article V. Subject to such stockholder approvals as may be provided for herein, the Board of Directors is further authorized to determine or alter the rights, preferences, privileges and restrictions granted to or imposed upon any wholly unissued series of Preferred Stock, and to increase or decrease (but not below the number of shares of such series then outstanding) the number of shares of any series of Preferred Stock. In case the number of shares of any series shall be so decreased, the shares constituting such decrease shall resume the status that they had prior to the adoption of the resolution or amendment originally fixing the number of shares of such series.

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

IN WITNESS WHEREOF, Isis Pharmaceuticals, Inc. has caused this Certificate of Amendment to be signed by its duly authorized officers this day of _____, 2006.

By: _____
B. Lynne Parshall
Executive Vice President

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**AMENDMENT NO. 1 TO
ISIS PHARMACEUTICALS, INC.
2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN
ADOPTED BY THE BOARD OF DIRECTORS FEBRUARY 28, 2006**

SUBJECT TO APPROVAL BY STOCKHOLDERS

This Amendment No. 1 to the Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan (the "Amendment"), is effective as of _____, 2006.

A. WHEREAS, the Board of Directors of Isis approved an amendment to the Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan (the "NED"), as more fully described below.

NOW THEREFORE, the NED is hereby amended as follows:

All capitalized terms not otherwise defined herein, will have the meanings ascribed to them in the NED.

ARTICLE 1. AMENDMENT

1.1 Amendment and Restatement of Section 4(a). Section 4(a) of the NED is hereby amended, restated and replaced in its entirety by the following language:

"(a) **Share Reserve**. Subject to the provisions of Section 11(a) relating to Capitalization Adjustments, the Common Stock that may be issued pursuant to Options shall not exceed in the aggregate 850,000 shares of Common Stock."

1.2 Amendment and Restatement of Section 6(b). Section 6(b) of the NED is hereby amended, restated and replaced in its entirety by the following language:

"(b) **Annual Grants**. Without any further action of the Board, after the effective date of this Amendment, a Non-Employee Director shall be granted an Annual Grant as follows: On July 1 of each year, beginning on July 1, 2006, each person who is then a Non-Employee Director automatically shall be granted an Annual Grant to purchase 12,500 shares of Common Stock on the terms and conditions set forth herein. Should the date of grant set forth above be a legal holiday, then such grant shall be made on the next business day."

1.3 Except as specifically provided in this Amendment, all other terms and conditions of the NED will remain in full force and effect.

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ISIS PHARMACEUTICALS, INC.

2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN

ADOPTED BY THE BOARD OF DIRECTORS SEPTEMBER 11, 2001

APPROVED BY STOCKHOLDERS MAY 31, 2002

EFFECTIVE DATE: MAY 31, 2002

1. PURPOSES.

(a) **Amendment and Restatement**. This Plan is an amendment and restatement of the Isis Pharmaceuticals, Inc. 1992 Non-Employee Directors' Stock Option Plan.

(b) **Eligible Option Recipients**. The persons eligible to receive Options are the Non-Employee Directors of the Company.

(c) **Available Options**. The purpose of the Plan is to provide a means by which Non-Employee Directors may be given an opportunity to benefit from increases in value of the Common Stock through the granting of Nonstatutory Stock Options.

(d) **General Purpose**. The Company, by means of the Plan, seeks to retain the services of its Non-Employee Directors, to secure and retain the services of new Non-Employee Directors and to provide incentives for such persons to exert maximum efforts for the success of the Company and its Affiliates.

2. DEFINITIONS.

(a) **"Affiliate"** means any parent corporation or subsidiary corporation of the Company, whether now or hereafter existing, as those terms are defined in Sections 424(e) and (f), respectively, of the Code.

(b) **“Annual Grant”** means an Option granted annually to all Non-Employee Directors who meet the criteria specified in subsection 6(b) of the Plan.

(c) **“Board”** means the Board of Directors of the Company.

(d) **“Capitalization Adjustment”** has the meaning ascribed to that term in Section 11(a).

(e) **“Change in Control”** means the occurrence, in a single transaction or in a series of related transactions, of any one or more of the following events:

(i) any Exchange Act Person becomes the Owner, directly or indirectly, of securities of the Company representing more than 50% of the combined voting power of the Company’s then outstanding securities other than by virtue of a merger, consolidation or similar transaction and other than by a purchase of securities directly from the Company;

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Notwithstanding the foregoing, a Change in Control shall not be deemed to occur solely because the level of Ownership held by any Exchange Act Person (the “Subject Person”) exceeds the percentage threshold specified above of the outstanding voting securities as a result of a repurchase or other acquisition of voting securities by the Company reducing the number of shares outstanding, provided that if a Change in Control would occur (but for the operation of this sentence) as a result of the acquisition of voting securities by the Company, and after such share acquisition, the Subject Person becomes the Owner of any additional voting securities (other than through a purchase directly from the Company) that, assuming the repurchase or other acquisition had not occurred, increases the percentage of the then outstanding voting securities Owned by the Subject Person over the percentage threshold specified above, then a Change in Control shall be deemed to occur.

(ii) there is consummated a merger, consolidation or similar transaction involving (directly or indirectly) the Company and, immediately after the consummation of such merger, consolidation or similar transaction, the stockholders of the Company immediately prior thereto do not Own, directly or indirectly, outstanding voting securities representing more than 50% of the combined outstanding voting power of the surviving Entity in such merger, consolidation or similar transaction or more than 50% of the combined outstanding voting power of the parent of the surviving Entity in such merger, consolidation or similar transaction;

(iii) the stockholders of the Company approve or the Board approves a plan of complete dissolution or liquidation of the Company, or a complete dissolution or liquidation of the Company shall otherwise occur;

(iv) there is consummated a sale, lease, license or other disposition of all or substantially all of the consolidated assets of the Company and its Subsidiaries, other than a sale, lease, license or other disposition of all or substantially all of the consolidated assets of the Company and its Subsidiaries to an Entity, more than 50% of the combined voting power of the voting securities of which are Owned by stockholders of the Company in substantially the same proportions as their Ownership of the Company immediately prior to such sale, lease, license or other disposition; or

(v) individuals who, on the date this Plan is adopted by the Board, are members of the Board (the “Incumbent Board”) cease for any reason to constitute at least a majority of the members of the Board; (*provided, however*, that if the appointment or election (or nomination for election) of any new Board member was approved or recommended by a majority vote of the members of the Incumbent Board then still in office, such new member shall, for purposes of this Plan, be considered as a member of the Incumbent Board).

Notwithstanding the foregoing or any other provision of this Plan, the definition of Change in Control (or any analogous term) in an individual written agreement between the Company or any Affiliate and the Optionholder shall supersede the foregoing definition with respect to Options subject to such agreement (it being understood, however, that if no definition of Change in Control or any analogous term is set forth in such an individual written agreement, the foregoing definition shall apply).

(f) **“Code”** means the Internal Revenue Code of 1986, as amended.

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(g) **“Common Stock”** means the common stock of the Company.

(h) **“Company”** means Isis Pharmaceuticals, Inc., a Delaware corporation.

(i) **“Consultant”** means any person, including an advisor, (i) engaged by the Company or an Affiliate to render consulting or advisory services and who is compensated for such services or (ii) serving as a member of the Board of Directors of an Affiliate and who is compensated for such services. However, the term “Consultant” shall not include Directors who are not compensated by the Company for their services as Directors, and the payment of a director’s fee by the Company for services as a Director shall not cause a Director to be considered a “Consultant” for purposes of the Plan.

(j) **“Continuous Service”** means that the Optionholder’s service with the Company or an Affiliate, whether as an Employee, Director or Consultant, is not interrupted or terminated. A change in the capacity in which the Optionholder renders service to the Company or an Affiliate as an Employee, Consultant or Director or a change in the entity for which the Optionholder renders such service, provided that there is no interruption or termination of the Optionholder’s service with the Company or an Affiliate, shall not terminate an Optionholder’s Continuous Service. For example, a change in status from a Non-Employee Director of the Company to a Consultant of an Affiliate or an Employee of the Company shall not constitute an interruption of Continuous Service. The Board or the chief executive officer of the Company, in that party’s sole discretion, may determine whether Continuous Service shall be considered interrupted in the case of any leave of absence approved by that party, including sick leave, military leave or any other personal leave.

(k) **“Corporate Transaction”** means the occurrence, in a single transaction or in a series of related transactions, of any one or more of the following events:

- (i) a sale or other disposition of all or substantially all, as determined by the Board in its discretion, of the consolidated assets of the Company and its Subsidiaries;
- (ii) a sale or other disposition of at least 90% of the outstanding securities of the Company;
- (iii) a merger, consolidation or similar transaction following which the Company is not the surviving corporation; or
- (iv) a merger, consolidation or similar transaction following which the Company is the surviving corporation but the shares of Common Stock outstanding immediately preceding the merger, consolidation or similar transaction are converted or exchanged by virtue of the merger, consolidation or similar transaction into other property, whether in the form of securities, cash or otherwise.
- (l) **“Director”** means a member of the Board of Directors of the Company.
- (m) **“Disability”** means the permanent and total disability of a person within the meaning of Section 22(e)(3) of the Code.

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- (n) **“Employee”** means any person employed by the Company or an Affiliate. Service as a Director or payment of a director’s fee by the Company or an Affiliate shall not be sufficient to constitute “employment” by the Company or an Affiliate.
- (o) **“Entity”** means a corporation, partnership or other entity.
- (p) **“Exchange Act”** means the Securities Exchange Act of 1934, as amended.
- (q) **“Exchange Act Person”** means any natural person, Entity or “group” (within the meaning of Section 13(d) or 14(d) of the Exchange Act), except that “Exchange Act Person” shall not include (A) the Company or any Subsidiary of the Company, (B) any employee benefit plan of the Company or any Subsidiary of the Company or any trustee or other fiduciary holding securities under an employee benefit plan of the Company or any Subsidiary of the Company, (C) an underwriter temporarily holding securities pursuant to an offering of such securities, or (D) an Entity Owned, directly or indirectly, by the stockholders of the Company in substantially the same proportions as their Ownership of stock of the Company.
- (r) **“Fair Market Value”** means, as of any date, the value of the Common Stock determined as follows:
- (i) If the Common Stock is listed on any established stock exchange or traded on the Nasdaq National Market or the Nasdaq SmallCap Market, the Fair Market Value of a share of Common Stock shall be the closing sales price for such stock (or the closing bid, if no sales were reported) as quoted on such exchange or market (or the exchange or market with the greatest volume of trading in the Common Stock) on the last market trading day prior to the day of determination, as reported in The Wall Street Journal or such other source as the Board deems reliable.
- (ii) In the absence of such markets for the Common Stock, the Fair Market Value shall be determined in good faith by the Board.
- (s) **“Initial Grant”** means an Option granted to a Non-Employee Director who meets the criteria specified in subsection 6(a) of the Plan.
- (t) **“Non-Employee Director”** means a Director who is not an Employee.
- (u) **“Nonstatutory Stock Option”** means an Option not intended to qualify as an incentive stock option within the meaning of Section 422 of the Code and the regulations promulgated thereunder.
- (v) **“Officer”** means a person who is an officer of the Company within the meaning of Section 16 of the Exchange Act and the rules and regulations promulgated thereunder.
- (w) **“Option”** means a Nonstatutory Stock Option granted pursuant to the Plan.
- (x) **“Option Agreement”** means a written agreement between the Company and an Optionholder evidencing the terms and conditions of an individual Option grant. Each Option Agreement shall be subject to the terms and conditions of the Plan.

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- (y) **“Optionholder”** means a person to whom an Option is granted pursuant to the Plan or, if applicable, such other person who holds an outstanding Option.
- (z) **“Own,” “Owned,” “Owner,” “Ownership”** A person or Entity shall be deemed to “Own,” to have “Owned,” to be the “Owner” of, or to have acquired “Ownership” of securities if such person or Entity, directly or indirectly, through any contract, arrangement, understanding, relationship or otherwise, has or shares voting power, which includes the power to vote or to direct the voting, with respect to such securities.
- (aa) **“Plan”** means this Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors’ Stock Option Plan, which is an amendment and restatement of the Isis Pharmaceuticals, Inc. 1992 Non-Employee Directors’ Stock Option Plan.
- (bb) **“Rule 16b-3”** means Rule 16b-3 promulgated under the Exchange Act or any successor to Rule 16b-3, as in effect from time to time.
- (cc) **“Securities Act”** means the Securities Act of 1933, as amended.
- (dd) **“Subsidiary”** means, with respect to the Company, (i) any corporation of which more than 50% of the outstanding capital stock having ordinary voting power to elect a majority of the board of directors of such corporation (irrespective of whether, at the time, stock of any other class or classes

of such corporation shall have or might have voting power by reason of the happening of any contingency) is at the time, directly or indirectly Owned by the Company, and (ii) any partnership in which the Company has a direct or indirect interest (whether in the form of voting or participation in profits or capital contribution) of more than 50%.

3. ADMINISTRATION.

- (a) **Administration by Board.** The Board shall administer the Plan. The Board may not delegate administration of the Plan to a committee.
- (b) **Powers of Board.** The Board shall have the power, subject to, and within the limitations of, the express provisions of the Plan:
 - (i) To determine the provisions of each Option to the extent not specified in the Plan.
 - (ii) To construe and interpret the Plan and Options granted under it, and to establish, amend and revoke rules and regulations for its administration. The Board, in the exercise of this power, may correct any defect, omission or inconsistency in the Plan or in any Option Agreement, in a manner and to the extent it shall deem necessary or expedient to make the Plan fully effective.
 - (iii) To amend the Plan or an Option as provided in Section 12.
 - (iv) To terminate or suspend the Plan as provided in Section 13.

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(v) Generally, to exercise such powers and to perform such acts as the Board deems necessary or expedient to promote the best interests of the Company and that are not in conflict with the provisions of the Plan.

(c) **Effect of Board's Decision.** All determinations, interpretations and constructions made by the Board in good faith shall not be subject to review by any person and shall be final, binding and conclusive on all persons.

(d) **Arbitration.** Any dispute or claim concerning any Option granted (or not granted) pursuant to the Plan or any disputes or claims relating to or arising out of the Plan shall be fully, finally and exclusively resolved by binding arbitration conducted pursuant to the Commercial Arbitration Rules of the American Arbitration Association in San Diego, California. The Company shall pay all arbitration fees. In addition to any other relief, the arbitrator may award to the prevailing party recovery of its attorney's fees and costs. By accepting an Option, Optionholders and the Company waive their respective rights to have any such disputes or claims tried by a judge or jury.

4. SHARES SUBJECT TO THE PLAN.

(a) **Share Reserve.** Subject to the provisions of Section 11(a) relating to Capitalization Adjustments, the Common Stock that may be issued pursuant to Options shall not exceed in the aggregate 600,000 shares of Common Stock.

(b) **Reversion of Shares to the Share Reserve.** If any Option shall for any reason expire or otherwise terminate, in whole or in part, without having been exercised in full, the shares of Common Stock not acquired under such Option shall revert to and again become available for issuance under the Plan.

(c) **Source of Shares.** The shares of Common Stock subject to the Plan may be unissued shares or reacquired shares, bought on the market or otherwise.

5. ELIGIBILITY.

The Options as set forth in Section 6 of the Plan automatically shall be granted under the Plan to all Non-Employee Directors.

6. NON-DISCRETIONARY GRANTS.

(a) **Initial Grants.** Without any further action of the Board, each person who is elected or appointed for the first time after the effective date of this amendment and restatement of the Plan to be a Non-Employee Director automatically shall, upon the date of his or her initial election or appointment to be a Non-Employee Director by the Board or stockholders of the Company, as applicable, be granted an Initial Grant to purchase 20,000 shares of Common Stock on the terms and conditions set forth herein.

(b) **Annual Grants.** Without any further action of the Board, after the effective date of this amendment and restatement of the Plan, a Non-Employee Director shall be granted an Annual Grant as follows: On July 1 of each year, beginning on July 1, 2002, each person who is

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then a Non-Employee Director automatically shall be granted an Annual Grant to purchase 10,000 shares of Common Stock on the terms and conditions set forth herein. Should the date of grant set forth above be a legal holiday, then such grant shall be made on the next business day.

7. OPTION PROVISIONS.

Each Option shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. Each Option shall include (through incorporation of provisions hereof by reference in the Option or otherwise) the substance of each of the following provisions:

- (a) **Term.** No Option shall be exercisable after the expiration of 10 years from the date it was granted.

(b) **Exercise Price.** The exercise price of each Option shall be 100% of the Fair Market Value of the Common Stock subject to the Option on the date the Option is granted. Notwithstanding the foregoing, an Option may be granted with an exercise price lower than that set forth in the preceding sentence if such Option is granted pursuant to an assumption or substitution for another option in a manner satisfying the provisions of Section 424(a) of the Code.

(c) **Consideration.** The purchase price of Common Stock acquired pursuant to an Option shall be paid in cash at the time the Option is exercised.

(d) **Transferability.** An Option will not be transferable except as determined by the Board.

(e) **Exercise Schedule.** The Option shall be exercisable as the shares of Common Stock subject to the Option vest.

(f) **Vesting Schedule.** The Option shall vest and become exercisable as follows:

(i) **Initial Grants:** one-fourth of the shares subject to the Option shall vest on each annual anniversary of the date of grant provided that the Optionholder has, during the entire year prior to such vesting date, continuously served as a Non-Employee Director or as an Employee of or Consultant to the Company or any Affiliate, whereupon such option shall become fully exercisable in accordance with its terms with respect to that portion of the shares represented by that installment.

(ii) **Annual Grants:** one-fourth of the shares subject to the Option shall vest on each annual anniversary of the date of grant provided that the Optionholder has, during the entire year prior to such vesting date, continuously served as a Non-Employee Director or as an Employee of or Consultant to the Company or any Affiliate, whereupon such option shall become fully exercisable in accordance with its terms with respect to that portion of the shares represented by that installment.

(g) **Termination of Continuous Service.** In the event that an Optionholder's Continuous Service terminates (other than upon the Optionholder's death or Disability), the

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Optionholder may exercise his or her Option (to the extent that the Optionholder was entitled to exercise such Option as of the date of termination) but only within such period of time ending on the earlier of (i) the date 3 months following the termination of the Optionholder's Continuous Service (or such longer or shorter period specified in the Option Agreement), or (ii) the expiration of the term of the Option as set forth in the Option Agreement. If, after termination, the Optionholder does not exercise his or her Option within the time specified in the Option Agreement, the Option shall terminate.

(h) **Extension of Termination Date.** An Optionholder's Option Agreement may also provide that if the exercise of the Option following the termination of the Optionholder's Continuous Service (other than upon the Optionholder's death or Disability) would be prohibited at any time solely because the issuance of shares of Common Stock would violate the registration requirements under the Securities Act, then the Option shall terminate on the earlier of (i) the expiration of the term of the Option set forth in subsection 7(a) or (ii) the expiration of a period of 3 months after the termination of the Optionholder's Continuous Service during which the exercise of the Option would not be in violation of such registration requirements.

(i) **Disability of Optionholder.** In the event that an Optionholder's Continuous Service terminates as a result of the Optionholder's Disability, the Optionholder may exercise his or her Option (to the extent that the Optionholder was entitled to exercise such Option as of the date of termination), but only within such period of time ending on the earlier of (i) the date 12 months following such termination (or such longer or shorter period specified in the Option Agreement) or (ii) the expiration of the term of the Option as set forth in the Option Agreement. If, after termination, the Optionholder does not exercise his or her Option within the time specified herein, the Option shall terminate.

(j) **Death of Optionholder.** In the event that (i) an Optionholder's Continuous Service terminates as a result of the Optionholder's death or (ii) the Optionholder dies within the period (if any) specified in the Option Agreement after the termination of the Optionholder's Continuous Service for a reason other than death, then the Option may be exercised (to the extent the Optionholder was entitled to exercise such Option as of the date of death) by the Optionholder's estate, by a person who acquired the right to exercise the Option by bequest or inheritance or by a person designated to exercise the Option upon the Optionholder's death pursuant to subsection 7(d), but only within the period ending on the earlier of (1) the date 18 months following the date of death (or such longer or shorter period specified in the Option Agreement) or (2) the expiration of the term of such Option as set forth in the Option Agreement. If, after death, the Option is not exercised within the time specified herein, the Option shall terminate.

8. COVENANTS OF THE COMPANY.

(a) **Availability of Shares.** During the terms of the Options, the Company shall keep available at all times the number of shares of Common Stock required to satisfy such Options.

(b) **Securities Law Compliance.** The Company shall seek to obtain from each regulatory commission or agency having jurisdiction over the Plan such authority as may be required to grant Options and to issue and sell shares of Common Stock upon exercise of the

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Options; provided, however, that this undertaking shall not require the Company to register under the Securities Act the Plan, any Option or any Common Stock issued or issuable pursuant to any such Option. If, after reasonable efforts, the Company is unable to obtain from any such regulatory commission or agency the authority which counsel for the Company deems necessary for the lawful issuance and sale of Common Stock under the Plan, the Company shall be relieved from any liability for failure to issue and sell Common Stock upon exercise of such Options unless and until such authority is obtained.

9. USE OF PROCEEDS FROM STOCK.

Proceeds from the sale of Common Stock pursuant to Options shall constitute general funds of the Company.

10. MISCELLANEOUS.

(a) **Acceleration of Exercisability and Vesting.** The Board shall have the power to accelerate the time at which an Option may first be exercised or the time during which an Option or any part thereof will vest in accordance with the Plan, notwithstanding the provisions in the Option stating the time at which it may first be exercised or the time during which it will vest.

(b) **Stockholder Rights.** No Optionholder shall be deemed to be the holder of, or to have any of the rights of a holder with respect to, any shares of Common Stock subject to such Option unless and until such Optionholder has satisfied all requirements for exercise of the Option pursuant to its terms.

(c) **No Service Rights.** Nothing in the Plan or any instrument executed or Option granted pursuant thereto shall confer upon any Optionholder any right to continue to serve the Company as a Non-Employee Director or shall affect the right of the Company or an Affiliate to terminate (i) the employment of an Employee with or without notice and with or without cause, (ii) the service of a Consultant pursuant to the terms of such Consultant's agreement with the Company or an Affiliate or (iii) the service of a Director pursuant to the Bylaws of the Company or an Affiliate, and any applicable provisions of the corporate law of the state in which the Company or the Affiliate is incorporated, as the case may be.

(d) **Investment Assurances.** The Company may require an Optionholder, as a condition of exercising or acquiring Common Stock under any Option, (i) to give written assurances satisfactory to the Company as to the Optionholder's knowledge and experience in financial and business matters and/or to employ a purchaser representative reasonably satisfactory to the Company who is knowledgeable and experienced in financial and business matters and that he or she is capable of evaluating, alone or together with the purchaser representative, the merits and risks of exercising the Option; and (ii) to give written assurances satisfactory to the Company stating that the Optionholder is acquiring the Common Stock subject to the Option for the Optionholder's own account and not with any present intention of selling or otherwise distributing the Common Stock. The foregoing requirements, and any assurances given pursuant to such requirements, shall be inoperative if (1) the issuance of the shares of Common Stock upon the exercise or acquisition of Common Stock under the Option has been registered under a then currently effective registration statement under the Securities Act or (2)

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as to any particular requirement, a determination is made by counsel for the Company that such requirement need not be met in the circumstances under the then applicable securities laws. The Company may, upon advice of counsel to the Company, place legends on stock certificates issued under the Plan as such counsel deems necessary or appropriate in order to comply with applicable securities laws, including, but not limited to, legends restricting the transfer of the Common Stock.

(e) **Withholding Obligations.** To the extent provided by the terms of an Option Agreement, the Optionholder may satisfy any federal, state or local tax withholding obligation relating to the exercise or acquisition of Common Stock under an Option by any of the following means (in addition to the Company's right to withhold from any compensation paid to the Optionholder by the Company) or by a combination of such means: (i) tendering a cash payment; (ii) authorizing the Company to withhold shares of Common Stock from the shares of Common Stock otherwise issuable to the Optionholder as a result of the exercise or acquisition of Common Stock under the Option, provided, however, that no shares of Common Stock are withheld with a value exceeding the minimum amount of tax required to be withheld by law (or such lower amount as may be necessary to avoid variable award accounting); or (iii) delivering to the Company owned and unencumbered shares of Common Stock.

11. ADJUSTMENTS UPON CHANGES IN STOCK.

(a) **Capitalization Adjustments.** If any change is made in, or other event occurs with respect to, the Common Stock subject to the Plan, or subject to any Option, without the receipt of consideration by the Company (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 the Company) (each, a "Capitalization Adjustment"), the Plan will be appropriately adjusted in the class(es) and maximum number of securities subject both to the Plan pursuant to subsection 4(a) and to the nondiscretionary Options specified in Section 6, and the outstanding Options will be appropriately adjusted in the class(es) and number of securities and price per share of Common Stock subject to such outstanding Options. The Board shall make such adjustments, and its determination shall be final, binding and conclusive. (The conversion of any convertible securities of the Company shall not be treated as a transaction "without receipt of consideration" by the Company.)

(b) **Dissolution or Liquidation.** In the event of a dissolution or liquidation of the Company, then all outstanding Options shall terminate immediately prior to the completion of such dissolution or liquidation.

(c) **Corporate Transaction.** In the event of a Corporate Transaction, any surviving corporation or acquiring corporation may assume any or all Options outstanding under the Plan or may substitute similar options for Options outstanding under the Plan (it being understood that similar options include, but are not limited to, options to acquire the same consideration paid to the stockholders or the Company, as the case may be, pursuant to the Corporate Transaction). In the event that any surviving corporation or acquiring corporation does not assume any or all such outstanding Options or substitute similar options for such outstanding Options, then with respect

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to Options that have been neither assumed nor substituted and that are held by Optionholders whose Continuous Service has not terminated prior to the effective time of the Corporate Transaction, the vesting of such Options (and, if applicable, the time at which such Options may be exercised) shall (contingent upon the effectiveness of the Corporate Transaction) be accelerated in full to a date prior to the effective time of such Corporate Transaction as the Board shall determine (or, if the Board shall not determine such a date, to the date that is 5 days prior to the effective time of the Corporate Transaction), and the Options shall terminate if not exercised at or prior to such effective time. With respect to Options outstanding under the Plan that have been neither assumed nor substituted and that are held by Optionholders whose Continuous Service has terminated prior to the effective time of the Corporate Transaction, the vesting of such Options (and, if applicable, the time at which such Option may be exercised) shall not be accelerated unless otherwise provided in a written agreement between the Company or any Affiliate and the holder of such Option, and such Options shall terminate if not exercised prior to the effective time of the Corporate Transaction.

(d) Change in Control. Notwithstanding any other provisions of the Plan to the contrary, if a Change in Control occurs and the Optionholder's Continuous Service has not terminated prior to the effective date of such Change in Control, then the vesting and exercisability of the shares of Common Stock subject to the Optionholder's Options shall be accelerated in full as of the effective date of the Change in Control. Following such Change in Control (other than a Change in Control resulting from a plan of complete dissolution or liquidation of the Company) and notwithstanding any other provision of the Plan to the contrary and provided that the Optionholder's Continuous Service has not terminated prior to the effective date of the Change in Control, then the Optionholder's Options shall expire on the earliest of (i) 12 months following the effective date of such Change in Control or (ii) the Expiration Date indicated in the Optionholder's Grant Notice.

(e) Parachute Payments. If any payment or benefit the Optionholder would receive pursuant to a Change in Control from the Company or otherwise ("Payment") would (i) constitute a "parachute payment" within the meaning of Section 280G of the Code, and (ii) but for this sentence, be subject to the excise tax imposed by Section 4999 of the Code (the "Excise Tax"), then such Payment shall be reduced to the Reduced Amount. The "Reduced Amount" shall be either (x) the largest portion of the Payment that would result in no portion of the Payment being subject to the Excise Tax or (y) the largest portion, up to and including the total, of the Payment, whichever amount, after taking into account all applicable federal, state and local employment taxes, income taxes, and the Excise Tax (all computed at the highest applicable marginal rate), results in the Optionholder's receipt, on an after-tax basis, of the greater amount of the Payment notwithstanding that all or some portion of the Payment may be subject to the Excise Tax. If a reduction in payments or benefits constituting "parachute payments" is necessary so that the Payment equals the Reduced Amount, reduction shall occur in the following order unless the Optionholder elects in writing a different order (*provided, however*, that such election shall be subject to Company approval if made on or after the effective date of the event that triggers the Payment): reduction of cash payments; cancellation of accelerated vesting of Options or other equity-based awards; reduction of employee benefits. In the event that acceleration of vesting of Options or other equity-based compensation is to be reduced, such acceleration of vesting shall be cancelled in the reverse order of the date of grant

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of the Optionholder's Options or other equity-based awards unless the Optionholder elects in writing a different order for cancellation.

The accounting firm engaged by the Company for general audit purposes as of the day prior to the effective date of the Change in Control shall perform the foregoing calculations. If the accounting firm so engaged by the Company is serving as accountant or auditor for the individual, entity or group effecting the Change in Control, the Company shall appoint a nationally recognized accounting firm to make the determinations required hereunder. The Company shall bear all expenses with respect to the determinations by such accounting firm required to be made hereunder.

The accounting firm engaged to make the determinations hereunder shall provide its calculations, together with detailed supporting documentation, to the Optionholder and the Company within 15 calendar days after the date on which the Optionholder's right to a Payment is triggered (if requested at that time by the Optionholder or the Company) or such other time as requested by the Optionholder or the Company. If the accounting firm determines that no Excise Tax is payable with respect to a Payment, either before or after the application of the Reduced Amount, it shall furnish the Company and the Optionholder with an opinion reasonably acceptable to the Optionholder that no Excise Tax will be imposed with respect to such Payment. Any good faith determinations of the accounting firm made hereunder shall be final, binding and conclusive upon the Optionholder and the Company.

12. AMENDMENT OF THE PLAN AND OPTIONS.

(a) Amendment of Plan. The Board at any time, and from time to time, may amend the Plan. However, except as provided in Section 11(a) relating to Capitalization Adjustments, no amendment shall be effective unless approved by the stockholders of the Company to the extent stockholder approval is necessary to satisfy the requirements of Rule 16b-3 or any Nasdaq or securities exchange listing requirements.

(b) Stockholder Approval. The Board, in its sole discretion, may submit any other amendment to the Plan for stockholder approval.

(c) No Impairment of Rights. Rights under any Option granted before amendment of the Plan shall not be impaired by any amendment of the Plan unless (i) the Company requests the consent of the Optionholder and (ii) the Optionholder consents in writing.

(d) Amendment of Options. The Board at any time, and from time to time, may amend the terms of any one or more Options; provided, however, that the rights under any Option shall not be impaired by any such amendment unless (i) the Company requests the consent of the Optionholder and (ii) the Optionholder consents in writing.

13. TERMINATION OR SUSPENSION OF THE PLAN.

(a) Plan Term. The Board may suspend or terminate the Plan at any time. Unless sooner terminated, the Plan shall terminate on the day before the tenth anniversary of the date the Plan is approved by the stockholders of the Company. No Options may be granted under the Plan while the Plan is suspended or after it is terminated.

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(b) No Impairment of Rights. Suspension or termination of the Plan shall not impair rights and obligations under any Option granted while the Plan is in effect except with the written consent of the Optionholder.

14. EFFECTIVE DATE OF PLAN.

The Plan shall become effective as determined by the Board, but no Option shall be exercised unless and until the Plan has been approved by the stockholders of the Company, which approval shall be within 12 months before or after the date the Plan is adopted by the Board.

15. CHOICE OF LAW.

ANNUAL MEETING OF STOCKHOLDERS OF
ISIS PHARMACEUTICALS, INC.

May 3, 2006

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

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

THE BOARD OF DIRECTORS RECOMMENDS A VOTE "FOR" THE ELECTION OF DIRECTORS AND "FOR" PROPOSALS 2, 3 and 4.
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 2009 Annual Meeting of Stockholders and elect Joseph Klein, III to hold office until the 2007 Annual Meeting of Stockholders. | 2. To approve an amendment to the Isis Restated Certificate of Incorporation to increase the authorized number of shares of Common Stock from 100,000,000 to 200,000,000 shares. | FOR | AGAINST | ABSTAIN |
| | | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

NOMINEES:

- | | | | |
|-----------------------|---|-----------------------|---------------------------|
| <input type="radio"/> | FOR ALL NOMINEES | <input type="radio"/> | Richard D. DiMarchi |
| <input type="radio"/> | WITHHOLD AUTHORITY FOR ALL NOMINEES | <input type="radio"/> | Christopher F.O. Gabrieli |
| <input type="radio"/> | FOR ALL EXCEPT (See instructions below) | <input type="radio"/> | Joseph Klein, III |
| | | <input type="radio"/> | Frederick T. Muto |

- | | | | |
|--|-----------------------|-----------------------|-----------------------|
| 3. To approve an amendment to the 2002 Non-Employee Directors' Stock Option Plan to (i) increase the total number of shares reserved for issuance under the Directors' Plan from 600,000 shares to 850,000 shares, and (ii) increase the annual non-discretionary stock option grant for Isis' nonemployee directors from 10,000 share to 12,500 shares. | FOR | AGAINST | ABSTAIN |
| | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 4. To ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2006 fiscal year. | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

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

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:

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 3, 2006

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 Wednesday, May 3, 2006 at 9:00 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, 2, 3 AND 4 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 3, 2006

PROXY VOTING INSTRUCTIONS

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

COMPANY NUMBER

-OR-

TELEPHONE - Call toll-free **1-800-PROXIES** (1-800-776-9437) from any touch-tone telephone and follow the instructions.

Have your proxy card available when you call.

ACCOUNT NUMBER

-OR-

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

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.

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

THE BOARD OF DIRECTORS RECOMMENDS A VOTE "FOR" THE ELECTION OF DIRECTORS AND "FOR" PROPOSALS 2, 3 and 4.
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 2009 Annual Meeting of Stockholders and elect Joseph Klein, III to hold office until the 2007 Annual Meeting of Stockholders.	2.	To approve an amendment to the Isis Restated Certificate of Incorporation to increase the authorized number of shares of Common Stock from 100,000,000 to 200,000,000 shares.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>		
NOMINEES:								
<input type="radio"/>	FOR ALL NOMINEES	<input type="radio"/>	Richard D. DiMarchi	3.	To approve an amendment to the 2002 Non-Employee Directors' Stock Option Plan to (i) increase the total number of shares reserved for issuance under the Directors' Plan from 600,000 shares to 850,000 shares, and (ii) increase the annual non-discretionary stock option grant for Isis' nonemployee directors from 10,000 share to 12,500 shares.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<input type="radio"/>	WITHHOLD AUTHORITY FOR ALL NOMINEES	<input type="radio"/>	Christopher F.O. Gabrieli	4.	To ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2006 fiscal year.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
<input type="radio"/>	FOR ALL EXCEPT (See instructions below)	<input type="radio"/>	Joseph Klein, III					
		<input type="radio"/>	Frederick T. Muto					

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:

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.