

SCHEDULE 14A INFORMATION

Proxy Statement Pursuant to Section 14(a) of
the Securities Exchange Act of 1934

Filed by the Registrant

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Check the appropriate box:

- Preliminary Proxy Statement
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 Definitive Proxy Statement
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Isis Pharmaceuticals, Inc.

(Name of Registrant as Specified In Its Charter)

(Name of Person(s) Filing Proxy Statement if other than the Registrant)

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April 20, 2009

ISIS PHARMACEUTICALS, INC.
1896 Rutherford Road
Carlsbad, CA 92008

NOTICE OF
2009 ANNUAL MEETING OF STOCKHOLDERS
AND PROXY STATEMENT

Dear Stockholders,

I am pleased to invite you to Isis Pharmaceuticals' 2009 Annual Meeting of Stockholders. We will host the meeting at our offices in Carlsbad, California on Tuesday, June 2 at 3:00 p.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 2009, 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 be sure to vote your shares as soon as possible to ensure your representation at the meeting. We are distributing our Notice of Annual Meeting and Proxy Materials using the Notice and Access procedures established by the United States Securities and Exchange Commission. As a result, you will receive in the mail a notice regarding the availability of proxy materials. This notice is important because it contains a control number and instructions that will allow you to access our proxy materials and vote electronically by the Internet or request printed proxy materials so you may vote by telephone or mail.

If you are a stockholder of record (that is, if your stock is registered with us in your own name), you may also 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 Broadridge Financial Solutions, Inc. that also 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.

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 of the presentation will be available at www.isispharm.com.⁽¹⁾ In this document, the words "Isis," "we," "our" and "us" refer only to Isis Pharmaceuticals, Inc. and its subsidiaries, including Regulus Therapeutics Inc., and not any other person or entity.

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 2009 ANNUAL MEETING OF STOCKHOLDERS

Date: Tuesday, June 2, 2009
Time: 3:00 p.m., Pacific Time
Place: Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008

Dear Stockholders,

At our 2009 Annual Meeting, we will ask you to:

- elect Richard D. DiMarchi and Frederick T. Muto to serve as a director for a three-year term;
- approve the amendment and restatement of our 2000 Employee Stock Purchase Plan (ESPP) to:
 - extend the ESPP so that it will terminate on June 2, 2019;
 - limit the evergreen provision such that it only adds 150,000 shares to the ESPP each year;
 - limit the offering periods under the ESPP to a maximum of six months; and
 - impose a minimum six-month holding period on shares purchased under the ESPP;
- ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2009 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 April 6, 2009 you may vote at the Annual Meeting.

By order of the Board of Directors,

B. Lynne Parshall

Carlsbad, California
April 20, 2009

ALL STOCKHOLDERS ARE CORDIALLY INVITED TO ATTEND THE MEETING IN PERSON. WHETHER OR NOT YOU EXPECT TO ATTEND THE MEETING, PLEASE VOTE BY PHONE OR INTERNET BY FOLLOWING THE INSTRUCTIONS INCLUDED IN THIS PROXY STATEMENT AND YOUR NOTICE REGARDING THE AVAILABILITY OF PROXY MATERIALS OR PROXY CARD. ALTERNATIVELY, YOU MAY REQUEST A WRITTEN PROXY STATEMENT, AND COMPLETE, DATE, SIGN AND RETURN YOUR PROXY AS PROMPTLY AS POSSIBLE IN ORDER TO ENSURE YOUR REPRESENTATION AT THE MEETING. IF YOU RECEIVE YOUR PROXY MATERIALS BY MAIL, WE WILL INCLUDE A RETURN ENVELOPE (WHICH IS POSTAGE PREPAID IF MAILED IN THE UNITED STATES) FOR THAT PURPOSE. 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 BROKER, BANK OR OTHER NOMINEE A PROXY ISSUED IN YOUR NAME.

**ISIS PHARMACEUTICALS, INC.
1896 Rutherford Road
Carlsbad, CA 92008**

PROXY STATEMENT

INFORMATION ABOUT THE 2009 ANNUAL MEETING AND VOTING

General

The enclosed proxy materials have been provided to you by the Board of Directors of Isis Pharmaceuticals, Inc., a Delaware corporation, for use at the 2009 Annual Meeting of Stockholders to be held on Tuesday, June 2, 2009, at 3:00 p.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 92008. This Proxy Statement summarizes the information you will need to vote in an informed manner.

Important Notice Regarding the Availability of Proxy Materials for the Annual Meeting of Stockholders to be held on June 2, 2009.

We are distributing our Notice of Annual Meeting and proxy materials using the Notice and Access procedures established by the United States Securities and Exchange Commission. As a result, you will receive in the mail a notice regarding the availability of proxy materials. This notice is important because it contains a control number and instructions that will allow you to access our proxy materials and vote electronically by the Internet or request printed proxy materials so you may vote by telephone or mail.

This Proxy Statement and the accompanying Annual Report are available at www.proxyvote.com where you vote your shares.

Among other things, the Proxy Statement contains information regarding:

- the date, time and location of the meeting;
- a list of the matters being submitted to the stockholders; and
- information concerning voting in person.

Electronic Delivery of Isis Pharmaceuticals, Inc. Stockholder Communications

We are pleased to offer to our stockholders the benefits and convenience of electronic delivery of Annual Meeting materials, including:

- delivering the Proxy Statement, Annual Report and related materials by email to our stockholders;
- stockholder voting on-line;
- reducing the amount of bulky documents stockholders receive; and
- reducing our printing and mailing costs associated with more traditional delivery methods.

We encourage you to conserve natural resources and to reduce printing and mailing costs by signing up for electronic delivery of Isis' stockholder communications after you place your current vote at www.proxyvote.com.

Voting Rights, Outstanding Shares and Quorum

We will make this Proxy Statement and the accompanying proxy card available on or about April 20, 2009 to all stockholders who are entitled to vote. Only stockholders who owned our common stock at the close of business on April 6, 2009 are entitled to vote at the Annual Meeting. On this record date, we had 98,045,171 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. We will count your shares towards the quorum only if you submit a valid proxy vote or vote at the meeting. We will count abstentions and broker non-votes towards the quorum requirement.

Each share of our common stock that you own entitles you to one vote. Your notice of availability of proxy materials and proxy card indicates the number of shares of our common stock that you owned at the close of business on April 6, 2009. 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 you do not want to elect a particular Director, you may simply withhold your "For" vote. The inspector of elections will count abstentions towards the vote total for each proposal, and abstentions will have the same effect as "Against" votes. Broker non-votes have no effect and the inspector of elections will not count them towards the vote total for any proposal.

If your broker holds your shares as your nominee, that is, in "street name," you will need to obtain a proxy form from the institution that holds your shares and follow the instructions included on that form regarding how to instruct your broker to vote your shares. If you do not give instructions to your broker, your broker can vote your shares with respect to "discretionary" items, but not with respect to "non-discretionary" items. Discretionary items are proposals considered routine under the rules of the New York Stock Exchange on which a broker may vote shares held in street name in the absence of your voting instructions. Both the proposal to elect Directors and to ratify Ernst & Young LLP as independent auditors are discretionary items. Proposal 2 regarding our ESPP is a non-discretionary item. If you do not give your broker instructions for a non-discretionary item, the inspector of elections will treat your shares as broker non-votes.

You may vote in one of the following ways:

- vote through the Internet by following the instructions included with your notice of availability of proxy materials or proxy card;
- if you have received proxy materials electronically or by mail, you may vote by phone by following the instructions included with your proxy card;
- complete, sign, date and return your proxy card in the postage paid envelope provided; or
- attend the 2009 Annual Meeting and vote in person.

If you receive more than one notice of availability of proxy materials or proxy cards, your shares are registered in more than one name or are registered in different amounts. Please complete, sign and date and return *each* separate proxy card or vote by phone or through the internet by following the instructions included with each notice or proxy card to properly vote your shares.

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 2009.

Solicitation

Our Board of Directors is soliciting your proxy to vote at the Annual Meeting. Isis will bear the entire cost of soliciting proxies, including preparing, assembling, making available on the Internet and printing and mailing this Proxy Statement, the proxy card and any additional information furnished to stockholders. We will furnish copies of solicitation materials to banks, brokerage houses, fiduciaries and custodians holding in their name 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. Our Directors, officers or other employees may supplement original solicitation of proxies by telephone, electronic mail or personal solicitation. We will not pay our Directors and employees any additional compensation for soliciting proxies.

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

If you plan on submitting your vote by phone or through the Internet we must receive it by 11:59 p.m., Eastern Time, on June 1, 2009. 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 www.proxyvote.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.

To vote your shares by phone, you must first request that we send proxy materials to you by following the instructions included in your notice regarding availability of proxy materials. Once you have received your proxy materials, you may vote using a touch-tone telephone by calling 1-800-690-6903 and following the recorded instructions. Please have your proxy card available at the time you vote.

For Shares Registered in the Name of a Broker or Bank

If you hold your Isis stock in street name, you should receive instructions for voting your shares from your bank, broker or other agent, rather than from our proxy card.

A number of brokers and banks are participating in a program provided by Broadridge Financial Solutions, Inc. 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 Broadridge 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.

Stockholder Proposals

If you have a proposal or Director nomination that you would like us to include in our Proxy Statement and form of proxy for, or to present at the 2010 Annual Meeting of Stockholders, you must send the proposal to Isis by no later than December 21, 2009. Stockholders wishing to submit proposals or Director nominations that are not to be included in such Proxy Statement and proxy must do so no earlier than the close of business on February 2, 2010 and no later than the close of business on March 4, 2010. Stockholders should also 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 eight members with two classes consisting of three Directors each and one class consisting of two Directors. Each class serves a three-year term and we hold elections each year at the Annual Meeting to elect the Directors whose terms are expiring.

In addition, 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, 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.

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 guidance and strategic oversight us on our stockholders' behalf.

Information about the 2009 Elections

The Board has nominated two Directors for election at the 2009 Annual Meeting. Each of the nominees currently serves as one of our Directors. Dr. DiMarchi and Mr. Muto have served as a Director since December 2004 and March 2001, respectively, and have been re-elected by our stockholders each successive term. If re-elected, Dr. DiMarchi and Mr. Muto will serve until the 2012 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. As a result, the two nominees receiving the most "For" votes (among votes properly cast in person or by proxy) will be elected. We will vote the shares represented by executed proxies for the election of the two nominees listed below, unless the proxy specifically withholds the authority to vote in favor of the nominees. 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, we may vote your proxy 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 2012 Annual Meeting

Richard D. DiMarchi, Ph.D., age 56, 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. He previously served as Chairman of the Chemistry Department, and is a co-founder of Marcadia Biotech and Ambrx, Inc., privately held biotechnology companies. 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.

Frederick T. Muto, age 55, has served as a Director of Isis since March 2001. Mr. Muto joined the law firm of Cooley Godward Kronish LLP, outside counsel to Isis, in 1980 and became a partner in 1986. He is a founding partner of Cooley Godward Kronish LLP's San Diego office and serves as the partner

in charge of that office. Mr. Muto also serves on that firm's executive, management and compensation committees.

The Nominating, Governance and Review Committee made its report to the Board on February 20, 2009. Following that report, the Board determined it would be in the best interests of Isis and its stockholders to nominate Dr. DiMarchi and Mr. Muto as Directors to be elected at the Annual Meeting.

THE BOARD UNANIMOUSLY RECOMMENDS A VOTE "FOR" THE ELECTION OF EACH OF THE ABOVE NOMINEES

Biographies of Directors Whose Terms Expire at the 2010 Annual Meeting

Stanley T. Crooke, M.D., Ph.D., age 64, is 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 worked for SmithKline Beckman Corporation, a pharmaceutical company, where his titles included President of Research and Development of SmithKline and French Laboratories.

Joseph Klein, III, age 48, 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. From September 2003 to December 2008, Mr. Klein also served as a Venture Partner of Red Abbey Venture Partners, L.P., a life science 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. For over nine years from 1989 to 1998, Mr. Klein was a health care investment analyst at T. Rowe Price Associates, Inc., where he was the founding portfolio manager of the T. Rowe Price Health Sciences Fund, Inc. Mr. Klein serves on the board of directors of four other publicly-traded biotechnology companies: BioMarin Pharmaceutical Inc. since June 2005; OSI Pharmaceuticals, Inc. since July 2006; PDL BioPharma, Inc. since July 2007; and Savient Pharmaceuticals, Inc. since May 2006. Mr. Klein serves on the board of directors of The Prospector Funds, Inc., an SEC Registered Investment Company that manages two no-load mutual funds. Mr. Klein also serves on the boards of private and non-profit entities.

John C. Reed, M.D., Ph.D., age 50, has served as a Director of Isis since February 2002. Dr. Reed has been the President and Chief Executive Officer of Burnham Institute for Medical Research, an independent, nonprofit, public benefit organization dedicated to basic biomedical research, since January 2002. Dr. Reed has been with Burnham Institute for the past sixteen years, serving as the Deputy Director of the Cancer Center beginning in 1994, as Scientific Director of the Institute beginning in 1995, and as Cancer Center Director in 2002. He also currently serves as an adjunct professor in the medical schools at University of California San Diego School of Medicine and San Diego State University's Biology department. Dr. Reed was recognized as the world's most highly cited scientist in the field of cell biology for the decade 1995-2005. He is the author of over 725 scientific and medical journal publications.

Biographies of Directors Whose Terms Expire at the 2011 Annual Meeting

Spencer R. Berthelsen, M.D., age 57, has served as a Director of Isis since May 2002. Since 1980, he has practiced Internal Medicine with the Kelsey Seybold Clinic, a 330 physician medical group based in the Texas Medical Center in Houston. Dr. Berthelsen has served in various senior leadership positions at Kelsey Seybold, including Chairman of the Department of Internal Medicine, Medical Director and Managing Director. He has been Chairman of their Board of Directors since October 2001. He is a Clinical Professor of Medicine at 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 54, has served as a Director of Isis since September 2000. She has been our Chief Operating Officer since December 2007 and previously served as our Executive Vice President since December 1995. She has served as 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 (now Cooley Godward Kronish LLP), outside counsel to Isis, where she was a partner from 1986 to 1991. Ms. Parshall is a member of the American, California and San Diego bar associations. Ms. Parshall serves on the board of directors of CardioDynamics International Corporation, a publicly held medical technology company.

Joseph H. Wender, age 64, has served as a Director of Isis since January 1994. Mr. Wender 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. Mr. Wender worked at GSC Group from 2005 through 2007 where he was a Senior Managing Director, member of the Management Committee, and Chairman of the Finance Committee. Since January 2008, he has been a Senior Consultant to Goldman Sachs & Co. He sits on the Board of Affinity Financial, a privately-held Internet financial institution, and Vintrust, a privately-held wine management company. He is also an Independent Trustee of the Schwab Family of Funds.

Independence of the Board of Directors

As required under the Nasdaq Global 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 Nominating, Governance and Review Committee of the Board of Directors. The Nominating, Governance and Review Committee consults with our legal 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 Chief Operating Officer, respectively. In making this determination, the Board found that none of these Directors or nominees for Director had a material or other disqualifying relationship with Isis. With respect to Mr. Muto who is a partner of Cooley Godward Kronish LLP, our outside legal counsel, and Dr. DiMarchi who had a consulting agreement with Isis that was terminated in 2008, each is independent for purposes other than serving on the Audit Committee, of which neither is 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. If you wish to communicate with the independent Directors about your concerns or issues, you may address correspondence to a particular Director

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 individual exercise of independent judgment with regard to Isis.

Meetings and Attendance; Committee Members

The Board of Directors met eight times in 2008, four regularly scheduled meetings and four special meetings, and acted by unanimous written consent three times. During 2008, all Directors attended at least 75% or more of the aggregate of the meetings of the Board and the committees on which they served, held during the period for which he or she was a director or committee member. We encourage each member of the Board to attend the Annual Meeting of Stockholders. Last year, Dr. Berthelsen, Dr. Croke, Mr. Klein and Ms. Parshall attended our 2008 Annual Meeting of Stockholders.

Board Committee Members

The table below provides membership and meeting information for fiscal 2008 for each of the Board committees and identifies our current Board and Committee members.

Name	Audit	Compensation	Nominating, Governance and Review
Dr. Spencer R. Berthelsen	X	X*	X*
Dr. Stanley T. Croke	—	—	—
Dr. Richard D. DiMarchi	—	X	—
Mr. Joseph Klein	X	—	—
Mr. Frederick T. Muto(1)	—	—	—
Ms. B. Lynne Parshall	—	—	—
Dr. John C. Reed	—	X	X
Mr. Joseph H. Wender	X*	—	—
Total meetings in fiscal year 2008	4(2)	2(3)	3

* Committee Chairperson

(1) Mr. Muto serves as counsel to the Nominating, Governance & Review Committee.

(2) Acted by written consent one time as well.

(3) Acted by written consent fifteen times as well. Our Compensation Committee acts by unanimous written consent each month to confirm stock options granted in connection with new hires and promotions.

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 35 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 2008, the Audit Committee met four times and acted by unanimous written consent twice. We have attached our Audit Committee charter to this Proxy Statement as Appendix A and you can find the charter on our corporate website at www.isispharm.com.⁽²⁾ Each member meets the membership criteria set forth in the attached Audit Committee charter and as stated above.

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

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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, as delegated by the Compensation Committee, may award stock options to employees who are below director level in accordance with guidelines adopted by the Compensation Committee. The Non-Management Stock Option Committee has one member, Dr. Crooke.

The Compensation Committee met two times in 2008 and acted by unanimous written consent fifteen times. You can find our Compensation Committee charter on our corporate website at www.isispharm.com.⁽³⁾

Beginning in 2007, the Compensation Committee reviews with management Isis' Compensation Discussion and Analysis ("CD&A") to consider whether to recommend that we include the CD&A in our proxy statements and other filings.

The charter of the Compensation Committee grants the Compensation Committee full access to all books, records, facilities and personnel of the Company, as well as authority to obtain, at the expense of Isis, advice and assistance from internal and external legal, accounting or other advisors and consultants and other external resources that the Compensation Committee considers necessary or appropriate in the performance of its duties. In particular, the Compensation Committee has the sole authority to retain compensation consultants to assist in its evaluation of executive and Director compensation, including the authority to approve the consultant's reasonable fees and other retention terms.

Compensation Committee Interlocks and Insider Participation

As noted above, during the fiscal year ended December 31, 2008, our Compensation Committee was composed of Drs. Berthelsen, DiMarchi and Reed. None of the members of the Compensation 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.

Nominating, Governance and Review Committee

Role and Responsibilities

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, independence 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 three times during 2008. You can find our Nominating, Governance and Review Committee charter on our corporate 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.

Director Nominations - Quality Standards

The Nominating, Governance and Review Committee believes that candidates for Director should have certain minimum qualifications. As a result, the Board adopted membership standards and believes that the Board members should meet the minimum membership requirements listed below.

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.

In addition to these minimum standards, the Nominating, Governance and Review Committee will consider 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 commitment to rigorously represent the long-term interests of our stockholders.

Director Nominations - Process

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 or not a stockholder recommended the candidate.

The Committee reviews new candidates for Director in the context of the Board's composition, Isis' operating requirements and our stockholders' long-term interests. In conducting this assessment, the Committee considers diversity, maturity, skills, the minimum membership requirements discussed above, 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. The Committee then uses its network of contacts to compile a list of potential candidates, but may also engage, if it deems appropriate, a paid 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 determines whether each candidate is independent, which determination is based upon applicable Nasdaq listing standards, applicable SEC rules and regulations and the advice of counsel, if necessary. Finally, the Committee 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.

Stockholder Recommendations for Directors

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 Secretary of Isis at the following address: 1896 Rutherford Road, Carlsbad, CA 92008, by December 21, 2009. 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.

To date, the Board has not received or rejected a timely Director nominee for election at the upcoming meeting from a stockholder or stockholders holding more than 5% of the Company's voting stock.

Stockholder Communications with the Board of Directors

We make every effort to ensure that our Board or individual Directors as applicable, hear the views of stockholders, and provide appropriate responses 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. The Secretary will compile the communications and will submit them 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 relates to questionable accounting or auditing matters involving Isis will be promptly and directly forwarded to the Audit Committee. Other than the processes described above, our Board has not adopted a formal written process for stockholder communications with the Board. We believe our Board's responsiveness to stockholder communications has been excellent.

Code of Ethics and Business Conduct

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, 2008 by incorporating by reference to the Current Report on Form 8-K we filed with the SEC on December 5, 2008. We also have posted our 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\(4\)](http://www.isispharm.com(4)).

Corporate Governance Guidelines

In 2003, the Board of Directors documented the governance practices followed by the Company by adopting corporate governance guidelines to ensure that the Board will have the necessary authority and practices in place to review and evaluate the Company's business operations as needed and to make decisions that are independent of the Company's management. The guidelines are also intended to align our Directors' and management's interests with those of our stockholders. The corporate governance guidelines set forth the practices the Board intends to follow with respect to board composition and selection, board meetings and involvement of senior management, Chief Executive Officer performance evaluation and succession planning, and Board committees and compensation. The Board adopted the corporate governance guidelines to, among other things, reflect changes to the Nasdaq listing standards and SEC rules adopted to implement provisions of the Sarbanes-Oxley Act of 2002. You may view our corporate governance guidelines, as well as the charters for each committee of the Board, at [www.isispharm.com\(4\)](http://www.isispharm.com(4)).

(4) 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 AMENDMENT AND RESTATEMENT OF THE 2000 EMPLOYEE STOCK PURCHASE PLAN

Stockholders are requested in this Proposal 2 to approve an amendment and restatement of our 2000 Employee Stock Purchase Plan (ESPP) to:

- extend the ESPP so that it will terminate on June 2, 2019;
- limit the evergreen provision such that it only adds 150,000 shares to the ESPP each year;
- limit the offering periods under the ESPP to a maximum of six months; and
- impose a minimum six-month holding period on shares purchased under the ESPP.

Our Board adopted the amendment and restatement of the ESPP to: preserve an important benefit we offer our employees and help align our employees' interests with our stockholders through ownership; but at the same time address concerns our Board and management had regarding potential dilution under the ESPP.

Specifically, we believe:

- The 6-month holding period we propose encourages long-term ownership by our employees in our stock;
- Lowering the evergreen formula from 200,000 shares per year to 150,000 shares per year reduces dilution; and
- The maximum offering period of 6-months reduces dilution.

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 2009 Annual Meeting will be required to approve the extensions to the ESPP.

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

Purpose

The purpose of the ESPP is to retain the services of our employees and to provide incentives to exert maximum efforts for the success of the Company by allowing eligible employees to purchase Isis Common Stock through payroll deductions on favorable terms. Our Board and stockholders originally adopted and approved the ESPP in January 2000.

Administration

The Board administers the ESPP. The Board can construe and interpret the ESPP and, subject to the provisions of the ESPP, determine when and how rights to purchase our Common Stock will be granted pursuant to an Offering, to determine the provisions of each Offering, and to designate which of our affiliates will be eligible to participate in the ESPP. The Board can delegate administration of the ESPP to a committee composed of at least two members of the Board. The Board has delegated administration of the ESPP to the Compensation Committee. The "Board" refers to the Compensation Committee as well as to the Board of Directors itself throughout the remainder of this section.

Eligibility, Participation

Isis' employees who work at least 20 hours a week and have been employed for a continuous period set by the Board, no more than two years, are eligible to participate in an Offering. Currently, we have approximately 260 employees who are eligible to participate in the ESPP. An employee's participation in an Offering will terminate automatically upon termination of employment. Isis' Officers may participate in an Offering, but the Board may

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limit the participation of certain highly compensated employees. An employee's participation in the ESPP (together with other stock purchase plans of Isis or Isis' affiliates but not including stock awards option or stock award plans) may not exceed \$25,000 in any calendar year. In addition, any employee owning 5% or more of our total combined voting power may not participate. Employees desiring to participate in an Offering must provide an appropriate notice to the Company. Employees may terminate participation in any Offering at any time, except as limited by the Board.

Terms of Offering

Each eligible employee can designate a percentage of his or her earnings up to 10%, or such lower percentage designated by the Board, during the Offering Period to be deducted and used to purchase Isis Common Stock in the Offering. We deposit the payroll deductions with the general funds of the Company. The Board may allow certain changes to payroll deduction amounts for an Offering. The Board may also designate a maximum dollar amount for purchases during an Offering.

The Board may also specify a maximum number of shares for an Offering per employee for the Offering and for each purchase date under an Offering.

The purchase price of stock our participating employees purchase under the ESPP will be the lesser of (i) an amount equal to 85% of the fair market value of the stock at the beginning of the Offering; or (ii) an amount equal to 85% of the fair market value of the stock on the purchase date. On each purchase date under an Offering, we will apply each participant's accumulated payroll deductions to purchase our Common Stock. As amended by this Proposal 2, the ESPP allows Offerings to last as long as 6 months. We currently have two Offerings a year under the ESPP that last approximately 6 months each. The first Offering runs from January through June of each year and the second Offering runs from July to December.

Minimum Holding Period

As proposed by this Proposal 2, beginning with the offering ending in January 1, 2010, participants must hold the stock they purchase under the ESPP for a minimum of 6 months from the date of purchase.

Duration, Amendment and Termination

The Board may suspend or terminate the ESPP at any time. No rights may be granted under the ESPP while the ESPP is suspended or after it is terminated. Unless sooner terminated, prior to this proposed amendment, the ESPP will terminate in January 2010. If the stockholders approve this Proposal 2, the ESPP will terminate in January 2020.

Shares Subject to the ESPP; Evergreen Provision

As of March 31, 2009, there were 325,404 shares subject to the ESPP. We expect to issue these shares as part of this year's Offerings under the ESPP.

As amended by this Proposal 2, the ESPP contains an "evergreen" provision that adds 150,000 shares to the ESPP on January 1 of each year, starting with 2010. Before the proposed amendment, the evergreen formula added 200,000 shares to the ESPP on January 1 of each year.

The maximum number of shares that may be purchased by an eligible employee on a purchase date cannot exceed 75,000 shares. The maximum aggregate number of shares available to be purchased by all eligible employees under an Offering will be the lesser of (i) 75,000 shares (plus any shares that were available but unpurchased in the previous Offering) and (ii) the number of shares remaining available under the ESPP at the beginning of the Offering period. If the aggregate purchase of shares of Common Stock upon exercise of rights granted under the Offering would exceed the maximum aggregate number of shares available, the Board will make a pro rata allocation of the shares available in a uniform and equitable manner.

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Adjustments Upon Change in Stock

If any change is made in the stock under the ESPP due to a change in corporate capitalization through reincorporation, stock dividend, stock split, reverse stock split, combination or reclassification of shares, the ESPP and any Offering will be appropriately adjusted in the class(es) and maximum number of securities subject to the ESPP and price of shares under an the Offering. The Board will make the adjustment and their determination will be final, binding and conclusive.

In the event of: (1) a dissolution, liquidation or sale of all or substantially all of the assets of Isis, (2) a merger or consolidation in which Isis is not the surviving corporation, or (3) a reverse merger in which Isis is 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 or (4) any other capital reorganization in which more than fifty percent (50%) of the securities of Isis entitled to vote are sold or otherwise exchanged, then any surviving corporation may assume outstanding rights or substitute similar rights for those under the ESPP. If the surviving corporation does not assume the outstanding rights or substitutes similar rights, participants' accumulated payroll deductions will be used to purchase Common Stock immediately prior to the transaction described above and the participants' rights under the ongoing Offering will be terminated immediately following that purchase.

Tax Information

Participation in the ESPP is intended to qualify for the favorable federal tax treatment accorded employee stock purchase plans under Section 423 of the Internal Revenue Code. Under these provisions, a participant will be taxed on amounts withheld as if actually received. However, no income will be taxable to a participant until disposition of the shares acquired.

If the stock is disposed of more than two years after the beginning of the Offering and more than one year after the stock is transferred to the participant, the lesser of (i) the excess of the fair market value of the stock at the time of the disposition over the exercise price or (ii) the excess of the fair market value of the stock as of the beginning of the Offering over the exercise price (determined as of the beginning of the Offering period) will be treated as ordinary income. Any further gain or any loss will be taxed as a capital gain or loss.

If the stock is sold or disposed of before the expiration of either of the holding periods described above, the excess of the fair market value of the stock on the exercise date over the exercise price generally will be treated as ordinary income at the time of the disposition, and Isis may, in the future, be required to withhold income taxes relating to the ordinary income from other payments made to the participant. The balance of any gain will be treated as capital gain. Even if the stock is later disposed of for less than its fair market value on the exercise date, the same amount of ordinary income is attributed to the participant and a capital loss is recognized equal to the difference between the sales price and the fair market value of the stock on the exercise date.

Any capital gain or loss realized by a participant upon the disposition of stock acquired under the ESPP will be long- or short-term depending on whether the stock has been held for more than one year.

There are no federal income tax consequences to Isis by reason of the grant or exercise of rights under the ESPP. Isis generally is entitled to a deduction for amounts taxed as ordinary income to a participant upon disposition by a participant of stock before the expiration of the holding periods described above.

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New Plan Benefits

Because benefits under the ESPP will depend on employees' elections to participate and to purchase shares under the ESPP at various future dates, it is not possible to determine the benefits that our executive officers and other employees will receive under the ESPP. Non-employee directors are not eligible to participate in the ESPP. The following table presents certain information with respect to shares purchased through our ESPP during the fiscal year ended December 31, 2008 to each executive officer named in the Summary Compensation Table under "Executive Compensation—Compensation of Executive Officers." This information regarding purchases for the fiscal year ended December 31, 2008 is for illustration only and may not be indicative of purchases that the officers will make in the future under the ESPP. Shares from our ESPP are purchased on January 1 and July 1 of each year.

NEW PLAN BENEFITS

2000 Employee Stock Purchase Plan

<u>Name and Position</u>	<u>Number of Shares Purchased</u>	<u>Purchase Price of Shares</u>
Stanley T. Crooke Chairman, Chief Executive Officer and President	— —	— —
B. Lynne Parshall Director, Chief Operating Officer & Chief Financial Officer	876 1,285	\$ 8.3045 \$ 11.7980
C. Frank Bennett Senior Vice President, Antisense Research	195 145	\$ 8.3045 \$ 11.7980
Richard S. Geary Senior Vice President, Development	1,393 741	\$ 8.3045 \$ 11.7980
Kleanthis G. Xanthopoulos Senior Vice President, President/Chief Executive Officer of Regulus Therapeutics Inc.	— —	— —

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Equity Compensation Plan Information

The following table sets forth information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of December 31, 2008.

<u>Plan Category</u>	<u>Number of Shares to be Issued Upon Exercise of Outstanding Options</u>	<u>Weighted Average Exercise Price of Outstanding Options</u>	<u>Number of Shares Remaining Available for Future Issuance</u>
Equity compensation plans approved by stockholders(a)	6,165,000	\$ 9.16	4,084,000(c)
Equity compensation plans not approved by stockholders(b)	3,151,000	\$ 13.09	277,000
Total	<u>9,316,000</u>	\$ 10.49	<u>4,361,000</u>

(a) Consists of three Isis plans: 1989 Stock Option Plan, 2002 Non-Employee Directors' Stock Option Plan and ESPP.

(b) Consists of the 2000 Broad-Based Equity Incentive Plan, more fully described below.

(c) Of these shares, 190,976 remained available for purchase under the ESPP as of December 31, 2008. The ESPP incorporates an evergreen formula pursuant to which on January 1 of each year through and including 2009, we automatically increased the aggregate number of shares reserved for issuance under the plan by 200,000 shares. Following approval of Proposal 2, the increase will be 150,000 shares per year.

Description of 2000 Broad-Based Equity Incentive Plan

We adopted the 2000 Broad-Based Equity Incentive Plan, or 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 non statutory 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. The Board has delegated administration of the 2000 Plan to the Compensation Committee of the Board, and the Compensation Committee has delegated administration of the 2000 Plan to the Non-Management Stock Option Committee with respect to certain option grants to employees who are not our executive officers. The Board has the power to construe and interpret the 2000 Plan and, subject to the provisions of the 2000 Plan, to select the persons to whom stock awards are to be made, to designate the number of shares to be covered by each stock award, to establish vesting schedules, to specify the exercise price and the type of consideration to be paid to us upon exercise or purchase.

As of December 31, 2008, the 2000 Plan had 5,990,000 shares authorized for issuance, options to purchase an aggregate of 3,151,000 shares had been granted and were outstanding under the 2000 Plan, options to purchase an aggregate of 2,562,000 shares had been exercised under the 2000 Plan, and 277,000 shares remained available for grant thereunder.

Options granted under the 2000 Plan generally have a term of seven or ten years, have an exercise price equal to the fair market value at the time of grant, can only be exercised with a cash payment and vest at the rate of 25% per year after the first year and then at the rate of 2.08% per month thereafter during the option holder's employment or service as a consultant, employee or director. Options granted pursuant to the April 2003 stock option exchange program as discussed in the Notes to the Consolidated Financial Statements, expired on December 31, 2008. 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), we will adjust the 2000 Plan appropriately in the class(es) and maximum number of securities subject to the 2000 Plan, and we will adjust the outstanding stock awards appropriately 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. We will not treat the conversion of any of our convertible securities as a transaction without receipt of consideration.

In the event of our dissolution or liquidation, 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
- 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, we will accelerate the vesting of such stock awards in full and the stock awards will terminate if not exercised (if applicable) at or prior to such event.

Change of Control Under the 2000 Plan

With respect to the 2000 Plan, 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
- 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, such stock awards automatically vest in full and the stock awards will terminate if not exercised 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 prior to such event.

In addition, the vesting of Dr. Crooke's and Ms. Parshall's stock options will accelerate in the event of a change in control, as further described under Retention and Change of Control Agreements below.

2002 Non-Employee Directors' Stock Option Plan ("Directors' Plan")

At both December 31, 2008 and March 31, 2009, a total of 524,000 options were granted and outstanding, 322,750 of which were vested and exercisable; options to purchase an aggregate of 113,000 shares had been exercised, and 213,000 shares were available for future grant under the Directors' Plan.

Employee Stock Purchase Plan

In 2000, our Board of Directors adopted, and the stockholders subsequently approved, the ESPP and we reserved 200,000 shares of common stock for issuance thereunder. Please refer to the description of the ESPP set forth in Proposal 2 starting on page 12. During 2008, our employees purchased 147,148 shares under the ESPP at prices ranging from \$8.3045 to \$11.798 per share. At December 31, 2008, 190,976 were available for purchase under the ESPP. At March 31, 2009, 325,404 shares were available for purchase under the ESPP.

PROPOSAL 3

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 2009 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 2009 Annual Meeting to answer any questions and make a statement should they desire 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.

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 2009 Annual Meeting will be required to ratify the selection of Ernst & Young LLP.

As of December 31, 2008, 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. As an additional measure to ensure auditor independence, beginning in 2004, the Audit Committee engaged Deloitte Tax LLP as the Company's primary tax advisor. All fees described below were pre-approved by the Audit Committee.

Audit Fees:

For the fiscal years ended December 31, 2008 and 2007, the fees billed by Ernst & Young LLP related primarily to the integrated audit of our financial statements and reviews of our interim financial statements for such fiscal years were \$506,000 and \$489,000, respectively. In addition, Ernst & Young LLP billed us \$44,000 and \$241,000 in 2008 and 2007, respectively, related to the accounting consultations for our partnership activities and our convertible debt offering in January 2007. Furthermore in 2008 and 2007, Ernst & Young LLP billed us \$65,000 in each year for the audit of our subsidiary, Regulus Therapeutics Inc.

Audit Related Fees:

During the fiscal year ended December 31, 2007, 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 \$5,000. For the year ended December 31, 2008, there were no audited related fees billed by Ernst & Young LLP.

Tax Fees:

During the fiscal year ended December 31, 2007, the aggregate fees billed by Ernst & Young LLP related to the preparation of information requested in connection with a Franchise Tax Board audit were \$21,000. For the year ended December 31, 2008, there were no fees billed by Ernst & Young LLP for tax related matters. In 2008 and 2007, we utilized Deloitte Tax LLP for the majority of our tax services.

Financial Information Systems Design and Implementation Fees:

During the fiscal years ended December 31, 2008 and 2007, there were no fees billed by Ernst & Young LLP for information technology consulting.

All Other Fees:

During the fiscal years ended December 31, 2008 and 2007, all other fees billed by Ernst & Young LLP were \$2,000 and \$3,000, respectively. These fees were for a subscription to an online accounting and tax information service.

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

During the fiscal year ended December 31, 2008, 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 UNANIMOUSLY RECOMMENDS A VOTE "FOR" APPROVAL OF PROPOSAL 3**SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT**

This table outlines the ownership of our common stock as of March 31, 2009 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)
FMR LLC (3) 82 Devonshire Street Boston, MA 02109	12,747,873	13.0
Federated Investors, Inc. (4) Federated Investors Tower Pittsburgh, PA 15222-3779	9,445,028	9.6
Barclays Global Investors (Deutschland) AG (5) Apianstrasse 6, D-85774 Unterfohring, Germany	5,219,692	5.3
Genzyme Corporation (6) 500 Kendall Street Cambridge, MA 02142	5,000,000	5.1
Spencer R. Berthelsen (7)	96,245	*
Stanley T. Crooke (8)	1,731,449	1.8
Richard D. DiMarchi (9)	36,875	*
Joseph Klein, III (10)	32,475	*
Frederick T. Muto (11)	70,375	*
B. Lynne Parshall (12)	411,467	*
John C. Reed (13)	76,875	*
Joseph H. Wender (14)	99,875	*
C. Frank Bennett (15)	181,795	*

Richard S. Geary (16)	58,238	*
Kleanthis G. Xanthopoulos (17)	21,250	*
All Directors and executive officers as a group (ten persons)(18)	2,795,669	2.8

*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 97,965,475 shares of common stock outstanding on March 31, 2009, adjusted as required by rules promulgated by the SEC.
- (3) Fidelity Management & Research Company ("Fidelity"), a wholly-owned subsidiary of FMR LLC and an investment adviser registered under Section 203 of the Investment Advisers Act of 1940, is the beneficial owner of 12,747,873 shares as a result of acting as investment adviser to various investment companies. The ownership of one investment company, Fidelity Growth Company Fund, amounted to 9,700,131 shares.
- (4) Represents shares of our common stock beneficially owned by registered investment companies and separate accounts advised by Federated Equity Management Company of Pennsylvania and Federated Global Investment Management Corp. (the "Investment Advisers") as of December 31, 2008. The Investment Advisers are wholly owned subsidiaries of FII Holdings, Inc., which is a wholly owned subsidiary of Federated Investors, Inc., the Parent. All of the Parent's outstanding voting stock is held in the Voting Shares Irrevocable Trust (the "Trust") for which John F. Donahue, Rhodora J. Donahue and J. Christopher Donahue act as trustees (collectively, the "Trustees"). The beneficial ownership also includes \$20,000,000 of our convertible promissory notes which, if converted, would represent 1,367,522 shares of common stock.
- (5) Represents shares of our common stock beneficially owned by Barclays Global Investors (Deutschland) AG. Of these shares, Barclays Global Investors, NA holds sole dispositive power over 2,165,831 shares and sole voting power over 1,883,024 shares; Barclays Global Fund Advisors holds sole voting and dispositive powers on 3,053,861 shares.
- (6) On January 7, 2008 Isis entered into a Stock Purchase Agreement with Genzyme Corporation pursuant to which Isis issued and sold to Genzyme 5,000,000 shares of common stock for an aggregate purchase price of \$150,000,000, representing a per share purchase price of \$30.
- (7) Includes 70 shares owned by Dr. Berthelsen's daughter for which he disclaims beneficial ownership. Includes 66,875 shares of common stock issuable upon exercise of options held by Dr. Berthelsen that are exercisable on or before May 30, 2009.
- (8) Includes 814,252 shares of common stock issuable upon exercise of options held by Dr. Crooke that are exercisable on or before May 30, 2009. Also includes 41,806 shares of common stock issuable upon exercise of options held by Rosanne Crooke, Dr. Crooke's wife, that are exercisable on or before May 30, 2009. Dr. Crooke disclaims beneficial ownership of the shares of common stock owned and issuable upon exercise of options held by his wife.
- (9) Includes 36,875 shares of common stock issuable upon exercise of options held by Dr. DiMarchi that are exercisable on or before May 30, 2009.
- (10) Includes 24,375 shares of common stock issuable upon exercise of options held by Mr. Klein that are exercisable on or before May 30, 2009 and 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 Kronish LLP Salary Deferral and Profit Sharing Plan and 68,875 shares of common stock issuable upon exercise of options held by Mr. Muto that are exercisable on or before May 30, 2009.
- (12) Includes 348,516 shares of common stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before May 30, 2009, 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 May 30, 2009.

- (13) Includes 76,875 shares of common stock issuable upon exercise of options held by Dr. Reed that are exercisable on or before May 30, 2009.
- (14) Includes 68,875 shares of common stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before May 30, 2009.
- (15) Includes 181,108 shares of common stock issuable upon exercise of options held by Dr. Bennett that are exercisable on or before May 30, 2009.
- (16) Includes 58,238 shares of common stock issuable upon exercise of options held by Dr. Geary that are exercisable on or before May 30, 2009.
- (17) Includes 21,250 shares of common stock issuable upon exercise of options held by Dr. Xanthopoulos that are exercisable on or before May 30, 2009.
- (18) Includes an aggregate of 1,846,760 shares issuable upon exercise of options held by all current Directors and executive officers as a group that are exercisable on or before May 30, 2009.

Section 16(a) Beneficial Ownership Reporting Compliance

Section 16(a) of the Securities Exchange Act, as amended, 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, 2008, all Section 16(a) filing requirements applicable to our officers, Directors and greater than ten percent beneficial owners were complied with except the stock option exercise by Dr. Bennett on August 20, 2008 effected pursuant to a Rule 10b5-1 trading plan adopted by Dr. Bennett on July 30, 2008 was filed a day late due to an administrative oversight. Also, stock options granted to two officers, David Ecker and Michael Treble, on January 2, 2008 were not filed until January 10, 2008 due to delays in processing the information necessary to complete the filing.

EXECUTIVE COMPENSATION

Compensation Discussion and Analysis

Compensation Overview and the Role of the Compensation Committee

We have designed our executive compensation to attract and retain executives who can help us meet our business objectives and to motivate them to enhance long-term stockholder value. The Compensation Committee of the Board of Directors manages and oversees our executive compensation program. At the end of each year, and as otherwise required, the Compensation Committee approves the total compensation for each of our executive officers. In addition, the full Board of Directors reviews and approves the Compensation Committee's recommendations regarding the compensation of executive officers.

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.

Compensation Philosophy & Objectives

We created a compensation system that is simple and supports the characteristics and behaviors that we feel will make us successful: individual excellence, effective collaboration and teamwork, willingness to take prudent risks, and honesty and openness. Our system is designed to be fair and reward individuals based on their contributions. As a result, we do not institute artificial limits on rewards. In order to attract and retain individuals that perform in the top 25% we consistently try to target actual total annual cash compensation at the 75th percentile of the biotech market for our size company. Although we do not necessarily recruit at the 75th percentile, we do expect that top performers will earn at or above that level. This basic tenet of our compensation practices allows us to recruit and retain top talent, and reflects Isis' position among biotech companies. We recognize achievements in many ways including salary increases, promotions, cash bonus opportunities and stock options. We designed our compensation philosophy to encourage ownership in Isis and its ideals by all employees.

We believe our compensation system focuses our organization on achieving critical objectives. We ensure that these objectives are aggressive and we define excellent performance as a year in which we have met most of the objectives. At Isis, we expect people to achieve very complicated tasks and understand that we are doing science which is difficult to predict. We reward for that success. Our compensation system also reinforces desired behaviors. We expect outstanding performance from every individual and we expect every person at Isis to accept responsibility for making Isis a great place to work. We expect everyone to behave respectfully and supportively to each other and to never forget our commitment to the patients we serve and our obligations to stockholders.

Elements of Executive Compensation

Employees in our organization do not share either accountability or responsibility equally for strategic and/or tactical decisions. It is well ingrained in our culture that not everyone should share the same level of risk/reward for

the consequences of these decisions. As a result, we have structured the various components of our compensation systems to reflect accountability both for the successes or failures (both long-term and short-term) of the company and of individuals. Our senior management team is paid for results and their use of judgment; therefore, the more senior the person, the greater percentage of “at risk” compensation. The more junior employees are compensated for accomplishing their work well and therefore have a lower “at risk” portion to their total compensation.

The executive officers’ annual compensation consists of three elements: base salary, a cash incentive bonus and stock option grants. The cash incentive bonus is the only element of these three that does not apply to all employees, but is available to employees at the director level and above. In addition, our executive officers receive the retirement and other benefits offered to all employees, as described in more detail below.

- Base Salary (including Annual Merit Increase);
- Cash Bonus;
- Stock Options (including Annual Merit Stock Option Awards); and
- Retirement & Other Benefits.

We consider many factors in determining the amounts we grant to our executives for each of these three elements. These considerations may include:

- The Compensation Committee’s performance assessment of the CEO and executive officers;
- Competitive compensation practices;
- Individual performance and contributions to company objectives;
- Increased efficiencies and process improvements;
- Effective collaboration and teamwork;
- Individual expertise, skills and knowledge;
- The need to retain and motivate; and
- The degree of risk taking assumed.

A large degree of discretion is allowed in setting the appropriate increases based on these and other possible factors. We do not have specific weightings assigned to these performance factors and the importance of each factor can vary among the executive officers.

Base Salary

The primary component of our compensation is base salary. We categorize our jobs in a system called broad-banding. That is to say that there are relatively few job levels within the company, but the scope of responsibility and accountability which an employee may assume is broad. We do not have salary ranges, and therefore we do not set salary maximums. It is therefore possible that someone may be in a lower job level, but his/her salary may reach levels which exceed those of someone in a higher job level. We have chosen not to have multiple levels and salary limits because years of experience has shown us that these approaches often create unnecessary bureaucracy and a loss of talented individuals.

We determine base compensation levels throughout the company primarily by market forces. First, we look externally at what comparable companies in the geographical or recruiting area are paying for comparable jobs. We use AON’s Radford Biotechnology Survey to obtain this information targeting the 75th percentile and companies of a similar size (150-499 employees). Examples of companies within this group are: Arena Pharmaceuticals, Cytokinetics, Exelixis, Inc., Incyte Corporation, Medarex, Inc., MGI Pharma, Inc., Neurocrine Biosciences, Inc., OSI Pharmaceuticals, Inc., Vical Incorporated, and Zymogenetics, Inc. We then look at the salary required to attract a particular candidate. The third step is to determine whether the scope of job responsibilities and internal equity warrant a given base salary.

Base salary is guaranteed to all employees as wages for hours worked. It represents consideration for the performance of job responsibilities. This portion of total cash compensation is not at risk and may increase based on how well an individual performs his/her job responsibilities.

Each year our employees are eligible to receive an appropriate merit salary increase. The Compensation Committee sets a Company-wide merit increase budget percentage based on external factors such as the average merit increase being used by comparable companies, as well as the performance of the Company. The Company-wide merit increase budget percentage serves as the basis for each individual salary increase. For the merit increase for all our employees, including our executive officers, we may increase or decrease the Company-wide merit increase budget percentage depending upon the respective individual’s contribution to Isis.

To set each individual’s annual merit increase, the Compensation Committee evaluates each individual officer’s performance. With respect to all executive officers, other than the CEO, the Compensation Committee gives great deference to our senior management’s written evaluation of each individual executive officer. The Compensation Committee shows deference since our senior management team is in the best position to evaluate our executive officers’ day-to-day and overall performance. The Compensation Committee then meets in executive session and evaluates the CEO’s performance, primarily based upon the CEO’s achievement of set objectives for the year. At the end of this process, the Compensation Committee determines the CEO’s merit increase and approves or recommends changes to the merit increases for the remaining executive officers. The CEO has no role in determining his own compensation.

The executive officer’s new salaries for the upcoming year are calculated as follows:

Current Base Salary (x) Merit Increase = Increase to Base Salary

For example, Dr. Crooke's 2009 salary (\$683,649) was calculated as follows:

<u>2008 Base Salary</u>	(x)	<u>Merit Increase</u>	=	<u>Increase to Base Salary</u>
\$648,009	(x)	5.5%	=	\$35,640

The average merit increase for all of our other executive officers was 5.2%. The 2008 merit budget approved by the Compensation Committee for the entire Company was 5% of salaries. This was a .5% decrease over the 2007 merit budget of 5.5%. This decrease was driven by the general decrease we observed in the outside market balanced against the very strong performance of the company in 2008 which the compensation committee believed deserved recognition. The Compensation Committee approved this budget based on Isis' outstanding accomplishments in 2008, as noted in the section entitled "2008 and Early 2009 Business Highlights" below, and competitive information on the planned merit increases provided by other local Biotech companies. Our Executive Director of Human Resources obtained planned merit increases by surveying local companies through the Biotech Employee Development Coalition and by reviewing data provided by AON's Radford Biotechnology Compensation Survey.

As part of the approval process, to ensure that the proposed merit increases are not unreasonable, the Compensation Committee analyzes the impact of the proposed merit increase on the CEO's salary by comparing it to AON's Radford Biotech Compensation Survey. In 2009, Dr. Crooke's proposed new base salary of \$683,649 placed him above the 90th percentile of Radford (\$649,801); based on this information further analysis was performed. The Compensation Committee reviewed the CEO compensation of twelve companies with similar market capitalizations as Isis(5), using the latest salary data that was publically available at the time. This information illustrated that Dr. Crooke's base pay was below the CEO average base salary of \$642,697 for these twelve companies and, as such, the Compensation Committee believed Dr. Crooke's 5.5% increase was appropriate based on his accomplishments for the year as well as the market data. The merit increases for all other executives, and their impact, were compared to Radford data only. The results as a whole showed that we pay our executives, on average, above the 90th percentile. The Compensation Committee determined that this was reasonable based on the longevity of many of our executive officers, as well as their performance in 2008. For example, the average tenure of our executive officers, excluding our CEO, is 12.5 years. The average tenure of our executive officers, including our CEO, is 13.6 years. The average tenure of Isis' current Executive Officers (i.e. excluding Ibis Biosciences and Regulus Therapeutics) is 18 years.

(5) These companies included Medarex, Inc., OSI Pharmaceuticals, Inc., Myriad Genetics, Inc., United Therapeutics, PDL BioPharma, Inc., Affymetrix, Inc., LifeCell Corporation, Alnylam Pharmaceuticals, Inc., Applera Corporation, Regeneron Pharmaceuticals, Inc., Cubist Pharmaceuticals Inc. and ZymoGenetics, Inc.

Cash Bonus – At Risk

The next component of an executive officer's compensation, as well as the compensation of our employees at the director and above level, is a cash bonus through our management by objective (MBO) bonus program. While we design individual salary to compensate an employee for his or her continued service and performance, we designed our cash bonus portion of total compensation to compensate employees for reaching specific objectives and for the judgment they use in making decisions. This portion of compensation is totally at risk. As such, bonus represents an opportunity for reward based upon the individual's level of accountability and depends on the relative success of both Isis and the individual. Our approach for awarding management by objective bonuses differs from salary increases because, unlike salary increases, market forces do not impact bonus amounts.

The actual amount of each officer's respective cash bonus is calculated based on the following formula:

Base Salary (x) Target MBO % (x) Company Success Factor (x) Individual Success Factor

The multipliers in this formula ensure that we award bonuses based on the Company's performance, as well as based on the individual's performance. For example, in 1999, the Company Success Factor was 0% due to the failures the Company faced at the time. This resulted in no cash bonuses for executive officers and director level and above employees. Conversely, in 2007 Isis had a seminal year and the Company Success Factor was 200%. This range represents the boundary conditions for our Company Success Factor and ensures that our employees are rewarded proportionately to the success of Isis.

We tie Target MBO percentages to the level of the position in Isis. For example, the Target MBO percentage for vice presidents is either 25% or 30%; the target MBO percentage for our COO is 35%. Unless an individual is promoted to a higher level at Isis, his or her Target MBO percentage does not change.

The Compensation Committee sets the Company Success Factor based on Isis' achievement of set objectives for the year. At the end of each year, the Compensation Committee meets to evaluate the overall performance of the Company. They measure Company performance based upon the achievement of goals that were set at the beginning of the year and agreed upon by our Board and upper management. The Compensation Committee may also consider unexpected accomplishments, as well as failures, that occurred through the year. The committee then reviews the MBO Company Success Factor history/events from all prior years to form a comparison for our current year's successes and/or failures.

Finally, the Compensation Committee approves each individual officer's Individual Success Factor, based on the same elements it used to evaluate the Individual Success Factor for salary increases.

Once the Compensation Committee has determined all of the elements of the formula above, they apply the formula to each individual officer. For example, Dr. Crooke's cash bonus based on his, as well as the Company's performance in 2008, was calculated as follows and equaled \$438,054:

<u>Base Salary</u>	(x)	<u>Target MBO %</u>	(x)	<u>Company Success Factor</u>	(x)	<u>Individual Success Factor</u>
\$648,009	(x)	40%	(x)	130%	(x)	130%

The average Target MBO percentage and Individual Success Factor for our other executive officers was 31% and 124%, respectively (not including the Executive Officers who did not participate in the 2008 MBO Bonus).

The Compensation Committee set the Company success factor for the 2008 MBO at 130% due to our strong achievements – two major accomplishments were the completion of the Genzyme deal for mipomersen and the sale of Ibis Biosciences to Abbott Molecular, Inc. This MBO target reflects a decrease from 200% in 2007 to 130% in 2008. This decrease acknowledges that we had a seminal year in 2007 for which Isis' employees were appropriately compensated at that time. The success factors we set in 2007 recognized the significant achievement of initiating both the Genzyme and Abbott transactions. Therefore, when setting the performance factors, we tried to balance the weight we gave initiating the Genzyme and Abbott transactions in 2007 against the weight we gave executing these transactions in 2008 to avoid "double counting." However, a large portion of the compensation associated with these deals was contingent upon Isis successfully executing the transactions in 2008. In fact, \$195 million of the \$215

million acquisition price in the Abbott transaction was completely at risk most of 2008. Similarly, new guidance provided by the FDA impacted the development plan for mipomersen and our agreed upon deliverables to Genzyme. The Company Success factor of 130% for 2008 recognizes Isis' ability to overcome these challenges, offset by the strong Company success factor we set for the 2007 bonuses. The section entitled "Evaluation of 2008; Business Highlights" below provides a full review of our accomplishments.

An executive officer's salary plus bonus represents the officer's total cash compensation. Our philosophy has been to have the CEO's total cash compensation be between 20-30 times the lowest level compensation. Dr. Crooke's total cash compensation is an average of 2 times greater than that of our other executive officers and 28.5 times that of the average cash compensation for our lowest level employees. This falls within industry standards, ISS guidelines, and our philosophy. For example, ISS has suggested a ratio of CEO to Executive level compensation of between 2 and 5.

Stock Options

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 and equity in Isis' growth.

Each year the Compensation Committee approves a budget that sets the number of stock options we can grant our employees for annual merit awards. We do not grant options that exceed this budget without the Compensation Committee's approval. Over the past five years, the average option budget set by the Compensation Committee has been approximately 2% of our outstanding common stock on an issued and outstanding basis. We believe the merit option budget is an important tool to balance our equity compensation objectives with stockholder interests. For 2008, the Compensation Committee set the option budget at 1.5 million shares, which represented 2% of our outstanding common stock on an issued and outstanding basis for that year. 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 each stock option, the Compensation Committee sets a vesting schedule that is typically over a 4-year period at the rate of 25% for the first year and then at the rate of 2.08% per month for 36 months thereafter during the optionee's employment. We have historically had low employee turnover, particularly in our management team and the members of our management have historically held their options for a long period of time before exercise. The low turnover is indicative of our employees' commitment to Isis and its technology. As such, we believe our officers see the long term value of our stock and therefore we do not require our employees to own a minimum number of shares of our stock, or hold shares of our stock they acquire for minimum periods of time.

To help avoid situations where our employees may benefit from transactions that harm our stockholders, our policies specifically prohibit all employees, including our executive officers, from taking a "short" position in our stock and otherwise hedging their position in our stock against a future drop in our stock price. In addition, we specifically prohibit all of our employees from trading derivative instruments based on our common stock (e.g. put or call options for our stock).

Finally, we have a Rule 10b5-1 trading program. When there is no material non-public information available, our Rule 10b5-1 trading program allows our executive officers, and other select employees, to establish plans that permit prearranged future sales of his or her securities. Except for purchases of our stock under our ESPP (but not subsequent sales of the stock) we do not allow our executive officers to buy or sell our stock outside of the Rule 10b5-1 trading program.

Perquisites

Isis is committed to using stockholder money responsibly, to building stockholder value and ensuring our processes are entirely transparent. As a result, Isis' policies do not provide for perquisites for any employees, including our executive officers.

Retirement & Other Benefits

Isis maintains a highly competitive position with regard to the benefits offered to all regular employees, including our executive officers. These benefits include medical, dental and vision insurance, basic life insurance, short-term disability/sick pay, vacation, holidays, a 401(k) plan with employer match, an ESPP and Accidental Death & Dismemberment (AD&D) insurance.

Recognizing that health care costs constitute a greater fraction of disposable income for lower paid employees, we have a progressive contribution premium for our health care benefits; the more money an Isis employee makes, the more he or she contributes to the costs of his/her family's health care.

Retention and Change of Control Agreements

Isis' retention agreements for our CEO and COO and the related severance compensation provisions are designed to meet the following objectives:

Change in Control: As part of our normal course of business, we engage in discussions with other biotechnology and pharmaceutical companies about possible collaborations, licensing and/or other ways in which the companies may work together to further our respective long-term objectives. In addition, many larger established pharmaceutical companies consider companies at similar stages of development to ours as potential acquisition targets. In certain scenarios, the potential for merger or being acquired may be in the best interests of our stockholders. As further described on pages 37-38 of this Proxy

Statement, we provide a component of severance compensation for our CEO and COO to promote their ability to act in the best interests of our stockholders even though they could be terminated as a result of the transaction.

Termination without Cause: If we terminate the employment of our COO “without cause” we will pay her the benefits described under “Post-Employment Compensation — Retention and Change of Control Agreements” of this Proxy Statement. This agreement provides us with more flexibility to make a change in senior management if such a change is in our and our stockholders’ best interests.

The employment agreement for our CEO of Regulus Therapeutics, Dr. Kleanthis Xanthopoulos, was designed to recruit and retain his services given the higher degree of risk associated with starting a new company that is based on a new technology. Regulus is a jointly owned company that we and Alnylam Pharmaceuticals, Inc. established to focus on the discovery, development and commercialization of microRNA-based therapeutics. This agreement meets the following objectives:

Change in Control: As part of the normal course of business, Dr. Xanthopoulos will engage in discussions with other biotechnology and pharmaceutical companies about possible collaborations, licensing and/or other ways in which the companies may work together to further our respective long-term objectives. In certain scenarios, the potential for merger or being acquired may be in our best interests. As further described on pages 37-38 of this Proxy Statement, we provide a component of severance compensation to promote his ability to act in the best interests of our stockholders even though he could be terminated as a result of the transaction.

Termination by the Company without Cause or by the Executive with Good Reason: If we terminate Dr. Xanthopoulos’ employment “without cause” we will pay him the benefits described under “Post-Employment Compensation — Retention and Change of Control Agreements” of this Proxy Statement. This agreement provides us with more flexibility to make a change in senior management if such a change is in ours and Alnylam’s best interests. This agreement also provides Dr. Xanthopoulos the opportunity to resign for Good Reason should the circumstances of his position change significantly from the arrangements made during his recruitment.

Evaluation of 2008; Business Highlights

2008 was a strong year for Isis. The antisense platform was validated; we experienced significant partnership activity; and we were financially strong. We met or exceeded most of our corporate objectives for the year and had a number of unbudgeted accomplishments. As mentioned earlier, we define excellent performance as a year in which we have met most of the corporate objectives. For 2008, we set very aggressive corporate objectives,

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primarily related to our cash position, clinical development, and the completion of the Ibis/Abbott Milestones and the sale of Ibis to Abbott. Isis met its corporate objectives in the following ways:

- **Financial Performance.** Isis is in its best cash position ever. We greatly exceeded our financial goals by exceeding our 2008 net operating loss guidance and our 2008 cash guidance of \$450 million. Isis ended 2008 with over \$490 million in cash, not including the \$175 million in cash Isis received in early 2009 for the sale of Ibis to Abbott.
- **Clinical Development.** Isis completed the licensing of mipomersen to Genzyme and made significant progress in its Phase 3 clinical trials. We plan to file an NDA for the initial indication in 2010. We also made progress in other areas of our cardiovascular and metabolic franchises by beginning two Phase 1 studies.
- **Ibis Subsidiary.** Abbott Molecular purchased Ibis for a total acquisition price of \$215 million, and we will receive earn out payments tied to sales of Ibis systems, including instruments and assay kits.

The Company exceeded most of its key corporate objectives for the year as well as adding a number of unbudgeted accomplishments. We did experience delays in two mipomersen studies (one due to the FDA’s delay) and failed to move one drug forward into development consideration.

The Compensation Committee set the Company Success Factors for salary and bonus as described above, based on Isis’ successful achievement of the corporate objectives for the year as well as Isis’ additional achievements, which are highlighted below:

Pipeline Highlights

We continued to expand our cardiovascular franchise with the addition of new drugs into development that enable us to broaden our therapeutic focus. Mipomersen, our flagship drug, matured appreciably during the last year. We and our partner, Genzyme, are currently evaluating mipomersen in four Phase 3 studies with an NDA filing for the initial indication planned for the second half of 2010.

- We licensed mipomersen to Genzyme as part of a strategic alliance and together with Genzyme we made significant progress on our mipomersen project.
- The transaction included a \$175 million licensing fee, a \$150 million equity investment at \$30 per share, over \$1.5 billion in potential commercial and developmental milestone payments for mipomersen, a share of profits for us on mipomersen ranging from 30 to 50 percent of commercial sales, and a preferred partner relationship for the development and commercialization of antisense drugs for central nervous system diseases and a number of rare diseases.
- We completed enrollment of our Phase 3 mipomersen study in homozygous FH subjects and initiated four additional mipomersen studies, including three Phase 3 studies in heterozygous FH, high-risk high-cholesterol and severe high-cholesterol subjects and a Phase 2 study in high-risk, high-cholesterol subjects who are intolerant to statins.
- We reported updated safety data on mipomersen from an ongoing open-label extension study that showed mipomersen continues to be well tolerated throughout longer-term treatment in FH patients who have been exposed to mipomersen from three to 23 months.
- We reported data from a Phase 2 mipomersen liver imaging study in heterozygous FH subjects.

- We reported two preclinical studies in which the lowering of apoB-100, resulted in the significant reduction of atherosclerotic plaques in murine models of atherosclerosis.
- We received a patent that broadly covers the use of antisense compounds targeting apoB messenger RNA except a ribozyme. It is the first allowance in a series of broad filings protecting the therapeutic use of targeting apoB for the lowering of all atherogenic lipids, including LDL-C and triglycerides.
- We published a preclinical study in *Circulation* showing that mipomersen lowers oxidized-LDL and Lp(a), a generally accepted independent risk factor for cardiovascular disease.

We continued to make progress in other programs in our cardiovascular franchise in which we believe there are significant opportunities for growth.

- We initiated a Phase 1 study of ISIS-CRP_{Rx}, an antisense drug that targets CRP.
- Together with BMS, we identified a development candidate that targets PCSK9 and received a \$2 million milestone payment from BMS.
- We provided information on earlier preclinical programs including our antithrombotic program during the 2008 American Heart Association conference.

Our metabolic disease franchise continued to expand with new research efforts focused on attractive targets for the treatment of obesity.

- We initiated a Phase 1 study of ISIS-SGLT2_{Rx}, an antisense drug that targets SGLT2 for type 2 diabetes.
- We highlighted our robust diabetes and obesity portfolio with nine presentations and posters at the 2008 American Diabetes Association meeting. This included new preclinical data relating to ISIS-SGLT2_{Rx} and results from eight research programs on novel targets that offer new mechanisms to address metabolic diseases, including obesity.

Cancer continues to be a disease in which antisense drugs could offer new treatment options to patients. We have begun to expand our internal focus on cancer and our partners are making excellent progress developing antisense drugs we have discovered to treat cancer.

- OncoGenex is evaluating OGX-011 in multiple Phase 2 studies in prostate, lung and breast cancer.
- OncoGenex has reported encouraging data on OGX-011, including recent Phase 2 data that showed OGX-011 provided an overall survival advantage when combined with standard first-line chemotherapy in prostate cancer patients compared to standard first-line chemotherapy alone.
- Previously reported data has shown better than expected survival when OGX-011 was combined with second-line chemotherapy as well as reduced levels of clusterin, OGX-011's target, and demonstrated durable reduction in pain and a decline in levels of PSA, a protein that is often elevated in patients with prostate cancer.
- OncoGenex reported survival data on OGX-011 from a Phase 1/2 study in patients with NSCLC. At two years, 30% of patients that had received OGX-011 with first-line chemotherapy were alive, comparing favorably to other previously reported studies in NSCLC.
- The FDA granted OGX-011 Fast Track Designation for use in combination with docetaxel for progressive metastatic prostate cancer.
- OncoGenex reached an agreement with the FDA on the design of a Phase 3 registration trial of OGX-011 in patients with castrate resistant prostate cancer, via the Special Protocol Assessment process.
- Lilly reported positive Phase 1 clinical trial results for LY2181308 that targets survivin for the treatment of cancer, and advanced LY2181308 into multiple Phase 2 trials.

In addition, many of our other partners are showing encouraging results with our antisense drugs in a broad range of diseases, including MS.

- ATL licensed ATL/TV1102, an antisense drug for patients with MS, to Teva.
- ATL and Teva reported encouraging Phase 2 results for ATL/TV1102 at the World Congress on Treatment and Research in Multiple Sclerosis showing that ATL/TV1102 demonstrated a highly significant effect on disease activity in MS patients after only two months of dosing.
- Atlantic Pharmaceuticals Limited received U.S. orphan drug designation for alicaforsen for the treatment of pouchitis.
- Excaliard Pharmaceuticals, Inc. selected a development compound, EXC001, for the local treatment of fibrosis and scarring.

- iCo Therapeutics Inc. reported interim data from an ongoing Phase 1 study evaluating iCo-007 in patients with diffuse diabetic macular edema that showed iCo-007 appears to be well tolerated.

- Altair Therapeutics Inc. advanced AIR645 into Phase 1 studies. AIR645 is an antisense drug we discovered and licensed to Altair in 2007 to treat respiratory conditions.
- Achaogen initiated Phase 1 studies on Achaogen's neoglycoside, Achaogen's next-generation aminoglycoside drug, ACHN-490. ACHN-490 is being developed to treat bacterial infections and incorporates our aminoglycosides technology that we licensed to Achaogen. We received a \$1 million milestone payment.

Corporate Highlights

Building upon our successes in 2007, we continued to improve our financial position in 2008, strengthening our balance sheet and bringing us closer to sustainable profitability driven by the successful execution of our business strategy.

- We exceeded our 2008 net operating loss guidance.
- We exceeded our 2008 cash guidance of \$450 million and ended 2008 with over \$490 million in cash.
- Our net loss applicable to common stock was \$12.0 million, and if we exclude our non-cash stock compensation expense, we finished the year with net income.
- In early 2009, we added \$175 million of cash to our balance sheet from the sale of our Ibis subsidiary.

We also added new patents to our intellectual property estate and expanded the scope of our core antisense patents.

- We were granted patents that significantly expand the scope of Isis' "Crooke" patent estate. U.S. Patent No. 7,432,250 and U.S. Patent No. 7,432,249 add broad claims that cover RNA-based product compositions and methods of treatment.

We recently sold our Ibis subsidiary to Abbott Molecular, Inc. We believe the sale of Ibis to AMI will help ensure that Ibis is both technically and commercially successful as Ibis moves its technology into the clinical diagnostics market.

- AMI purchased Ibis for a total acquisition price of \$215 million, and we will receive earn out payments tied to sales of Ibis systems, including instruments and assay kits.

Regulus Highlights

Regulus is a jointly owned company that we and Alnylam established to focus on the discovery, development and commercialization of microRNA-based therapeutics.

- Regulus entered into a strategic alliance with GSK, which could provide up to nearly \$600 million to Regulus, including a \$20 million upfront payment. The alliance focuses on the development of microRNA-targeted therapeutics to treat inflammatory diseases.
- Regulus and academic collaborators continue to advance the basic understanding of microRNAs and the role that microRNAs play in disease. These advances were published in some of the industry's leading scientific journals, including *Molecular and Cellular Biology*, *Cancer Cell* and *Nature*.

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.

Compensation of Executive Officers

The following table shows for the fiscal years ended December 31, 2008, 2007 and 2006 compensation awarded to or paid to, or earned by, the Company's Chief Executive Officer, Chief Financial Officer and its three other most highly compensated executive officers at December 31, 2008 (the "Named Executive Officers").

In 2008, we did not grant any stock awards or non-equity incentive plan compensation and we do not currently offer pension or non-qualified deferred compensation plans.

Summary Compensation Table for Fiscal 2008, 2007 and 2006

<u>Name and Principal Position</u>	<u>Year</u>	<u>Salary</u> <u>(\$)</u>	<u>Bonus(1)</u> <u>(\$)</u>	<u>Option</u> <u>Awards (2)</u> <u>(\$)</u>	<u>All Other</u> <u>Compensation (3)</u> <u>(\$)</u>	<u>Total</u> <u>(\$)</u>
Stanley T. Crooke, Chairman, President, Chief Executive Officer	2008	\$ 648,009	\$ 438,054	\$ 1,191,880	\$ 12,248	\$ 2,290,191
	2007	\$ 611,329	\$ 782,501	\$ 896,724	\$ 11,625	\$ 2,302,180
	2006	\$ 582,218	\$ 423,855	\$ 411,091	\$ 11,213	\$ 1,428,377
B. Lynne Parshall Director, Chief Operating Officer, Chief Financial Officer	2008	\$ 529,095	\$ 334,499	\$ 597,256	\$ 15,208	\$ 1,476,058
	2007	\$ 484,737	\$ 543,200	\$ 394,250	\$ 14,433	\$ 1,436,620
	2006	\$ 458,898	\$ 292,318	\$ 174,096	\$ 13,905	\$ 939,217

C. Frank Bennett	2008	\$	345,873	\$	170,625	\$	267,622	\$	15,136	\$	799,256
Senior Vice President, Antisense Research	2007	\$	323,959	\$	291,563	\$	173,982	\$	12,359	\$	801,863
	2006	\$	311,499	\$	151,856	\$	104,866	\$	12,661	\$	580,882
Richard Geary(4)	2008	\$	299,873	\$	150,150	\$	204,043	\$	11,559	\$	665,625
Senior Vice President, Development											
Kleanthis G. Xanthopoulos(5)	2008	\$	400,000	\$	223,080	\$	194,268	\$	15,208	\$	832,556
Chief Executive Officer of Regulus Therapeutics Inc.	2007	\$	33,333	\$	—	\$	22,573	\$	200,000	\$	255,906

- (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 2008 were paid in January 2009.
- (2) Non-cash amounts calculated utilizing the provisions of Statement of Financial Accounting Standards (“SFAS”) No. 123R, “Share-based Payment.” For more information, please see Note 4 of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2008 regarding assumptions underlying valuation of equity awards.
- (3) Includes AD&D, Basic Life, Medical, Dental, Vision, and 401(k) company contributions which are available to all employees. As an incentive to recruit Dr. Xanthopoulos to join Regulus Therapeutics, we paid Dr. Xanthopoulos a \$200,000 sign-on bonus.
- (4) Because Dr. Geary was not a Named Executive Officer in 2006 and 2007 and did not become an executive officer until August 2008, we are not disclosing compensation for such years as permitted by SEC regulations.
- (5) Because Dr. Xanthopoulos was not a Named Executive Officer in 2006 and did not join Isis until December 2007, we are not disclosing compensation for 2006 as permitted by SEC regulations. In connection with Regulus’ conversion into a C-Corporation in January 2009, Dr. Xanthopoulos is no longer an officer or employee of Isis.

Grants of Plan-Based Awards

The following table shows for the fiscal year ended December 31, 2008, certain information regarding grants of plan-based awards to the Named Executive Officers:

Grants of Plan-Based Awards in Fiscal 2008

Name	Grant Date	All Other Option Awards: Number of Securities Underlying Options (#)	Exercise or Base Price of Option Awards (\$/Sh)	Grant Date Fair Value of Stock and Option Awards(1) (\$)
Stanley T. Crooke	1/2/08	190,495	\$ 15.38	\$ 1,401,888
B. Lynne Parshall	1/2/08 (2)9/16/08	91,520 30,000	\$ 15.38 \$ 16.45	\$ 673,513 \$ 240,931
C. Frank Bennett	1/2/08	46,200	\$ 15.38	\$ 339,995
Richard S. Geary	1/1/08 1/2/08 8/16/08	(3)10,000 24,000 (4)10,000	\$ 15.75 \$ 15.38 \$ 19.08	\$ 75,363 \$ 176,620 \$ 93,156
Kleanthis G. Xanthopoulos(5)	—	—	—	—

- (1) Non-cash amounts calculated utilizing the provisions of SFAS. For more information, please see Note 4 of the consolidated financial statements in our Annual Report for the year ended December 31, 2008 regarding assumptions underlying valuation of equity awards.
- (2) Granted as a result of Ms. Parshall’s promotion to Chief Operating Officer.
- (3) Granted as a result of Dr. Geary’s promotion to Vice President.
- (4) Granted as a result of Dr. Geary’s promotion to Senior Vice President.
- (5) Because Dr. Xanthopoulos received an option to purchase 60,000 shares of Isis’ stock in connection with his hire in December 2007, Dr. Xanthopoulos did not receive options to purchase Isis stock in 2008.

Narrative to Summary Compensation Table and Grants of Plan-Based Awards Table

The Compensation Committee granted merit non-statutory stock options to the executive officers on January 2, 2008, the same date on which the committee granted stock awards to our other employees.

All of these stock options were granted out of our 1989 Plan or 2000 Plan. The options have a term of seven years and vest at the rate of 25% for the first year and then at the rate of 2.08% per month for 36 months thereafter during the optionee's employment.

For new hires and promotions for employees who are not executive officers, the Board has pre-approved standing resolutions that set the number of shares to be granted. The stock option exercise price is equal to 100% of the closing price on the date of hire or promotion, as applicable.

Outstanding Equity Awards at Fiscal Year-End – Executive Officers.

The following table shows for the fiscal year ended December 31, 2008, certain information regarding outstanding option awards at fiscal year-end for the Named Executive Officers.

Other than the options described in the table below, there were no equity incentive plan awards outstanding for the Named Executive Officers at December 31, 2008. In addition, there were no stock awards outstanding for the individuals named below at December 31, 2008.

Outstanding Option Awards At December 31, 2008

<u>Name</u>	<u>Number of Securities Underlying Unexercised Options (#) Exercisable</u>	<u>Number of Securities Underlying Unexercised Options (#) Unexercisable</u>	<u>(1)Full Vest Date</u>	<u>Option Exercise Price (\$)</u>	<u>Option Expiration Date</u>
Stanley T. Crooke	0	190,495	1/2/2012	\$ 15.3800	1/1/2015
	80,000	0	1/2/2008	\$ 6.8100	1/1/2014
	85,646	93,094	1/2/2011	\$ 11.1200	1/1/2014
	28,125	21,875	9/21/2010	\$ 7.2600	9/20/2013
	94,007	34,917	1/3/2010	\$ 5.2500	1/2/2013
	50,000	0	1/2/2007	\$ 6.8400	1/1/2013
	74,142	1,578	1/3/2009	\$ 5.8000	1/2/2012
	50,000	0	1/2/2005	\$ 9.6250	1/1/2011
	250,000	0	1/2/2002	\$ 6.8125	1/5/2010
B. Lynne Parshall	0	30,000	9/16/2012	\$ 16.4500	9/15/2015
	0	91,520	1/2/2012	\$ 15.3800	1/1/2015
	38,400	0	1/2/2008	\$ 6.8100	1/1/2014
	37,114	40,340	1/2/2011	\$ 11.1200	1/1/2014
	16,875	13,125	9/21/2010	\$ 7.2600	9/20/2013
	26,098	13,408	1/3/2010	\$ 5.2500	1/2/2013
	(2)10,000	0	1/3/2007	\$ 5.2500	1/2/2013
	25,000	0	1/2/2007	\$ 6.8400	1/1/2013
	9,632	631	1/3/2009	\$ 5.8000	1/2/2012
	(2)20,000	0	1/3/2008	\$ 5.8000	1/2/2012
28,000	0	1/2/2005	\$ 9.6250	1/1/2011	
119,910	0	1/6/2000	\$ 6.8125	1/5/2010	
	(2)30,090	0	1/6/2001	\$ 6.8125	1/5/2010
C. Frank Bennett	0	46,200	1/2/2012	\$ 15.3800	1/1/2015
	28,800	0	1/2/2008	\$ 6.8100	1/1/2014
	17,320	18,825	1/2/2011	\$ 11.1200	1/1/2014
	12,110	8,212	1/3/2010	\$ 5.2500	1/2/2013
	11,500	0	1/2/2007	\$ 6.8400	1/1/2013
	16,522	533	1/3/2009	\$ 5.8000	1/2/2012
	19,000	0	1/2/2006	\$ 21.0500	1/1/2012
	20,000	0	1/2/2005	\$ 9.6250	1/1/2011
	32,000	0	1/6/2004	\$ 6.8100	1/5/2010
1,000	0	1/1/2004	\$ 6.2500	12/31/2009	

<u>Name</u>	<u>Number of Securities Underlying Unexercised Options (#) Exercisable</u>	<u>Number of Securities Underlying Unexercised Options (#) Unexercisable</u>	<u>(1)Full Vest Date</u>	<u>Option Exercise Price (\$)</u>	<u>Option Expiration Date</u>
Richard S. Geary	0	10,000	8/16/2012	\$ 19.0800	8/15/2015
	0	24,000	1/2/2012	\$ 15.3800	1/1/2015
	0	10,000	1/1/2012	\$ 15.7500	12/31/2014
	1,049	0	1/2/2008	\$ 6.8100	1/1/2014
	9,125	9,917	1/2/2011	\$ 11.1200	1/1/2014
	6,060	5,626	1/3/2010	\$ 5.2500	1/2/2013
	4,707	337	1/3/2009	\$ 5.8000	1/2/2012
	8,000	0	1/2/2006	\$ 21.0500	1/1/2012
	8,480	0	1/2/2005	\$ 9.6250	1/1/2011

	5,000	0	8/1/2004	\$	11.5625	7/31/2010
Kleanthis G. Xanthopoulos	15,000	16,250	12/3/2011	\$	17.6800	12/2/2014

- (1) These options vest at the rate of 25% for the first year and then at the rate of 2.08% per month for 36 months thereafter during the optionee's employment.
- (2) Includes an aggregate of 60,090 shares of common stock issuable upon exercise of options which Ms. Parshall transferred to her two daughters.

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Option Exercises

The following table shows for the fiscal year ended December 31, 2008, certain information regarding option exercises and stock vested during the last fiscal year with respect to the Named Executive Officers:

Option Exercises in Fiscal 2008(1)

Name	Option Awards	
	Number of Shares Acquired on Exercise (2) (#)	Value Realized on Exercise (\$)
Stanley T. Crooke	(3)7,300	\$ 3,150.68
	(3)200	\$ 86.32
	(3)7,500	\$ 2,343.75
	(3)7,482	\$ 57,259.75
	(3)12,000	\$ 11,865.60
	(3)8,000	\$ 4,652.00
B. Lynne Parshall	(3)1,250	\$ 539.50
	(3)8,000	\$ 7,910.40
	(3)7,000	\$ 4,070.50
	(3)3,750	\$ 1,618.50
	(3)5,000	\$ 1,562.50
C. Frank Bennett	10,000	\$ 100,800.00
	(3)7,500	\$ 41,898.75
	6,500	\$ 84,532.50
	1,000	\$ 13,000.00
	500	\$ 6,502.50
	(3)7,500	\$ 38,216.25
Richard S. Geary	(3)3,950	\$ 19,206.87
	(3)3,050	\$ 14,830.62
Kleanthis G. Xanthopoulos	—	—

- (1) Isis currently does not utilize stock awards as part of its compensation plan. As such, the Company does not include information regarding stock awards that would otherwise appear as blank columns in this table.
- (2) All exercises and resulting sales were made pursuant to the individual's Rule 10b5-1 trading plan.
- (3) Options exercised because they otherwise would have expired on 12/31/08.

Post-Employment Compensation

Pension Benefits and Nonqualified Deferred Compensation

We do not provide pension arrangements or post-retirement health coverage for our executives or employees. Our executive officers are eligible to participate in our 401(k) contributory defined contribution plan. In any plan year, we will contribute to each participant a matching contribution equal to 25% of the first 6% of the participant's compensation that has been contributed to the plan. In 2008, the maximum matching contribution was \$3,450. We do not provide any nonqualified defined contribution or other deferred compensation plans.

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Employment Agreements

All of our employees, including our executive officers, are employees-at-will and as such do not have employment contracts with us, except in the case of some retention agreements, the details of which are provided below.

Retention and Change of Control Agreements

In December 2008, the Company amended and restated its severance agreements with Stanley T. Crooke and B. Lynne Parshall to clarify the provisions of such agreements in light of Section 409A of the Internal Revenue Code.

Specifically, these severance agreements provide the following severance benefits:

- Dr. Crooke will be eligible to receive a lump sum 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 of Isis; and
- Ms. Parshall will be eligible to receive a lump sum severance payment equal to:
 - 18 months of her then-current base salary in the event that her employment is terminated without cause; and
 - 30 months of her then-current base salary in the event that her employment is terminated as a result of a change of control of Isis.

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

In addition, on May 16, 2007, the Compensation Committee approved amending the stock option agreements of Dr. Crooke and Ms. Parshall, such that in the event of a change of control, the vesting and exercisability of their stock options will be accelerated in full, to the extent permitted by the applicable stock option plan.

In December 2008, Regulus Therapeutics Inc., a jointly owned company that we and Alnylam established to focus on the discovery, development and commercialization of microRNA-based therapeutics, formalized its employment agreement with Kleanthis Xanthopoulos, Regulus' President and CEO. Dr. Xanthopoulos' agreement provides the following severance benefits:

- Dr. Xanthopoulos will be eligible to receive a severance payment equal to:
 - 18 months salary continuation of his then-current base salary in the event that his employment is terminated by Regulus without cause or by Dr. Xanthopoulos for good reason (as defined in the agreement); or
 - a lump sum equal to 24 months of his then-current base salary, plus two times his discretionary bonus amount in the event that his employment is terminated as a result of a change of control of Isis or Alnylam before December 31, 2009, or a change of control of Regulus; and
- In addition, in each circumstance described above, Regulus will continue to pay 18 months of the premiums for group health plan continuation coverage under Title X of the Consolidated Omnibus Budget Reconciliation Act of 1985, as amended (COBRA) and the vesting of Dr. Xanthopoulos' options to purchase Regulus' common stock will accelerate in full.

Conditions

As a condition to receiving payments under each of the retention and change of control agreements described above, the officer is required to return all of Isis' property and information and sign an agreement releasing Isis from liability.

Potential Payments Upon Termination or Change-Of-Control

The following table estimates the payments that would be required under the agreements described above that were effective as of December 31, 2008. This table estimates the payments based upon either a termination without cause or a termination in connection with a change of control assuming either occurred on December 31, 2008. Unless otherwise indicated in the table, the payments are payable in a lump sum. The estimates in this table are forward-looking statements. Please see special note regarding forward-looking statements on page 43 of this Proxy Statement.

Name	Termination Event	
	Termination Without Cause	Termination in a Change of Control
Stanley T. Crooke	—	\$ 1,944,027
B. Lynne Parshall	\$ 793,642	\$ 1,322,736
Kleanthis G. Xanthopoulos(1)	\$ 630,000	\$ 1,176,000

(1) Isis' subsidiary, Regulus Therapeutics Inc., would be responsible for paying Dr. Xanthopoulos the amounts set forth in the table above. The \$630,000 payable for termination without cause would be through salary continuation.

Director Compensation

We pay our non-employee Directors a fee of \$30,000 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, 2008, we paid total fees of \$30,000 to each of our non-employee Directors.

In 2008, each non-employee Director also received automatic stock option grants under our 2002 Non-Employee Directors' Stock Option Plan. On July 1, 2008, under the 2002 Non-Employee Directors' Stock Option Plan, each of our non-employee Directors serving at that time received an option to purchase 15,000 shares of our common stock, at an exercise price of \$13.88 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 Global Market. The options vest over a four-year period in equal annual installments.

The following table shows for the fiscal year ended December 31, 2008 certain information with respect to the compensation of all non-employee Directors of the Company:

Director Compensation for Fiscal 2008

Name	Fees Earned or Paid in Cash (\$)	Option Awards (\$)	All Other Compensation (\$)	Total (\$)
Spencer R. Berthelsen	\$ 30,000	\$ 137,099	—	\$ 167,099
Richard D. DiMarchi	\$ 30,000	\$ 137,099	\$ 2,000	\$ 169,099
Joseph Klein	\$ 30,000	\$ 137,099	—	\$ 167,099
Frederick T. Muto	\$ 30,000	\$ 137,099	—	\$ 167,099
John C. Reed	\$ 30,000	\$ 137,099	—	\$ 167,099
Joseph H. Wender	\$ 30,000	\$ 137,099	—	\$ 167,099

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Outstanding Equity Awards at Fiscal Year-End – Directors

The following table shows for the fiscal year ended December 31, 2008, certain information regarding outstanding awards at fiscal year end of all non-employee Directors of the Company:

Name	Number of Securities Underlying Unexercised Options (#)	
	Exercisable	Unexercisable
Spencer R. Berthelsen	66,875	33,125
Richard D. DiMarchi	36,875	33,125
Joseph Klein	24,375	35,625
Frederick T. Muto	68,875	33,125
John C. Reed	76,875	33,125
Joseph H. Wender	68,875	33,125

Certain Relationships and Related Transactions

The Company has provided some of the information below because it may be of interest to our stockholders when evaluating the proposals contained in this Proxy Statement. Inclusion of a transaction in this section does not necessarily mean that the transaction qualifies as a related party transaction under the securities laws.

Rosanne Crooke, the wife of Dr. Crooke, our Chairman and Chief Executive Officer, is a non-executive employee of Isis working part time at 30 hours per week. Dr. Rosanne Crooke's compensation is approved by the Compensation Committee and is commensurate with the compensation of other employees at the same level at Isis. For the fiscal years ended 2006, 2007 and 2008, she received the following compensation:

Name	Year	Salary (\$)	Bonus(1) (\$)	Option Awards(2) (\$)	All Other Compensation(3) (\$)	Total (\$)
Rosanne Crooke	2008	\$ 140,002	\$ 45,501	\$ 61,416	\$ 3,331	\$ 250,250
	2007	\$ 132,452	\$ 74,173	\$ 62,984	\$ 2,622	\$ 272,231
	2006	\$ 114,951	\$ 15,144	\$ 18,211	\$ 2,226	\$ 150,532

- (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 2008 were paid in January 2009.
- (2) Non-cash amounts calculated utilizing the provisions of SFAS. For more information, please see Note 4 of the consolidated financial statements in our Annual Report for the year ended December 31, 2008 regarding assumptions underlying valuation of equity awards. Represents an option to purchase 6,000 shares of the Isis' common stock at an exercise price of \$5.25 per share Dr. Rosanne Crooke received on January 3, 2006; represents an option to purchase 5,958 shares of the Company's common stock at an exercise price of \$11.12 per share that Dr. Rosanne Crooke received on January 2, 2007 and 5,000 shares of the Isis' common stock at an exercise price of \$9.92 per share that Dr. Rosanne Crooke received on May 1, 2007 for her promotion; and represents an option to purchase 8,300 shares of the Company's common stock at an exercise price of \$15.38 per share that Dr. Rosanne Crooke received on January 2, 2008.
- (3) Includes AD&D, Basic Life, Medical, Dental, Vision, and 401(k) company contributions which are available to all employees.

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One of our Directors, Mr. Muto, who was elected by the Board in March 2001, is a partner at Cooley Godward Kronish LLP, our outside counsel. We paid Cooley Godward Kronish LLP an aggregate of \$147,075 for Isis and \$66,788 for Regulus in fees in 2008 for legal services, which amount is substantially less than five percent of Cooley's gross revenues for its 2008 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.

Policies and Procedures Regarding Related Party Transactions

All transactions with related persons, as defined under SEC regulations, are approved by a committee of the Board composed entirely of independent Directors. The Compensation Committee of the Board approves all compensation paid to employees that may qualify as a related person and the Audit Committee approves all other related party transactions, as specified in its charter. These approvals are only made at committee meetings, or by unanimous written consent in lieu of a meeting, and are recorded in the minutes of the committee.

For transactions that do not qualify as related party transactions, but may otherwise present a conflict of interest, our Code of Ethics and Business Conduct requires the Board (for our executive officers and Directors) or the CEO or COO (for non-executive officers) to determine that no conflict of interest exists.

Our policies and procedures specifically prohibit personal loans to our executive officers and any officer with a title of Vice President or higher.

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COMPENSATION COMMITTEE REPORT(6)

The Compensation Committee has:

- reviewed and discussed the Compensation Discussion and Analysis included in this Proxy Statement with management; and
- based on this review and discussion, the Compensation Committee recommended to the Board of Directors that the Compensation Discussion and Analysis be included in the Company's Proxy Statement relating to the 2009 Annual Meeting of stockholders.

The Compensation Committee

Spencer R. Berthelsen, *Chairman*

Richard D. DiMarchi

John C. Reed

(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.

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AUDIT COMMITTEE REPORT(7)

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, 2008 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 applicable requirements of the Public Company Accounting Oversight Board regarding Ernst & Young LLP's communications with the Audit Committee concerning independence. The Audit Committee also discussed with our independent auditors the matters required by the Statement on Auditing Standards No. 61, as amended.

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, 2008 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.

The Audit Committee

Joseph H. Wender, *Chairman*

Spencer R. Berthelsen

Joseph Klein, III

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

(7) 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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will promptly provide you a separate Proxy Statement. Stockholders who currently receive multiple copies of the Proxy Statement or Notice of Internet Availability of Proxy Materials 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, 2008 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 2009 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. The Annual Report is not incorporated into this Proxy Statement and is not considered soliciting material.

By Order of the Board of Directors,

B. Lynne Parshall
Secretary

April 20, 2009

Special Note Regarding Forward-Looking Statements

This Proxy Statement includes forward-looking statements regarding Isis Pharmaceuticals’ business, the financial position and outlook for Isis as well as Regulus, its majority-owned subsidiary, and the therapeutic and commercial potential of the Company’s technologies and products in development. Any statement describing Isis’ goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such products. Isis’ forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis’ forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis’ programs are described in additional detail in Isis’ annual report on Form 10-K for the year ended December 31, 2008, which is on file with the SEC. Copies of these and other documents are available from the Company.

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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.

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APPENDIX B
ISIS PHARMACEUTICALS, INC.

AMENDED AND RESTATED 2000 EMPLOYEE STOCK PURCHASE PLAN

Approved by the Board of Directors February 27, 2009

Subject to Stockholder Approval

1. PURPOSE.

(a) The purpose of this Amended and Restated 2000 Employee Stock Purchase Plan (the "Plan") is to provide a means by which employees of Isis Pharmaceuticals, Inc. (the "Company") and its Affiliates, as defined in Subsection 1(b), which are designated as provided in Subsection 2(b), may be given an opportunity to purchase common stock of the Company (the "Common Stock"). This Plan supersedes and replaces the 2000 Employee Stock Purchase Plan adopted by the Company's stockholders on June 8, 2000, as amended.

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

(c) The Company, by means of the Plan, seeks to retain the services of its employees, to secure and retain the services of new employees, and to provide incentives for such persons to exert maximum efforts for the success of the Company.

(d) The Company intends that the rights to purchase stock of the Company granted under the Plan be considered options issued under an "employee stock purchase plan" as that term is defined in Section 423(b) of the Code.

2. ADMINISTRATION.

(a) The Plan shall be administered by the Board of Directors (the "Board") of the Company unless and until the Board delegates administration to a Committee, as provided in Subsection 2(c). Whether or not the Board has delegated administration, the Board shall have the final power to determine all questions of policy and expediency that may arise in the administration of the Plan.

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

(i) To determine when and how rights to purchase stock of the Company shall be granted and the provisions of each offering of such rights (which need not be identical).

(ii) To designate from time to time which Affiliates of the Company shall be eligible to participate in the Plan.

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(iii) To construe and interpret the Plan and rights 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, in a manner and to the extent it shall deem necessary or expedient to make the Plan fully effective.

(iv) To amend the Plan as provided in Section 13.

(v) To terminate or suspend the Plan as provided in Section 15.

(vi) 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 its Affiliates and to carry out the intent that the Plan be treated as an "employee stock purchase plan" within the meaning of Section 423 of the Code.

(c) The Board may delegate administration of the Plan to a Committee composed of not fewer than two (2) members of the Board (the "Committee"). If administration is delegated to a Committee, the Committee shall have, in connection with the administration of the Plan, the powers theretofore possessed by the Board, subject, however, to such resolutions, not inconsistent with the provisions of the Plan, as may be adopted from time to time by the Board. The Board may abolish the Committee at any time and revert in the Board the administration of the Plan.

3. SHARES SUBJECT TO THE PLAN.

(a) Subject to the provisions of Section 12 relating to adjustments upon changes in stock, the stock that may be sold pursuant to rights granted under the Plan shall not exceed in the aggregate one hundred fifty thousand (150,000) shares of Common Stock (the "Reserved Shares"). Through the first nine (9) anniversaries of the Effective Date of the Plan, on January 1 of each year the number of Reserved Shares will be increased automatically by one hundred fifty thousand (150,000) shares. If any right granted under the Plan shall for any reason terminate without having been exercised, the Common Stock not purchased under such right shall again become available for the Plan.

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

4. GRANT OF RIGHTS; OFFERING.

The Board or the Committee may from time to time grant or provide for the grant of rights to purchase Common Stock of the Company under the Plan to eligible employees (an "Offering") on a date or dates (the "Offering Date(s)") selected by the Board or the Committee. Each Offering shall be in such form and shall contain such terms and conditions as the Board or the Committee shall deem appropriate, which shall comply with the requirements of

Section 423(b)(5) of the Code that all employees granted rights to purchase stock under the Plan shall have the same rights and privileges. The terms and conditions of an Offering shall be incorporated by reference into the Plan and treated as part of the Plan. The provisions of separate Offerings need not be identical, but each Offering shall include (through incorporation of the provisions of this Plan by reference in the document comprising the Offering or otherwise)

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the period during which the Offering shall be effective, which period shall not exceed six (6) months beginning with the Offering Date, and the substance of the provisions contained in Sections 5 through 8, inclusive.

5. ELIGIBILITY.

(a) Rights may be granted only to employees of the Company or, as the Board or the Committee may designate as provided in Subsection 2(c), to employees of any Affiliate of the Company. Except as provided in Subsection 5(b), an employee of the Company or any Affiliate shall not be eligible to be granted rights under the Plan unless, on the Offering Date, such employee has been in the employ of the Company or any Affiliate for such continuous period preceding such grant as the Board or the Committee may require, but in no event shall the required period of continuous employment be greater than two (2) years. In addition, unless otherwise determined by the Board or the Committee and set forth in the terms of the applicable Offering, no employee of the Company or any Affiliate shall be eligible to be granted rights under the Plan, unless, on the Offering Date, such employee's customary employment with the Company or such Affiliate is for at least twenty (20) hours per week and at least five (5) months per calendar year. The Company, in its sole discretion, may exclude from participation in the Plan employees of the Company or any Affiliate of the Company who reside and/or perform services in certain specific jurisdictions if the laws of those jurisdictions make participation in the Plan impractical.

(b) The Board or the Committee may provide that each person who, during the course of an Offering, first becomes an eligible employee of the Company or designated Affiliate will, on a date or dates specified in the Offering which coincides with the day on which such person becomes an eligible employee or occurs thereafter, receive a right under that Offering, which right shall thereafter be deemed to be a part of that Offering. Such right shall have the same characteristics as any rights originally granted under that Offering, as described herein, except that:

(i) the date on which such right is granted shall be the "Offering Date" of such right for all purposes, including determination of the exercise price of such right;

(ii) the period of the Offering with respect to such right shall begin on its Offering Date and end coincident with the end of such Offering; and

(iii) the Board or the Committee may provide that if such person first becomes an eligible employee within a specified period of time before the end of the Offering, he or she will not receive any right under that Offering.

(c) No employee shall be eligible for the grant of any rights under the Plan if, immediately after any such rights are granted, such employee owns stock possessing five percent (5%) or more of the total combined voting power or value of all classes of stock of the Company or of any Affiliate. For purposes of this Subsection 5(c), the rules of Section 424(d) of the Code shall apply in determining the stock ownership of any employee, and stock which such employee may purchase under all outstanding rights and options shall be treated as stock owned by such employee.

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(d) An eligible employee may be granted rights under the Plan only if such rights, together with any other rights granted under "employee stock purchase plans" of the Company and any Affiliates, as specified by Section 423(b)(8) of the Code, do not permit such employee's rights to purchase stock of the Company or any Affiliate to accrue at a rate which exceeds twenty-five thousand dollars (\$25,000) of fair market value of such stock (determined at the time such rights are granted) for each calendar year in which such rights are outstanding at any time.

(e) Officers of the Company and any designated Affiliate shall be eligible to participate in Offerings under the Plan; *provided, however*, that the Board may provide in an Offering that certain employees who are highly compensated employees within the meaning of Section 423(b)(4)(D) of the Code shall not be eligible to participate.

6. RIGHTS; PURCHASE PRICE.

(a) On each Offering Date, each eligible employee, pursuant to an Offering made under the Plan, shall be granted the right to purchase up to the number of shares of Common Stock of the Company purchasable with a percentage designated by the Board or the Committee not exceeding ten percent (10%) of such employee's Earnings (as defined in Subsection 7(a)) during the period which begins on the Offering Date (or such later date as the Board or the Committee determines for a particular Offering) and ends on the date stated in the Offering, which date shall be no later than the end of the Offering. In addition, the Board or the Committee may specify a maximum dollar amount that each employee may use to purchase shares during any Offering made under the Plan. The Board or the Committee shall establish one or more dates during an Offering (the "Exercise Date(s)") on which rights granted under the Plan shall be exercised and purchases of Common Stock carried out in accordance with such Offering.

(b) In connection with each Offering made under the Plan, the Board or the Committee may specify a maximum number of shares that may be purchased by any employee as well as a maximum aggregate number of shares that may be purchased by all eligible employees pursuant to such Offering. In addition, in connection with each Offering that contains more than one Exercise Date, the Board or the Committee may specify a maximum aggregate number of shares which may be purchased by all eligible employees on any given Exercise Date under the Offering. If the aggregate purchase of shares upon exercise of rights granted under the Offering would exceed any such maximum aggregate number, the Board or the Committee shall make a pro rata allocation of the shares available in as nearly a uniform manner as shall be practicable and as it shall deem to be equitable.

(c) The purchase price of stock acquired pursuant to rights granted under the Plan shall be not less than the lesser of:

(i) an amount equal to eighty-five percent (85%) of the fair market value of the stock on the Offering Date; or

- (ii) an amount equal to eighty-five percent (85%) of the fair market value of the stock on the Exercise Date.

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7. PARTICIPATION; WITHDRAWAL; TERMINATION.

(a) An eligible employee may become a participant in the Plan pursuant to an Offering by delivering a participation agreement to the Company within the time specified in the Offering, in such form as the Company provides. Each such agreement shall authorize payroll deductions of up to the maximum percentage specified by the Board or the Committee of such employee's Earnings during the Offering. "Earnings" is defined as the total compensation paid to an employee including all salary, wages (including amounts thereof elected to be deferred by the employee, that would otherwise have been paid, under any arrangement established by the Company that is intended to comply with Section 125, Section 401(k), Section 402(h) or Section 403(b) of the Code or that provides non-qualified deferred compensation), which shall include overtime pay, commissions, bonuses and other remuneration paid directly to the employee, but shall exclude profit sharing, the cost of employee benefits paid for by the Company or an Affiliate, education or tuition reimbursements, imputed income arising under any group insurance or benefit program, traveling expenses, business and moving expense reimbursements, income received in connection with stock options, contributions made by the Company or an Affiliate under any employee benefit plan, and similar items of compensation, as determined by the Board or the Committee. The payroll deductions made for each participant shall be credited to an account for such participant under the Plan and shall be deposited with the general funds of the Company. A participant may reduce (including to zero) or increase such payroll deductions, and an eligible employee may begin such payroll deductions, after the beginning of any Offering only as provided for in the Offering. A participant may make additional payments into his or her account only if specifically provided for in the Offering and only if the participant has not had the maximum permitted amount withheld during the Offering.

(b) At any time during an Offering, a participant may terminate his or her payroll deductions under the Plan and withdraw from the Offering by delivering to the Company a notice of withdrawal in such form as the Company provides. Such withdrawal may be elected at any time prior to the end of the Offering except as provided by the Board or the Committee in the Offering. Upon such withdrawal from the Offering by a participant, the Company shall distribute to such participant all of his or her accumulated payroll deductions (reduced to the extent, if any, such deductions have been used to acquire stock for the participant) under the Offering, without interest, and such participant's interest in that Offering shall be automatically terminated. A participant's withdrawal from an Offering will have no effect upon such participant's eligibility to re-enroll in the Offering or to participate in any other Offerings under the Plan but such participant will be required to deliver a new participation agreement in order to participate in subsequent Offerings under the Plan.

(c) Rights granted pursuant to any Offering under the Plan shall terminate immediately upon cessation of any participating employee's employment with the Company and any designated Affiliate, for any reason, and the Company shall distribute to such terminated employee all of his or her accumulated payroll deductions (reduced to the extent, if any, such deductions have been used to acquire stock for the terminated employee), under the Offering, without interest.

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(d) Rights granted under the Plan shall not be transferable by a participant otherwise than by will or the laws of descent and distribution, or by a beneficiary designation as provided in Section 14 and, otherwise during his or her lifetime, shall be exercisable only by the person to whom such rights are granted.

8. EXERCISE; MINIMUM HOLDING PERIOD.

(a) On each Exercise Date specified therefor in the relevant Offering, each participant's accumulated payroll deductions and other additional payments specifically provided for in the Offering (without any increase for interest) will be applied to the purchase of whole shares of stock of the Company, up to the maximum number of shares permitted pursuant to the terms of the Plan and the applicable Offering, at the purchase price specified in the Offering. No fractional shares shall be issued upon the exercise of rights granted under the Plan. The amount, if any, of accumulated payroll deductions remaining in each participant's account after the purchase of shares which is less than the amount required to purchase one share of stock on the final Exercise Date of an Offering shall be held in each such participant's account for the purchase of shares under the next Offering under the Plan, unless such participant withdraws from such next Offering, as provided in Subsection 7(b), or is no longer eligible to be granted rights under the Plan, as provided in Section 5, in which case such amount shall be distributed to the participant after such final Exercise Date, without interest. The amount, if any, of accumulated payroll deductions remaining in any participant's account after the purchase of shares which is equal to the amount required to purchase whole shares of stock on the final Exercise Date of an Offering shall be distributed in full to the participant after such Exercise Date, without interest.

(b) No rights granted under the Plan may be exercised to any extent unless the shares to be issued upon such exercise under the Plan (including rights granted thereunder) are covered by an effective registration statement pursuant to the Securities Act of 1933, as amended (the "Securities Act") and the Plan is in material compliance with all applicable state, foreign and other securities and other laws applicable to the Plan. If on an Exercise Date in any Offering hereunder the Plan is not so registered or in such compliance, no rights granted under the Plan or any Offering shall be exercised and all payroll deductions accumulated during the Offering (reduced to the extent, if any, such deductions have been used to acquire stock) shall be distributed to the participants, without interest.

(c) With respect to any Common Stock of the Company purchased under any Offering initiated after the Effective Date, as a condition to participating in, and purchasing shares of Common Stock under this Plan, each participant irrevocably agrees that, without the prior written consent of the Company, such participant will not, directly or indirectly, (1) offer for sale, sell, pledge, or otherwise dispose of (or enter into any transaction or device that is designed to, or could be expected to, result in the disposition by any person at any time in the future of) any shares of Common Stock of the Company (the "Held Shares") purchased by such participant in an Offering that was initiated after the Effective Date, or (2) enter into any swap or other derivatives transaction that transfers to another, in whole or in part, any of the economic benefits or risks of ownership of the Held Shares, in each case before the passage of the

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six-month anniversary of the date the participant purchased the applicable Held Shares (the "Holding Period"). The Company may impose stop-transfer instructions with respect to the shares of Common Stock subject to the foregoing restriction until the end of the applicable Holding Period.

(d) Each participant understands and agrees that on any certificates evidencing the shares of Common Stock purchased under the Plan, the Company may place a legend, substantially in the form of the following:

THE SHARES EVIDENCED BY THIS CERTIFICATE CANNOT BE SOLD UNTIL [INSERT DATE THAT IS 6 MONTHS FROM DATE OF PURCHASE].

9. COVENANTS OF THE COMPANY.

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

(b) The Company shall seek to obtain from each federal, state, foreign or other regulatory commission or agency having jurisdiction over the Plan such authority as may be required to issue and sell shares of stock upon exercise of the rights granted under the Plan. If, after reasonable efforts, the Company is unable to obtain from any such regulatory commission or agency the authority which counsel for the Company deems necessary for the lawful issuance and sale of stock under the Plan, the Company shall be relieved from any liability for failure to issue and sell stock upon exercise of such rights unless and until such authority is obtained.

10. USE OF PROCEEDS FROM STOCK.

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

11. RIGHTS AS A STOCKHOLDER.

A participant shall not be deemed to be the holder of, or to have any of the rights of a holder with respect to, any shares subject to rights granted under the Plan unless and until the participant's shareholdings acquired upon exercise of rights under the Plan are recorded in the books of the Company.

12. ADJUSTMENTS UPON CHANGES IN STOCK.

(a) If any change is made in the stock subject to the Plan, or subject to any rights granted under the Plan, due to a change in corporate capitalization and without the receipt of consideration by the Company (through reincorporation, stock dividend, stock split, reverse stock split, combination or reclassification of shares), the Plan will be appropriately adjusted in the class(es) and maximum number of securities subject to the Plan pursuant to subsection 3(a), and the outstanding rights will be appropriately adjusted in the class(es) and number of securities and price per share of stock subject to such outstanding rights. Such adjustments shall be made by the Board, the determination of which shall be final, binding and conclusive.

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(b) In the event of: (1) a dissolution, liquidation or sale of all or substantially all of the assets of the Company, (2) a merger or consolidation in which the Company is not the surviving corporation, or (3) a reverse merger in which the Company is the surviving corporation but the shares of 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 or (4) any other capital reorganization in which more than fifty percent (50%) of the securities of the Company entitled to vote are sold or otherwise exchanged, then any surviving corporation may assume outstanding rights or substitute similar rights for those under the Plan. In the event that no surviving corporation assumes such outstanding rights or substitutes similar rights therefor, participants' accumulated payroll deductions will be used to purchase Common Stock immediately prior to the transaction described above and the participants' rights under the ongoing Offering terminated immediately following such purchase.

13. AMENDMENT OF THE PLAN.

(a) The Board at any time, and from time to time, may amend the Plan. However, except as provided in Section 12 relating to adjustments upon changes in stock, no amendment shall be effective unless approved by the stockholders of the Company within twelve (12) months before or after the adoption of the amendment, where the amendment will:

(i) Increase the number of shares reserved for rights under the Plan;

(ii) Modify the provisions as to eligibility for participation in the Plan (to the extent such modification requires stockholder approval in order for the Plan to obtain employee stock purchase plan treatment under Section 423 of the Code or to comply with the requirements of Rule 16b-3 promulgated under the Securities Exchange Act of 1934, as amended ("Rule 16b-3")); or

(iii) Modify the Plan in any other way if such modification requires stockholder approval in order for the Plan to obtain employee stock purchase plan treatment under Section 423 of the Code or to comply with the requirements of Rule 16b-3.

It is expressly contemplated that the Board may amend the Plan in any respect the Board deems necessary or advisable to provide eligible employees with the maximum benefits provided or to be provided under the provisions of the Code and the regulations promulgated thereunder relating to employee stock purchase plans and/or to bring the Plan and/or rights granted under it into compliance therewith.

(b) Rights and obligations under any rights granted before amendment of the Plan shall not be impaired by any amendment of the Plan, except with the consent of the person to whom such rights were granted, or except as necessary to comply with any laws or governmental regulations, or except as necessary to ensure that the Plan and/or rights granted under the Plan comply with the requirements of Section 423 of the Code.

14. DESIGNATION OF BENEFICIARY.

(a) A participant may file a written designation of a beneficiary who is to receive any shares and cash, if any, from the participant's account under the Plan in the event of such participant's death subsequent to the end of an Offering but prior to delivery to the participant of

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such shares and cash. In addition, a participant may file a written designation of a beneficiary who is to receive any cash from the participant's account under the Plan in the event of such participant's death during an Offering.

(b) Such designation of beneficiary may be changed by the participant at any time by written notice. In the event of the death of a participant and in the absence of a beneficiary validly designated under the Plan who is living at the time of such participant's death, the Company shall deliver such shares and/or cash to the executor or administrator of the estate of the participant, or if no such executor or administrator has been appointed (to the knowledge of the Company), the Company, in its sole discretion, may deliver such shares and/or cash to the spouse or to any one or more dependents or relatives of the participant, or if no spouse, dependent or relative is known to the Company, then to such other person as the Company may designate.

15. TERMINATION OR SUSPENSION OF THE PLAN.

(a) The Board in its discretion, may suspend or terminate the Plan at any time. No rights may be granted under the Plan while the Plan is suspended or after it is terminated.

(b) Rights and obligations under any rights granted while the Plan is in effect shall not be altered or impaired by suspension or termination of the Plan, except as expressly provided in the Plan or with the consent of the person to whom such rights were granted, or except as necessary to comply with any laws or governmental regulation, or except as necessary to ensure that the Plan and/or rights granted under the Plan comply with the requirements of Section 423 of the Code.

(c) Notwithstanding the foregoing, the Plan shall terminate on June 2, 2019 and no rights may be granted under the Plan after such termination.

16. EFFECTIVE DATE OF PLAN.

The Plan shall become effective on the date on which it is first approved by the stockholders of the Company (the "Effective Date").

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***** Exercise Your Right to Vote *****
IMPORTANT NOTICE Regarding the Availability of Proxy Materials

ISIS PHARMACEUTICALS, INC.



ISIS PHARMACEUTICALS, INC.
1896 RUTHERFORD ROAD
CARLSBAD, CA 92008

Meeting Information

Meeting Type: Annual
For holders as of: 4/6/2009
Date: 6/2/2009 **Time:** 3:00 p.m. Pacific Time

Location: Company's offices
1896 Rutherford Road
Carlsbad, CA 92008

You are receiving this communication because you hold shares in the company named above.

This is not a ballot. You cannot use this notice to vote these shares. This communication presents only an overview of the more complete proxy materials that are available to you on the Internet. You may view the proxy materials online at www.proxyvote.com or easily request a paper copy (see reverse side).

We encourage you to access and review all of the important information contained in the proxy materials before voting.

See the reverse side of this notice to obtain proxy materials and voting instructions.

M12739-P71856

Proxy Materials Available to VIEW or RECEIVE:

NOTICE AND PROXY STATEMENT FORM 10-K

How to View Online:

Have the 12-Digit Control Number available (located on the following page) and visit: www.proxyvote.com.

How to Request and Receive a PAPER or E-MAIL Copy:

If you want to receive a paper or e-mail copy of these documents, you must request one. There is NO charge for requesting a copy. Please choose one of the following methods to make your request:

- | | |
|-------------------------|--|
| 1) BY INTERNET: | www.proxyvote.com |
| 2) BY TELEPHONE: | 1-800-579-1639 |
| 3) BY E-MAIL*: | sendmaterial@proxyvote.com |

* If requesting materials by e-mail, please send a blank e-mail with the 12-Digit Control Number (located on the following page) in the subject line.

Requests, instructions and other inquiries sent to this e-mail address will NOT be forwarded to your investment advisor. To facilitate timely delivery, please make the request as instructed above on or before 5/19/2009.

— **How To Vote** —

Please Choose One of the Following Voting Methods

Vote In Person: Many stockholder meetings have attendance requirements including, but not limited to, the possession of an attendance ticket issued by the entity holding the meeting. Please check the meeting materials for any special requirements for meeting attendance. At the meeting, you will need to request a ballot to vote these shares.

Vote By Internet: To vote now by Internet, go to www.proxyvote.com. Have the 12-Digit Control Number available and follow the instructions.

Vote By Mail: You can vote by mail by requesting a paper copy of the materials, which will include a proxy card.

M12740-P71856

Voting Items

THE BOARD OF DIRECTORS RECOMMENDS A VOTE “FOR” ITEMS 1 THROUGH 3.

- To elect as Directors of Isis Pharmaceuticals, Inc. the nominees listed below.
 - Richard D. DiMarchi
 - Frederick T. Muto
- To approve the amendment and restatement of our 2000 Employee Stock Purchase Plan (ESPP) to: (i) extend the ESPP so that it will terminate on June 2, 2019; (ii) limit the evergreen provision such that it only adds 150,000 shares to the ESPP each year; (iii) limit the offering periods under the ESPP to a maximum of six months; and (iv) impose a minimum six-month holding period on shares purchased under the ESPP.
- To ratify the Audit Committee’s selection of Ernst & Young LLP as independent auditors for our 2009 fiscal year.

M12741-P71856



ISIS PHARMACEUTICALS, INC.
1896 RUTHERFORD ROAD
CARLSBAD, CA 92008

VOTE BY INTERNET - www.proxyvote.com

Use the Internet to transmit your voting instructions and for electronic delivery of information up until 11:59 P.M. Eastern Time the day before the cut-off date or meeting date. Have your proxy card in hand when you access the web site and follow the instructions to obtain your records and to create an electronic voting instruction form.

ELECTRONIC DELIVERY OF FUTURE STOCKHOLDER COMMUNICATIONS

If you would like to reduce the costs incurred by Isis Pharmaceuticals, Inc. in mailing proxy materials, you can consent to receiving all future proxy statements, proxy cards and annual reports electronically via e-mail or the Internet. To sign up for electronic delivery, please follow the instructions above to

vote using the Internet and, when prompted, indicate that you agree to receive or access stockholder communications electronically in future years.

VOTE BY PHONE - 1-800-690-6903

Use any touch-tone telephone to transmit your voting instructions up until 11:59 P.M. Eastern Time the day before the cut-off date or meeting date. Have your proxy card in hand when you call and then follow the instructions.

VOTE BY MAIL

Mark, sign and date your proxy card and return it in the postage-paid envelope we have provided or return it to Isis Pharmaceuticals, Inc., c/o Broadridge, 51 Mercedes Way, Edgewood, NY 11717.

TO VOTE, MARK BLOCKS BELOW IN BLUE OR BLACK INK AS FOLLOWS: x

M12727

KEEP THIS PORTION FOR YOUR RECORDS
DETACH AND RETURN THIS PORTION ONLY

THIS PROXY CARD IS VALID ONLY WHEN SIGNED AND DATED.

ISIS PHARMACEUTICALS, INC.

THE BOARD OF DIRECTORS RECOMMENDS A VOTE "FOR" ITEMS 1 THROUGH 3.

For All	Withhold All	For All Except
o	o	o

Vote On Directors

1. To elect as Directors of Isis Pharmaceuticals, Inc. the nominees listed below.

- 01) Richard D. DiMarchi
- 02) Frederick T. Muto

To withhold authority to vote For any individual nominee(s), mark "For All Except" and write the number(s) of the nominee(s) on the line below.

Vote On Proposals

2. To approve the amendment and restatement of our 2000 Employee Stock Purchase Plan (ESPP) to:
(i) extend the ESPP so that it will terminate on June 2, 2019; (ii) limit the evergreen provision such that it only adds 150,000 shares to the ESPP each year; (iii) limit the offering periods under the ESPP to a maximum of six months; and (iv) impose a minimum six-month holding period on shares purchased under the ESPP.

For	Against	Abstain
o	o	o

3. To ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2009 fiscal year.

o	o	o
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The shares represented by this proxy, when properly executed, will be voted in the manner directed herein by the undersigned Stockholder(s). **If no direction is made, this proxy will be voted FOR items 1 through 3.** If any other matters properly come before the meeting, or if cumulative voting is required, the persons named in this proxy will vote in their discretion.

P71856

Signature [PLEASE SIGN WITHIN BOX]

Date

Signature (Joint Owners)

Date

Directions

From Los Angeles and Points North:

- I-5S exit at Cannon Road
- Turn left- Continue on Cannon Road to Faraday
- Turn right on Faraday (light)
- Pass College
- Turn left onto Rutherford (look for Isis' signs) 1896 is located at your immediate right, immediately after the Marriott Residence Inn

From San Diego Airport, Downtown and Points South:

- I-5N exit Cannon Road, turn right
- Turn right on Faraday (light)
- Pass College
- Turn left onto Rutherford (look for Isis' signs) 1896 is located at your immediate right, immediately after the Marriott Residence Inn



Important Notice Regarding the Availability of Proxy Materials for the Annual Meeting:

The Notice and Proxy Statement and Form 10-K are available at www.proxyvote.com.

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ISIS PHARMACEUTICALS, INC.

THIS PROXY IS SOLICITED ON BEHALF OF THE BOARD OF DIRECTORS

ANNUAL MEETING OF STOCKHOLDERS

JUNE 2, 2009

The stockholder(s) hereby appoint(s) Stanley T. Crooke and B. Lynne Parshall, or either of them, as proxies, each with the power to appoint his or her substitute, and hereby authorizes them to represent and to vote, as designated on the reverse side of this ballot, all of the shares of Common Stock of Isis Pharmaceuticals, Inc. (the "Company") that the stockholder(s) is/are entitled to vote at the Annual Meeting of Stockholders to be held at 3:00 p.m., Pacific Time on June 2, 2009, at the Company's offices at 1896 Rutherford Road, Carlsbad, California 92008, and any adjournment or postponement thereof.

THIS PROXY, WHEN PROPERLY EXECUTED, WILL BE VOTED AS DIRECTED BY THE STOCKHOLDER(S). IF NO SUCH DIRECTIONS ARE MADE, THIS PROXY WILL BE VOTED FOR THE ELECTION OF THE NOMINEES LISTED ON THE REVERSE SIDE FOR THE BOARD OF DIRECTORS AND FOR EACH PROPOSAL.

PLEASE MARK, SIGN, DATE AND RETURN THIS PROXY CARD PROMPTLY USING THE ENCLOSED REPLY ENVELOPE

CONTINUED AND TO BE SIGNED ON REVERSE SIDE
