

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

SCHEDULE 14A INFORMATION

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

Filed by the Registrant x

Filed by a Party other than the Registrant o

Check the appropriate box:

- o Preliminary Proxy Statement
- o **Confidential, for Use of the Commission Only (as permitted by Rule 14a-6(e)(2))**
- x Definitive Proxy Statement
- o Definitive Additional Materials
- o Soliciting Material Pursuant to §240.14a-12

Isis Pharmaceuticals, Inc.

(Name of Registrant as Specified In Its Charter)

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

Payment of Filing Fee (Check the appropriate box):

- x No fee required.
- o Fee computed on table below per Exchange Act Rules 14a-6(i)(1) and 0-11.
 - (1) Title of each class of securities to which transaction applies:

 - (2) Aggregate number of securities to which transaction applies:

 - (3) Per unit price or other underlying value of transaction computed pursuant to Exchange Act Rule 0-11 (set forth the amount on which the filing fee is calculated and state how it was determined):

 - (4) Proposed maximum aggregate value of transaction:

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- o Fee paid previously with preliminary materials.
- o Check box if any part of the fee is offset as provided by Exchange Act Rule 0-11(a)(2) and identify the filing for which the offsetting fee was paid previously. Identify the previous filing by registration statement number, or the Form or Schedule and the date of its filing.
 - (1) Amount Previously Paid:

 - (2) Form, Schedule or Registration Statement No.:

 - (3) Filing Party:

 - (4) Date Filed:

April 23, 2012

ISIS PHARMACEUTICALS, INC.
2855 Gazelle Court
Carlsbad, CA 92010

**NOTICE OF
2012 ANNUAL MEETING OF STOCKHOLDERS
AND PROXY STATEMENT**

Dear Stockholders,

I am pleased to invite you to Isis Pharmaceuticals' 2012 Annual Meeting of Stockholders. We will host the meeting at our offices in Carlsbad, California on Thursday, June 7, 2012, at 2:00 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 2012, 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 through 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 telephone or through the Internet. If so, the voting form your nominee sends you will provide telephone and Internet voting 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 cannot attend, please note that we will make a webcast of the presentation available on the day of the meeting and for a limited time following the meeting at www.isispharm.com.(1) In this document, the words "Isis," "we," "our" and "us" refer only to Isis Pharmaceuticals, Inc. and its subsidiaries 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.
2855 Gazelle Court
Carlsbad, CA 92010**

NOTICE OF 2012 ANNUAL MEETING OF STOCKHOLDERS

Date: Thursday, June 7, 2012
Time: 2:00 p.m., Pacific Time
Place: Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

Dear Stockholders,

At our 2012 Annual Meeting, we will ask you to:

- **Proposal 1:** elect Frederick T. Muto to serve as a Director for a three-year term;
- **Proposal 2:** approve an amendment and restatement of the Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan, to, among other things,
 - provide for restricted stock unit awards; and
 - increase the shares reserved for issuance from 1,000,000 to 1,200,000 shares;
- **Proposal 3:** approve an extension to the term of the Isis Pharmaceuticals, Inc. Amended and Restated 1989 Stock Option Plan such that the new term will end on January 31, 2024;
- **Proposal 4:** make an advisory vote on executive compensation;
- **Proposal 5:** ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2012 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 9, 2012 you may vote at the Annual Meeting.

By order of the Board of Directors,

B. Lynne Parshall
Secretary

Carlsbad, California
April 23, 2012

ALL STOCKHOLDERS ARE CORDIALLY INVITED TO ATTEND THE MEETING IN PERSON. WHETHER OR NOT YOU EXPECT TO ATTEND THE MEETING, PLEASE VOTE BY TELEPHONE 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.
2855 Gazelle Court
Carlsbad, CA 92010

PROXY STATEMENT

QUESTIONS AND ANSWERS ABOUT THESE PROXY MATERIALS AND VOTING

Why did I receive a Notice regarding the availability of proxy materials on the Internet?

Isis' Board of Directors is soliciting your proxy to vote at the 2012 Annual Meeting of Stockholders, including at any adjournments or postponements of the meeting. We are distributing our Notice of Annual Meeting and Proxy Materials (the "Notice") using the Notice and Access procedures established by the United States Securities and Exchange Commission (the "SEC"). As a result, you received in the mail the 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 through the Internet or request printed proxy materials so you may vote by telephone or mail. 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 intend to mail the Notice on or about April 23, 2012 to all stockholders of record entitled to vote at the Annual Meeting.

Will I receive any other proxy materials by mail?

We may choose to send you a proxy card, along with a second Notice, on or after May 3, 2012.

Where and when is the Annual Meeting and how do I attend?

We will hold the meeting on Thursday, June 7, 2012, at 2:00 p.m. Pacific Time at our offices located at 2855 Gazelle Court, Carlsbad, California. You may find directions to the Annual Meeting at [\(2\)](http://www.isispharm.com) We discuss below information on how to vote in person at the Annual Meeting.

If you cannot attend, please note that we will make a webcast of the presentation available on the day of the meeting and for a limited time following the meeting at [\(2\)](http://www.isispharm.com)

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.

Who can vote at the Annual Meeting?

Only stockholders of record at the close of business on April 9, 2012 may vote at the Annual Meeting. On this record date, there were 100,183,526 shares of common stock outstanding and entitled to vote.

Stockholder of Record: Shares Registered in Your Name

If on April 9, 2012 your shares were registered directly in your name with our transfer agent, American Stock Transfer & Trust Company, then you are a stockholder of record. As a stockholder of record, you may vote in person at the meeting or vote by proxy. Whether or not you plan to attend the meeting, we urge you to fill out and return the proxy card or vote by proxy over the telephone or on the Internet as instructed under "How do I vote" below to ensure your vote is counted.

(2) Any information that is included on or linked to our website is not part of this Proxy Statement or any registration statement or report that incorporates this Proxy Statement by reference.

Beneficial Owner: Shares Registered in the Name of a Broker or Bank

If on April 9, 2012 your shares were not held in your name, but rather in an account at a brokerage firm, bank, dealer or other similar organization, then you are the beneficial owner of shares held in “street name” and that organization is forwarding the Notice to you. The organization holding your account is considered to be the stockholder of record for purposes of voting at the Annual Meeting. As a beneficial owner, you may direct your broker or other agent regarding how to vote the shares in your account. 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. (“Broadridge”) that also allows you to vote by telephone or through the Internet. If so, the voting form your nominee sends you will provide telephone and Internet instructions. You are also invited to attend the Annual Meeting.

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.

What am I voting on?

There are five matters scheduled for a vote:

- Proposal 1: elect Frederick T. Muto to serve as a Director for a three-year term;
- Proposal 2: approve an amendment and restatement of the Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors’ Stock Option Plan, to, among other things,
 - provide for restricted stock unit awards; and
 - increase the shares reserved for issuance from 1,000,000 to 1,200,000 shares;
- Proposal 3: approve an extension to the term of the Isis Pharmaceuticals, Inc. Amended and Restated 1989 Stock Option Plan such that the new term will end on January 31, 2024;
- Proposal 4: make an advisory vote on executive compensation; and
- Proposal 5: ratify the Audit Committee’s selection of Ernst & Young LLP as independent auditors for our 2012 fiscal year.

What if another matter is properly brought before the meeting?

The Board of Directors knows of no other matters that will be presented for consideration at the Annual Meeting. If any other matters are properly brought before the meeting, the persons named in the accompanying proxy intend to vote on those matters in accordance with their best judgment.

How do I vote?

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 telephone 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 2012 Annual Meeting and vote in person.

The procedures for voting are fairly simple:

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 telephone, 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 your broker or bank holds your shares 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. The proposal to ratify Ernst & Young LLP as independent auditors is a discretionary item. Proposals 1-4 regarding the election of a Director, approval of amendments to our equity incentive plans, and the advisory vote regarding executive compensation are non-discretionary items. 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.

A number of brokers and banks are participating in a program provided by Broadridge 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 telephone 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.

What if I return a proxy card or otherwise vote but do not make specific choices?

If you return a signed and dated proxy card or otherwise vote without marking voting selections, your proxyholder (one of the individuals named on your proxy card) will vote your shares as follows:

- “For” the election of the nominee for Director named in the proxy statement;
- “For” the approval of the amendment and restatement of the Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors’ Stock Option Plan;
- “For” the approval of extending the term of the Isis Pharmaceuticals, Inc. Amended and Restated 1989 Stock Option Plan;
- “For” the advisory approval of executive compensation; and
- “For” the ratification of the Audit Committee’s selection of Ernst & Young LLP as independent auditors for our 2012 fiscal year.

If any other matter is properly presented at the meeting, your proxyholder (one of the individuals named on your proxy card) will vote your shares using his or her best judgment.

Who is paying for this proxy solicitation?

Our Board of Directors is soliciting your proxy to vote at the Annual Meeting. We 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, but if we choose to engage Georgeson Stockholder Communications Inc. to render solicitation services, we will pay Georgeson its customary fee, which we estimate to be about \$12,000. 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.

What does it mean if I receive more than one Notice?

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

Can I change my vote after submitting my proxy?

Yes. 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 sent to 2855 Gazelle Court, Carlsbad, California 92010 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.

When are stockholder proposals due for next year’s Annual Meeting?

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 2013 Annual Meeting of Stockholders, you must send the proposal to us by no later than December 24, 2012. Stockholders wishing to submit proposals or Director nominations that are not to be included in such Proxy Statement and form of proxy must do so no later than the close of business on February 7, 2013. Stockholders should also review our bylaws, which contain additional requirements with respect to advance notice of stockholder proposals and Director nominations.

What is the quorum requirement?

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.

If there is no quorum, the holders of a majority of shares present at the meeting in person or represented by proxy may adjourn the meeting to another date.

How are votes counted?

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 9, 2012. 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. Except with respect to Proposal 1, election of a director, the inspector of election 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 election will not count them towards the vote total for any proposal. For Proposal 1, the inspector of election will not count abstentions and broker non-votes.

What are “broker non-votes”?

Broker non-votes occur when a beneficial owner of shares held in “street name” does not give instructions to the broker or nominee holding the shares as to how to vote on matters deemed “non-routine.” If your broker holds your shares in “street name,” and 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

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held in street name in the absence of your voting instructions. The proposal to ratify Ernst & Young LLP as independent auditors is a discretionary item. Proposals 1-4 regarding the election of a Director, approval of the amendments to our equity incentive plans, and the advisory vote regarding executive compensation are non-discretionary items. 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.

How many votes are needed to approve each proposal?

- For the election of a Director in an uncontested election, a Director nominee must receive a majority of the votes cast in person or by proxy in the election such that the number of shares voted “for” the nominee must exceed 50% of the votes cast with respect to that Director. Only “For” and “Withhold” votes will affect the outcome. Abstentions and broker non-votes will have no effect;
- To be approved, Proposal 2 regarding the amendment and restatement of the Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors’ Stock Option Plan must receive “For” votes from the holders of a majority of shares present and entitled to vote either in person or represented by proxy. If you mark your proxy to “Abstain” from voting, it will have the same effect as an “Against” vote. Broker non-votes will have no effect;
- To be approved, Proposal 3 regarding extending the term of the Isis Pharmaceuticals, Inc. Amended and Restated 1989 Stock Option Plan must receive “For” votes from the holders of a majority of shares present and entitled to vote either in person or represented by proxy. If you mark your proxy to “Abstain” from voting, it will have the same effect as an “Against” vote. Broker non-votes will have no effect;
- We will consider Proposal 4 regarding advisory approval of the compensation of our executive officers, to be approved if it receives “For” votes from the holders of a majority of shares either present in person or represented by proxy and entitled to vote. If you “Abstain” from voting, it will have the same effect as an “Against” vote. Broker non-votes will have no effect; and
- To be approved, Proposal 5, ratification of the selection of Ernst & Young LLP as our independent auditors for our 2012 fiscal year, must receive “For” votes from the holders of a majority of shares present in person or by proxy and entitled to vote. If you “Abstain” from voting, it will have the same effect as an “Against” vote.

How can I find out the results of the voting at the Annual Meeting?

We will announce preliminary voting results at the Annual Meeting. In addition, we will publish final voting results in a current report on Form 8-K that we expect to file within four business days after the Annual Meeting. If final voting results are not available to us in time to file a Form 8-K within four business days after the Annual Meeting, we intend to file a Form 8-K to publish preliminary results and, within four business days after we know the final results, file an additional Form 8-K to publish final results.

How can I elect to receive materials for future Annual Meetings electronically?

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 online;
- helping the environment by decreasing the use of paper documents;
- 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 our stockholder communications after you place your current vote at www.proxyvote.com.

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ELECTION OF DIRECTORS

Information about our Board of Directors

The Board is divided into three classes. Presently, the Board has seven members with two classes consisting of three Directors each and one class consisting of one Director. 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 the Board appoints. 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 the stockholders elect the Board member, he or she 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 our operation. The Board's goal is to optimize long-term value by providing guidance and strategic oversight to us on our stockholders' behalf.

Information about the 2012 Elections

The Board has nominated one Director for election at the 2012 Annual Meeting. The nominee currently serves as one of our Directors. Frederick T. Muto has served as a Director since March 2001 and has been re-elected by our stockholders each successive term. If re-elected, Mr. Muto will serve until the 2015 Annual Meeting or until his successor is elected and has qualified, or until his death, resignation or removal.

On December 13, 2011, the Board of Directors, upon recommendation of the Nominating, Governance and Review Committee, adopted our Amended and Restated Bylaws to, among other things, adopt a majority vote standard for the election of directors in uncontested elections. The new majority vote standard provides that to be elected, in an uncontested election, a director nominee must receive a majority of the votes cast in the election such that the number of shares voted "for" the nominee must exceed 50% of the votes cast with respect to that Director. The number of votes cast with respect to a Director's election excludes abstentions and broker non-votes with respect to that Director's election. In contested elections where the number of nominees exceeds the number of Directors to be elected, the vote standard will be a plurality of the shares present in person or by proxy and entitled to vote.

In addition, if a nominee who already serves as a Director is not elected, and no successor is elected, the Director will offer to tender his or her resignation to the Board of Directors. The Nominating, Governance and Review Committee will make a recommendation to the Board on whether to accept or reject the resignation, or whether to take other action. The Board will act on the Committee's recommendation and publicly disclose its decision and the rationale behind it within 90 days from the date of the certification of the election results. The Director who tenders his or her resignation will not participate in the recommendation of the Nominating, Governance and Review Committee or in the Board's decision. If a nominee's failure to be elected at the Annual Meeting results in a vacancy on the Board, then the Board can fill the vacancy.

The Nominating, Governance and Review Committee made its report to the Board on March 27, 2012. Following that report, the Board determined it would be in the best interests of Isis and its stockholders to nominate Mr. Muto as a Director to be elected at the Annual Meeting. We provide below a short biography for Mr. Muto and of each Director whose term of office will continue after the Annual Meeting. Mr. Muto has agreed to serve if elected, and we have no reason to believe that he cannot serve. However, if Mr. Muto cannot serve, we may vote your proxy for another nominee proposed by the Board, or the Board may reduce the number of authorized Directors.

Biography of the Nominee for Election for a Three-year Term Expiring at the 2015 Annual Meeting

Frederick T. Muto, age 58, has served as a Director of Isis since March 2001. Mr. Muto joined the law firm of Cooley LLP, outside counsel to Isis, in 1980 and became a partner in 1986. He is Chair of the firm's Business Department, a founding partner of Cooley LLP's San Diego office and serves on Cooley's management committee.

The Board believes Mr. Muto is uniquely suited to serve on the Board primarily because with over 30 years experience at one of the country's leading law firms focused on life sciences and technology companies, he provides us important advice regarding our strategic transactions, corporate governance and compensation matters.

THE BOARD UNANIMOUSLY RECOMMENDS A VOTE "FOR" THE ELECTION OF THE ABOVE NOMINEE.

Biographies of Directors Whose Terms Expire at the 2013 Annual Meeting

Stanley T. Crooke, M.D., Ph.D., age 67, 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.

The Board believes Dr. Crooke is uniquely suited to serve on the Board primarily because as the Chief Executive Officer and founder of Isis he has dedicated over 20 years to the discovery and development of antisense, our technology platform. He is the named inventor on some of the key patents in the field of RNA targeted therapeutics, and has over 30 years of drug discovery and development experience.

Joseph Klein, III, age 51, 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 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. Within the last five years, Mr. Klein formerly served on the board of directors of five publicly held biotechnology companies: BioMarin Pharmaceutical Inc., NPS Pharmaceuticals, Inc., OSI Pharmaceuticals, Inc., PDL BioPharma, Inc. and Savient Pharmaceuticals, Inc.

The Board believes that Mr. Klein is uniquely suited to serve on the Board and the Audit Committee because he is a Chartered Financial Analyst, and because he has extensive public company, venture investment, board, and financial advisory expertise in the life sciences industry.

John C. Reed, M.D., Ph.D., age 53, has served as a Director of Isis since February 2002. Dr. Reed served as the President and Chief Executive Officer since January 2002, and in 2010 he became CEO, Professor, and Donald Bren Chief Executive Chair, of Sanford-Burnham Medical Research Institute, an independent, nonprofit, public benefit organization dedicated to biomedical research. Dr. Reed has been with Sanford-Burnham Medical Research Institute for the past 19 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 University of Central Florida, and in the graduate Schools of Arts and Sciences at the University of Florida 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 approximately 800 scientific and medical journal publications. He currently serves as a director of Clovis Oncology, Inc. (formerly Pharmion Corporation), a publicly-traded specialty pharmaceutical company focused on oncology. Within the last five years, Dr. Reed formerly served as a director of Stratagene, Inc. and Repros Therapeutics Inc., both biopharmaceutical companies.

The Board believes Dr. Reed is uniquely suited to serve on the Board primarily because his scientific background and experience as the Chief Executive Officer of the prestigious Sanford-Burnham Medical Research Institute, as well as his extraordinary expertise reflected in his significant scientific and medical journal publications, help us evaluate our drug discovery and development opportunities.

Biographies of Directors Whose Terms Expire at the 2014 Annual Meeting

Spencer R. Berthelsen, M.D., age 60, has served as a Director of Isis since May 2002. Since 1980, he has practiced Internal Medicine with the Kelsey Seybold Clinic, a 370 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 has served as a Clinical Professor of Medicine at Baylor College of Medicine and the University of Texas Health Science Center of Houston. 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.

The Board believes Dr. Berthelsen is uniquely suited to serve on the Board because of his current position managing a large multispecialty group practice and 32 years of experience as a practicing physician.

B. Lynne Parshall, age 57, 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 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. Within the last five years, Ms. Parshall formerly served as a Director of CardioDynamics International Corporation and Corautus Genetics Inc., both biopharmaceutical companies.

The Board believes Ms. Parshall is uniquely suited to serve on the Board primarily because, as the Chief Operating Officer and an executive of the Company for nearly 20 years, she has valuable Company-specific experience and expertise. In addition, Ms. Parshall has over 25 years of experience structuring and negotiating strategic licensing and financing transactions in the life sciences field.

Joseph H. Wender, age 67, 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. Since January 2008, he has been a Senior Consultant to Goldman Sachs & Co. He is also an Independent Trustee of the Schwab Family of Funds and Director of Grandpoint Capital, a bank holding company.

The Board believes Mr. Wender is uniquely suited to serve on the Board primarily because with over 35 years of experience as an investment banker with Goldman, Sachs & Co., he provides us important advice regarding our financial reporting, corporate finance matters, strategic transactions, and compensation matters. Mr. Wender is also highly qualified to serve on the Audit Committee.

Independence of the Board of Directors

As required under The Nasdaq Stock Market ("Nasdaq") listing standards, a majority of the members of a listed Company's Board of Directors must qualify as "independent," as affirmatively determined by the 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 and applicable SEC rules and regulations, 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 and SEC rules and regulations, 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 has a material

Information Regarding the Board of Directors and its Committees

Board Committees and Leadership Structure

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 5605(a)(2) of the Nasdaq listing standards and applicable SEC rules and regulations;
- is not an officer or employee of Isis; and
- is free of any relationship that would interfere with his individual exercise of independent judgment with regard to Isis.

Our Chief Executive Officer is the Chairman of the Board. The Board believes that Isis’ CEO is best situated to serve as Chairman because he has served as CEO since Isis was formed over 23 years ago and he is the Director most familiar with our science, business and industry. Because of that experience, he is the Director most capable of effectively identifying strategic priorities and leading the discussion and execution of strategy. Independent Directors and management have different perspectives and roles in strategy development. Our independent Directors bring experience, oversight and expertise from outside the company and industry, while the CEO brings Company-specific experience and expertise. The Board believes that the combined role of Chairman and CEO promotes strategy development and execution, and facilitates information flow between management and the Board, which are essential to effective governance.

One of the key responsibilities of the Board is to develop strategic direction and hold management accountable for executing the established strategy. As part of each Board meeting, our independent Directors meet in executive session without the presence of our employee Directors. We do not formally have a single “lead independent director.” Instead the Chairpersons of the Audit Committee, the Compensation Committee, and the Nominating, Governance and Review Committee on a rotating basis preside over the executive sessions. This rotating approach provides added balance to the process, thereby ensuring healthy discussion since the same individual does not continuously lead each executive session. In addition, Mr. Wender (chairman of the Audit Committee) and Mr. Muto (independent Board member) are part of the committee that sets the agenda for each Board meeting. The Board believes the combined role of Chairman and CEO, together with the executive sessions and agenda setting described above, is in the best interest of stockholders because it provides the appropriate balance between developing strategy and independently overseeing management.

Risk Oversight

Our Board administers its risk oversight function directly and through both its Audit Committee and its Nominating, Governance and Review Committee. The Audit Committee oversees management of financial risks and related party transactions. The Nominating, Governance and Review Committee manages risks associated with the independence of the Board and potential conflicts of interests at the Board level, and periodically reviews our policies and procedures, and makes recommendations when appropriate. We provide a complete description of each committee and its respective roles and responsibilities on pages 11 through 14. While each committee is responsible for evaluating certain risks and overseeing the management of such risks, these committees regularly inform the entire Board of Directors about such risks through committee reports.

In addition to the formal compliance program, the Board, the Audit Committee and the Nominating, Governance and Review Committee encourage management to promote a corporate culture that understands risk management and incorporates it into the overall corporate strategy and day-to-day business operations. Our risk management structure also includes an ongoing effort to assess and analyze the most likely areas of future risk for Isis. As a result, the Board, the Audit Committee, and the Nominating, Governance and Review Committee periodically ask our executives to discuss the most likely sources of material future risks and how we are addressing any significant potential vulnerability.

Meetings and Attendance; Committee Members

The Board met five times in 2011, which included four regularly scheduled meetings and one special meeting. During 2011, all Directors attended 100% of the meetings of the Board except Dr. Berthelsen who attended 80%. In addition, all Directors attended 100% of the meetings of the Board committees on which they served. We encourage each member of the Board to attend the Annual Meeting of Stockholders.

Board Committee Members

The table below provides membership and meeting information for fiscal 2011 for each of the Board committees and identifies our current Board and Committee members.

<u>Name</u>	<u>Audit</u>	<u>Compensation</u>	<u>Nominating, Governance and Review</u>	<u>Attended 2011 Annual Meeting</u>
Dr. Spencer R. Berthelsen	X	X*	X*	X
Dr. Stanley T. Crooke	—	—	—	X
Dr. Richard D. DiMarchi(1)	—	X	—	X

Mr. Joseph Klein	X	—	—	X
Mr. Frederick T. Muto(2)	—	—	—	X
Ms. B. Lynne Parshall	—	—	—	X
Dr. John C. Reed	—	X	X	X
Mr. Joseph H. Wender(3)	X*	X	—	—
Total meetings in fiscal year 2011	4	3(3)	2	

* Committee Chairperson

- (1) Dr. DiMarchi resigned as a Director at the June 16, 2011 Board/Annual Meeting.
- (2) Mr. Muto serves as counsel to the Nominating, Governance and Review Committee.
- (3) Mr. Wender was appointed to the Compensation Committee at the June 16, 2011 Board meeting.
- (4) Also acted by written consent 14 times. 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, including a session with the auditors where Isis' employees and management are not present;
- 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;
- setting and approving our investment policy;

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- 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 SEC regulations. Our Board has determined that the Audit Committee's financial expert is Mr. Wender based on, among other things, his over 36 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 2011, the Audit Committee met four times and did not act by unanimous written consent. 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.(3) Each member meets the membership criteria set forth in the Audit Committee charter and as stated above.

Compensation Committee

The primary function of the Compensation Committee of the Board of Directors is to review, modify (as needed) and approve our overall compensation strategy and policies and approve the compensation and other terms of employment of our executive officers, including our Chief Executive Officer. We

include a full list of the Compensation Committee's responsibilities as part of the Compensation Discussion and Analysis ("CD&A") set forth on pages 39 through 46 of this Proxy Statement. The charter of the Compensation Committee grants the Compensation Committee full access to all of our books, records, facilities and personnel, as well as authority to obtain, at our expense, 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 independent 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.

We also have a Non-Management Stock Option Committee that, as delegated by the Compensation Committee, may award stock options and restricted stock unit awards 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 three times in 2011 and acted by unanimous written consent 14 times. You can find our Compensation Committee charter on our corporate website at www.isispharm.com.(3)

The Compensation Committee reviews with management Isis' CD&A to consider whether to recommend that we include the CD&A in our Proxy Statements and other filings.

(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.

Compensation Committee Interlocks and Insider Participation

As noted above, during the fiscal year ended December 31, 2011, our Compensation Committee was composed of Drs. Berthelsen, DiMarchi (until June 16, 2011) and Reed. Mr. Wender was appointed to the Compensation Committee at the June 16, 2011 Board meeting when Dr. DiMarchi resigned from the Board. 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 our Board of Directors. As part of this process, the Nominating, Governance and Review Committee will consider nominees recommended by our 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;
- periodically reviewing our policies and procedures and recommending appropriate changes, if any;
- annually reviewing and assessing the adequacy of our corporate governance guidelines and recommending any proposed changes to the Board for approval; and
- performing such other functions as may be necessary or convenient for the efficient discharge of the foregoing.

The Nominating, Governance and Review Committee met twice during 2011. You can find our Nominating, Governance and Review Committee charter on our corporate website at www.isispharm.com.(4)

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.

(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.

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 Isis' affairs;
- 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 - Diversity Discussion

In considering Director nominations, the Nominating Committee evaluates and considers the total mix of competencies represented on the Board as a whole, as well as the competencies each member, or nominee brings to the Board. In general, the constitution of the Board is diversified across three large categories: (1) investment banking, financial accounting and corporate governance experience; (2) medical and scientific expertise; and (3) employee versus non-employee directors. By selecting individuals who have investment banking, financial accounting and corporate governance backgrounds, we gain valuable experience that ensures we are managing our financial resources appropriately, reporting our financial results fairly and accurately, and generally running our business consistent with current good corporate practices. As a cutting edge drug discovery and development company, we also greatly benefit from Board members who themselves are scientists and medical doctors. This way we can set and adjust our strategy and objectives based on the results we generate from our research and development efforts. In different ways, these first two categories allow us to effectively manage our cash and make prudent investments in our technology to achieve the greatest likelihood of success. As a general rule, we try to evenly balance the Board members across these first two categories.

Regarding the third category, a mix of employee and non-employee directors offers different perspectives for the Board to consider when making decisions. Employee directors can provide the Board valuable insight regarding our day-to-day operations, which can help the Board make important management and compensation decisions. Non-employee directors can compare the opportunities and challenges presented to Isis against the facts and circumstances these Directors are experiencing outside Isis. As a rule, we have a significantly higher number of non-employee directors vs. employee directors. Finally, we do not discriminate against nominees on the basis of race, religion, national origin, sexual orientation, disability or any other basis prohibited by applicable law.

Director Nominations - Process

The Nominating, Governance and Review Committee will consider Director candidates our stockholders recommend. 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, our 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 included in our Proxy Statement may do so by delivering a written recommendation to the Secretary of Isis at the following address: 2855 Gazelle Court, Carlsbad, CA 92010, by December 24, 2012. Submissions must include:

- the name, age, business address and residence address of the nominee;
- the principal occupation or employment of the nominee;
- the stock ownership in Isis of the nominee;
- the stock ownership in Isis of the stockholder making the nomination, including any trading in derivative securities that may disguise ownership occurring within the last 12 months;
- the information relating to the nominee that is required to be disclosed in solicitations of proxies under applicable securities laws;

- the nominee’s written consent to being named in the proxy statement as a nominee and to serving as a director if elected;
- other information as we may reasonably require to determine the eligibility of the proposed nominee to serve as an independent director or that could be material to a reasonable stockholder’s understanding of the independence of the proposed nominee; and
- any voting commitments the nominee has to third parties.

In addition, the nominee will need to complete a written questionnaire regarding the background and qualifications of the nominee, and the background of any other person or entity on whose behalf the nomination is being made. The nominee must also agree to comply with all of our applicable publicly disclosed corporate governance, conflict of interest, confidentiality and stock ownership and trading policies and guidelines. The description of the requirements for Director nominations set forth above is qualified in its entirety by reference to our full and complete Amended and Restated Bylaws, a copy of which is available by contacting our Corporate Secretary; or as an exhibit to our Current Report on Form 8-K filed with the SEC on December 14, 2011. 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 our 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 2855 Gazelle Court, Carlsbad, CA 92010. If you wish to communicate with the independent Directors about your concerns or issues, you may address correspondence to a particular Director or to the independent Directors generally. If you do not name a particular Director, depending on the subject matter, we will forward the letter to the Chair of the Audit, Compensation, or Nominating, Governance and Review Committee. One or more of our employees designated by the Board will review these communications and will determine whether to present the materials 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, commercial 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

We have adopted a Code of Ethics that applies to all officers, Directors and employees. We 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.⁽⁵⁾

Corporate Governance Guidelines

In 2003, the Board of Directors documented the governance practices we follow by adopting corporate governance guidelines to ensure that the Board will have the necessary authority and practices in place to review and evaluate our business operations as needed and to make decisions that are independent of our 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.⁽⁵⁾

⁽⁵⁾ 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 AN AMENDMENT AND RESTATEMENT OF THE ISIS PHARMACEUTICALS, INC. 2002 NON-EMPLOYEE DIRECTORS’ STOCK OPTION PLAN

In this Proposal 2, we are requesting our stockholders approve an amendment and restatement of the Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors’ Stock Option Plan (the “Directors’ Plan”) which the Board of Directors adopted on March 27, 2012, subject to stockholder approval. The two primary purposes of the amendment and restatement are to:

- provide for a combination of stock options and restricted stock unit awards (“RSU”) under the Directors’ Plan, including as part of the non-discretionary awards; and
- increase the total number of shares authorized for issuance under the Directors’ Plan by 200,000 shares, from 1,000,000 shares to 1,200,000 shares, which will enable us to continue to grant awards to deserving individuals and remain competitive with our industry peers.

Background for the Current Requests and Expected Future Grant Practices

We believe granting a combination of RSU awards and stock options to our Directors will benefit Isis because it will:

- strengthen the retention value of the annual stock-based compensation;
- require fewer shares, thereby reducing dilution;
- provide the same stock-based compensation as our employees; and
- encourage long term holding because stock settlement for RSU awards does not require a same-day-sale.

We believe increasing the authorized shares under the Directors' Plan from 1,000,000 shares to 1,200,000 shares will benefit Isis because:

- having too few and less competitive equity compensation award types would limit our opportunities to attract unique and highly qualified talent because it would reduce our flexibility and ability to grant stock awards to our new and existing Directors; and
- with the additional 200,000 shares, we anticipate that we will not need to request additional shares under the Directors' Plan until at least the 2015 Annual Meeting.

The affirmative vote of a majority of the votes cast at the Annual Meeting, at which a quorum is present, either in person or by proxy, is required to approve the proposed amendment and restatement of the Directors' Plan discussed above. If you hold your shares through a broker and you do not instruct the broker on how to vote on this proposal, your broker will not have the authority to vote your shares. Abstentions and broker non-votes will each be counted as present for purposes of determining the presence of a quorum. If you indicate on your proxy to "Abstain" from voting, it will have the same effect as an "Against" vote for this proposal. Broker non-votes will not have any effect on the outcome of this proposal.

THE BOARD UNANIMOUSLY RECOMMENDS A VOTE "FOR" APPROVAL OF PROPOSAL 2.

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

Purpose

The purpose of the Directors' Plan is to:

- retain the services of persons now serving as our non-employee Directors;
- attract and retain the services of persons capable of serving on our Board of Directors; and
- incentivize our non-employee Directors to exert maximum efforts to promote our success.

Administration

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

Stock Subject To The Directors' Plan

An aggregate of 1,200,000 shares of common stock were authorized by the Board for issuance under the Directors' Plan, subject to stockholder approval of this Proposal 2. As of March 30, 2012, there were options to purchase 625,000 shares of common stock issued and outstanding under the Directors' Plan and Directors had exercised options to purchase 155,500 shares. On July 1, 2012, we expect to grant options to purchase a total of 75,000 shares under the Directors' Plan. This means that if our stockholders do not approve this Proposal 2, after July 1, 2012, we would only have approximately 144,500 shares remaining for future grant under the Directors' Plan, which would limit our ability to attract and retain capable Board members. However, if our stockholders approve this Proposal 2, then on July 1, 2012 we would grant a combination of stock options and RSU awards covering an aggregate of 62,500 shares, and following these grants we would have approximately 357,000 shares remaining for future grant under the Directors' Plan, which should allow us to properly incentivize our Directors at least until the 2015 Annual Meeting.

On March 30, 2012 the last reported sales price of our common stock on the Nasdaq Global Select Market was \$8.77 per share.

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

Eligibility, Option Grants, RSU Awards

The Directors' Plan, as amended by this Proposal 2, provides that we may only grant options and RSU awards to a non-employee Director. Under the Directors' Plan a "non-employee Director" is a Director of Isis or one of our affiliates who is not otherwise an employee of Isis or any affiliate. Five of our seven current Directors, all except Dr. Crooke and Ms. Parshall, are eligible to participate in the Directors' Plan.

Options granted under the Directors' Plan are nonstatutory stock options, meaning they are not intended to qualify as incentive stock options within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended (the "Code").

In the past, the Directors' Plan provided for nondiscretionary grants of stock options to the non-employee Directors as follows:

- an initial grant of an option to purchase 30,000 shares of common stock to each person when he or she first becomes a non-employee Director of Isis, and
- an annual grant, on July 1, or the next business day should such date be a Saturday, Sunday or holiday, of an option to purchase 15,000 shares of common stock to each non-employee Director.

Under the proposed amendments to the Directors' Plan under this Proposal 2, the 30,000 share initial nondiscretionary grants and 15,000 share annual nondiscretionary grants would be allocated between stock options and RSU awards using the same allocation methodology the Compensation Committee most recently approved for allocating the stock-based compensation for Isis' employees. Specifically, the Compensation Committee sets the percentage, between 0% and 100%, of stock-based compensation that will be allocated to stock options and RSU awards. We refer to the allocation for stock options as the "Option Allocation Percentage," and the allocation for RSU awards as the "RSU Allocation Percentage." For example, for 2012, the Compensation Committee has set the Option Allocation Percentage at 75% stock options and the RSU Allocation Percentage at 25% RSU awards. In addition, since RSU awards do not require the Directors to pay an exercise price, the RSU awards generally have a higher value than stock options. As such, the Compensation Committee sets an additional percentage to adjust the RSU allocation downward based on the value an RSU has on the date of grant versus a stock option. We call this additional percentage the "RSU:Option Valuation Ratio." For example, for 2012 the Compensation Committee has set the RSU:Option Valuation Ratio at 33.33%, because the Compensation Committee has determined that an RSU award for *one* share of Isis' common stock on the date of grant is worth about the same as an option to purchase *three* shares of Isis' common stock (i.e. 1:3 = 33.33%). The RSU:Option Valuation Ratio can never be more than 1:1, or 100%.

Therefore, if our stockholders approve this Proposal 2, the Directors' Plan will provide for nondiscretionary grants of stock options and RSU awards to the non-employee Directors as follows:

- *Initial Grants*
 - an initial grant of a stock option to purchase shares of common stock to each person when he or she first becomes a non-employee Director of Isis equal to 30,000 *multiplied by* the Option Allocation Percentage, and
 - an initial grant of an RSU Award to each person when he or she first becomes a non-employee Director of Isis in an amount equal to 30,000 *multiplied by* the RSU Allocation Percentage, as further adjusted by *multiplying by* the RSU:Option Value Ratio.
 - For example, using the Option Allocation Percentage of 75%, RSU Allocation Percentage of 25%, and the RSU:Option Value Ratio of 33.33% that have been approved for 2012 by the Compensation Committee, a new non-employee Director joining the Board in 2012 would receive an initial stock option to purchase 22,500 shares of common stock (i.e. 30,000 x 75%) and an RSU Award worth 2,500 shares of common stock (i.e. 30,000 x 25% x 33.33%).
- *Annual Grants*
 - an annual grant, on July 1, or the next business day should such date be on a Saturday, Sunday or holiday, of a stock option to purchase shares of common stock to each non-employee Director equal to 15,000 *multiplied by* the Option Allocation Percentage, and
 - an annual grant, on July 1, or the next business day should such date be on a Saturday, Sunday or holiday, of an RSU Award to each non-employee Director in an amount equal to 15,000 *multiplied by* the RSU Allocation Percentage, as further adjusted by *multiplying by* the RSU:Option Value Ratio.
 - For example, using the Option Allocation Percentage of 75%, RSU Allocation Percentage of 25%, and the RSU:Option Value Ratio of 33.33% that have been approved for 2012 by the Compensation Committee, on July 2, 2012, each non-employee Director would receive a stock option to purchase 11,250 shares of common stock (i.e. 15,000 x 75%) and an RSU Award worth 1,250 shares of common stock (i.e. 15,000 x 25% x 33.33%).

We believe the combination grant of stock options and RSU Awards provides a better incentive and retention value than just stock options, and requires fewer shares.

Terms of Options

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

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

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

A Director may exercise an option under the Directors' Plan by written notice to us, specifying the number of full shares of common stock to be purchased accompanied by payment of the purchase price.

Exercise Price; Payment. The exercise price of options granted under the Directors' Plan is equal to 100% of the fair market value of the common stock on the date granted; however, an option may be granted with a lower exercise price if the option is granted pursuant to an assumption or substitution for another option in a manner which satisfies the provision of Section 424(a) of the Code. Optionholders must pay the exercise price of options granted under

the Directors' Plan in cash, or pursuant to a "same-day-sale" under Regulation T. To the extent provided by the terms of an option, an optionholder may satisfy any federal, state or local tax withholding obligation relating to the exercise of such option by a cash payment upon exercise.

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

- an optionholders' spouse, children (by birth or adoption), stepchildren, grandchildren, or parents;
- a trust or other entity established solely for the optionholders' benefit or the benefit of the optionholders' spouse, children (by birth or adoption), stepchildren, grandchildren, or parents for estate planning purposes; or
- an organization which is exempt from taxation under Section 501(c)(3) of the Code or to which tax-deductible charitable contributions may be made under Section 170 of the Code.

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

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

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

Terms of Restricted Stock Unit Awards

Each RSU award under the Directors' Plan is subject to the following terms and conditions:

Consideration. At the time of grant of an RSU award, the Board will determine the consideration, if any, to be paid by the Participant upon delivery of each share of common stock subject to the RSU award. The consideration to be paid (if any) by the Participant for each share of common stock subject to an RSU award may be paid in any form of legal consideration that may be acceptable to the Board, in its sole discretion, and permissible under applicable law.

Vesting. Each RSU award will vest as follows: one-fourth of the shares subject to the RSU award shall vest on each annual anniversary of the date of grant provided that the RSU award recipient has, during the entire year prior to such vesting date, continuously served as a non-employee Director or as an employee of or consultant to Isis or one of our affiliates.

Payment. An RSU award may be settled by the delivery of shares of common stock, their cash equivalent, any combination thereof or in any other form of consideration, as determined by the Board and contained in the RSU award agreement.

Additional Restrictions. At the time of the grant of an RSU award, the Board, as it deems appropriate, may impose such restrictions or conditions that delay the delivery of the shares of common stock (or their cash equivalent) subject to an RSU award to a time after the vesting of such RSU award.

Dividend Equivalents. Dividend equivalents may be credited in respect of shares of common stock covered by an RSU award, as determined by the Board and contained in the RSU award agreement. At the sole discretion of the Board, such dividend equivalents may be converted into additional shares of common stock covered by the RSU award in such manner as determined by the Board. Any additional shares covered by the RSU award credited by reason of such dividend equivalents will be subject to all of the same terms and conditions of the underlying RSU award agreement to which they relate.

Termination of Continuous Service. Except as otherwise provided in the applicable award agreement, such portion of the RSU award that has not vested will be forfeited upon the RSU award recipient's termination of continuous service as a non-employee Director, or as an employee of or consultant to Isis or one of our affiliates.

Adjustment Provisions

If any change is made in, or other event occurs with respect to, the common stock subject to the Directors' Plan, or subject to any stock award, without the receipt of consideration by Isis (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by Isis) (each, a "Capitalization Adjustment"), the Directors' Plan will be appropriately adjusted in the class(es) and maximum number of securities subject both to the Directors' Plan pursuant to the shares reserve and to the nondiscretionary stock awards, and the outstanding stock awards will be appropriately adjusted in the class(es) and number of securities and price per share, if applicable, of common stock subject to such outstanding stock awards. The Board will make such adjustments, and its determination will be final, binding and conclusive. The conversion of any convertible securities of Isis will not be treated as a transaction "without receipt of consideration" by Isis.

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

If there is a dissolution or liquidation of Isis, then all outstanding stock awards under the Directors' Plan will terminate immediately prior to the completion of the dissolution or liquidation.

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

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

Option Repricing Prohibited

The Board cannot, without first obtaining the affirmative vote of a majority of the shares present or represented and entitled to vote at a duly convened meeting of stockholders, (1) reduce the exercise price of any stock options under the Directors' Plan that are currently outstanding, or (2) cancel any outstanding stock options under the Directors' Plan and grant in substitution therefore new stock options under the Directors' Plan at a lower exercise price, including entering into any "6 month and 1 day" cancellation and re-grant program, regardless of whether or not the cancelled stock options revert to and again become available for issuance under the Directors' Plan.

Duration, Amendment and Termination

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

Unless sooner terminated and subject to stockholder approval of this Proposal 2, the Directors' Plan will terminate on June 1, 2020.

Federal Income Tax Information

Nonstatutory Stock Options

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

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

Upon disposition of the stock, the optionholder will recognize a capital gain or loss equal to the difference between the selling price and the sum of the amount paid for such stock plus any amount recognized as ordinary income upon exercise of the option. Such gain or loss will be long-term or short-term depending on whether the stock was held for more than one year.

Restricted Stock Unit Awards

Generally, the recipient of a stock unit structured to conform to the requirements of Section 409A of the Code or an exception to Section 409A of the Code will recognize ordinary income at the time the stock is delivered equal to the excess, if any, of the fair market value of the shares of our common stock received over any amount paid by the recipient in exchange for the shares of our common stock. To conform to the requirements of Section 409A of the Code, the shares of our common stock subject to a stock unit award may generally be delivered only upon one of the following events: a fixed calendar date (or dates), separation from service, death, disability or a change in control. If delivery occurs on another date, unless the stock units otherwise comply with or qualify for an exception to the requirements of Section 409A of the Code, in addition to the tax treatment described above, the recipient will owe an additional 20% federal tax and interest on any taxes owed.

The recipient's basis for the determination of gain or loss upon the subsequent disposition of shares acquired from stock units will be the amount paid for such shares plus any ordinary income recognized when the stock is delivered.

Subject to the requirement of reasonableness, the provisions of Section 162(m) of the Code and the satisfaction of a tax reporting obligation, we will generally be entitled to a tax deduction equal to the taxable ordinary income realized by the recipient of the stock award.

New Plan Benefits Table

The following table presents certain information with respect to stock options and RSU awards we expect to grant under the Directors' Plan for services rendered during the fiscal year ending December 31, 2012 to our non-employee Directors, assuming stockholder approval of this Proposal 2. This table assumes that each non-employee Director continues as one of our Directors throughout the year and that we do not elect any additional non-employee Directors. This information is for illustration only and may not be indicative of grants that are made in the future under the Directors' Plan.

NEW PLAN BENEFITS AMENDED AND RESTATED 2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN

Name of Non-Employee Director	Number of Option Shares (15,000 x 75%)	Number of Restricted Stock Unit Awards (15,000 x 25% x 33.33%)
Spencer R. Berthelsen	11,250	1,250
Joseph Klein, III	11,250	1,250
Frederick T. Muto	11,250	1,250
John C. Reed	11,250	1,250
Joseph H. Wender	11,250	1,250
Non-Employee Directors as a Group	56,250	6,250

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PROPOSAL 3

AMENDMENT TO THE 1989 STOCK OPTION PLAN TO EXTEND THE TERM

In June 1989, our Board of Directors adopted, and our stockholders subsequently approved, our 1989 Stock Option Plan (the "1989 Plan"). In this Proposal 3, we are requesting stockholders to approve an amendment to the 1989 Plan to extend its term from January 31, 2014 to January 31, 2024. The Board of Directors approved the amendment on March 27, 2012, subject to stockholder approval.

Below is a high-level summary of the terms of the 1989 Plan. Please be sure to read the more detailed description of the 1989 Plan contained in this Proposal 3. The 1989 Plan, among other things:

- Has a term ending on January 31, 2024 if our stockholders approve this Proposal 3;
- Prohibits the repricing of any option outstanding under the 1989 Plan unless approved by our stockholders;
- Is limited to the grant of options and does not authorize stock bonuses or restricted stock awards;
- Limits the term of each newly granted option to 7 years;
- Requires that each newly granted option not become fully vested until a date at least two years after the date of grant, except in the case of certain corporate events;
- Limits our ability to accelerate the vesting of stock options to the death, disability, or retirement of the optionee, or a change of control;
- Requires all options outstanding under the 1989 Plan to have an exercise price of not less than 100% of the fair market value of our common stock on the date of grant;
- Is administered by our Compensation Committee, which is composed entirely of independent Directors; and
- Requires that the exercise price for options outstanding under the 1989 Plan can only be paid in cash.

Our management, Board and Compensation Committee believe that stock options are a key aspect of our ability to attract and retain qualified personnel in the face of intense competition for experienced scientists and other personnel among many pharmaceutical and health care companies. The Board, upon the recommendation of the Compensation Committee, has approved a ten year extension of the 1989 Plan.

In addition, our 2000 Broad-Based Equity Incentive Plan expired in January 2010, so we may no longer grant new options under the 2000 Broad-Based Equity Incentive Plan.

A total of 20,000,000 shares are authorized for issuance under the 1989 Plan. As of March 30, 2012, a total of 8,952,854 options were granted and outstanding, 5,001,328 of which were vested and exercisable; and options to purchase a total of 9,242,270 shares had been exercised under the 1989 Plan. This means that as of March 30, 2012, 1,804,876 shares were available under the 1989 Plan for future grant. The 1989 Plan is our primary vehicle for granting stock options to our employees. If our stockholders do not approve this Proposal 3, and as a consequence, the 1989 Plan expires on January 31, 2014, we cannot continue to grant options under the 1989 Plan. We do not want to lose what we believe is a valuable tool to recruit, retain and motivate our employees to increase stockholder value.

Required Vote and Board of Directors Recommendation

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 2012 Annual Meeting will be required to approve the amendment to the 1989 Plan. If you hold your shares through a broker and you do not instruct the broker on how to vote on this proposal, your broker will not have the authority to vote your shares. Abstentions and broker non-votes will each be counted as present for purposes of determining the presence of a quorum. If you indicate on your proxy to "Abstain" from voting, it will have the same effect as an "Against" vote for this proposal. Broker non-votes will not have any effect on the outcome of this proposal.

The Board of Directors believes that the proposed amendment of the 1989 Plan is in the best interests of Isis and our stockholders for the reasons stated above.

THE BOARD UNANIMOUSLY RECOMMENDS A VOTE “FOR” APPROVAL OF PROPOSAL 3.

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The following description of the 1989 Plan, as amended, is qualified in all respects by the specific terms of the 1989 Plan, a copy of which was filed with this Proxy Statement.

Purpose

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

Under the 1989 Plan, we cannot grant stock bonuses and restricted stock awards.

Administration

The 1989 Plan authorizes the Compensation Committee to administer the 1989 Plan. Each person serving on the Compensation Committee is a “non-employee Director” within the meaning of Rule 16b-3 of the Exchange Act, an “outside Director” within the meaning of Section 162(m) of the Code and an “independent Director” within the meaning of applicable Nasdaq listing standards. As used herein with respect to the 1989 Plan, the “Committee” refers to the Compensation Committee and the Non-Management Stock Option Committee.

The Committee has the power to construe and interpret the 1989 Plan and, subject to the provisions of the 1989 Plan, to:

- select the persons to whom Options are to be made;
- designate the number of shares covered by each Option;
- determine whether an Option is an incentive stock option or a supplemental stock option; and
- establish vesting schedules, to specify the exercise price and, subject to certain restrictions, specify any other terms.

We believe limiting administration to the Compensation Committee is important because the Compensation Committee must be composed entirely of independent Directors.

The Compensation Committee has delegated to the Non-Management Stock Option Committee the power to grant options, on predefined terms, to our employees who are below the level of director.

Eligibility

We may only grant incentive stock options under the 1989 Plan to our key employees, including officers. In addition, key employees, including officers, Directors and consultants are eligible to receive supplemental or nonstatutory options. As of March 30, 2012, we had approximately 339 employees and seven Directors who were eligible to receive options under the 1989 Plan.

We cannot grant an incentive stock option under the 1989 Plan to any person who, at the time of the grant, owns (or is deemed to own) stock representing more than 10% of the total combined voting power of all classes of our stock, unless the option exercise price is at least 110% of the fair market value of the stock subject to the option on the date of grant, and the term of the option does not exceed five years from the date of grant. In addition, the aggregate fair market value, determined at the time of grant, of the shares of common stock that an optionee may exercise under such incentive options during any calendar year may not exceed \$100,000. Further, the 1989 Plan contains a per-employee, per-calendar year grant limitation equal to 294,873 shares.

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Stock Subject to the 1989 Plan

A total of 20,000,000 shares of our common stock are authorized for issuance under the 1989 Plan. If options granted under the 1989 Plan expire or otherwise terminate without being exercised, the common stock not purchased pursuant to such options again becomes available for issuance under the 1989 Plan.

Option Budget and Potential Dilution

Each year the Compensation Committee approves a budget that sets the number of stock-based awards we can grant our employees for annual merit awards. We do not grant stock-based awards that exceed this budget without the Compensation Committee’s approval. Over the past five years, the average merit award stock budget set by the Compensation Committee has been approximately 1.6% of our outstanding common stock on an issued and outstanding basis. We believe the option budget is an important tool to balance our equity compensation objectives with stockholder interests. Since the option budget has historically been 1.6% of our outstanding common stock on an issued and outstanding basis, we believe we have administered our stock option plans in a way that minimizes the potential dilution to our stockholders.

Terms of Options

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

Exercise Price; Payment. The exercise price of Options under the 1989 Plan may not be less than the fair market value of the common stock subject to the Option on the date of the option grant, and in some cases may not be less than 110% of such fair market value (see “Eligibility” above). At March 30, 2012, the closing price of our common stock as reported on the Nasdaq Global Select Market was \$8.77 per share.

An optionholder must pay the exercise price of Options granted under the 1989 Plan either: in cash at the time of exercise or pursuant to a “same-day sale” program developed pursuant to Regulation T of the Federal Reserve Board.

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

Option Exercise. Options granted under the 1989 Plan may become exercisable in cumulative increments, or “vest,” as determined by the Compensation Committee. Shares covered by currently outstanding options under the 1989 Plan typically vest at the rate of 25% per year after year one and 2.08% per month thereafter for three years, as long as the optionee’s employment or service as a consultant or Director continues. We may set different vesting terms for future options we grant under the 1989 Plan. However, no Option granted to an employee will, unless otherwise provided by the 1989 Plan in very limited circumstances (see Effect of Certain Corporate Events below), become fully vested in a period of less than two years after the grant of such Option.

Limitation on Accelerated Vesting. The Compensation Committee has the power to accelerate the time during which an option may be exercised only in the case of the death, disability, or retirement of the optionee, or upon a change of control.

Term. The maximum term of options under the 1989 Plan is seven years, except that in certain cases the maximum term is five years (see “Eligibility”). With certain exceptions, options under the 1989 Plan terminate three months after the optionee ceases to render services to us.

Prohibition of Option Repricing

The 1989 Plan expressly provides that, without the approval of a majority of votes cast in person or by proxy at a meeting of stockholders, we cannot cancel outstanding options in exchange for granting new options at a lower exercise price or amend outstanding options to reduce the exercise price.

Adjustment Provisions

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

Effect of Certain Corporate Events

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

Duration, Amendment and Termination

The Compensation Committee may suspend or terminate the 1989 Plan without stockholder approval or ratification at any time or from time to time. Unless sooner terminated, the 1989 Plan will terminate on January 31, 2024, subject to stockholder approval of this Proposal 3. If our stockholders do not approve this Proposal 3, the 1989 Plan will terminate on January 31, 2014.

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

No Evergreen

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

Federal Income Tax Information

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

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

If a participant holds stock acquired through exercise of an incentive stock option for more than two years from the date on which the option is granted and more than one year from the date on which the shares are transferred to the participant upon exercise of the option, any gain or loss on a disposition of

Generally, if the participant disposes of the stock before the expiration of either of these holding periods (a “disqualifying disposition”), then at the time of disposition the participant will realize taxable ordinary income equal to the lesser of (i) the excess of the stock’s fair market value on the date of exercise over the exercise price, or (ii) the participant’s actual gain, if any, on the purchase and sale. The participant’s additional gain or any loss upon the disqualifying disposition will be a capital gain or loss, which will be long-term or short-term depending on whether the stock was held for more than one year.

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

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

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

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

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

Certain kinds of compensation, including qualified “performance-based compensation,” are disregarded for purposes of the deduction limitation. In accordance with Treasury Regulations issued under Section 162(m), compensation attributable to stock options will qualify as performance-based compensation if the award is granted by a compensation committee comprised solely of “outside Directors” and either (i) the plan contains a per-employee limitation on the number of shares for which such awards may be granted during a specified period, the per-employee limitation is approved by the stockholders, and the exercise price of the award is no less than the fair market value of the stock on the date of grant, or (ii) the award is granted (or exercisable) only upon the achievement (as certified in writing by the compensation committee) of an objective performance goal established in writing by the compensation committee while the outcome is substantially uncertain, the committee of outside directors certifies in writing prior to the granting (or vesting or settlement) of the award that the performance goal has been satisfied, and the stockholders have approved the material terms of the award (including the class of employees eligible for the award, the business criteria on which the performance goal is based, and the maximum amount, or formula used to calculate the maximum amount, payable upon attainment of the performance goal.)

New Plan Benefits

The following table presents certain information with respect to merit-based options granted during the fiscal year ended December 31, 2011 to (i) each executive officer named in the Summary Compensation Table under “Executive Compensation—Compensation of Executive Officers”, (ii) all executive officers as a group, (iii) all non-employee Directors as a group, and (iv) all non-executive officer employees as a group. This information regarding grants for the fiscal year ended December 31, 2011 is for illustration only and may not be indicative of grants that are made in the future under the 1989 Plan.

NEW PLAN BENEFITS

1989 STOCK OPTION PLAN

Name and Position	Number of Shares Underlying Options
Stanley T. Crooke Chairman, Chief Executive Officer and President	122,096
B. Lynne Parshall Director, Chief Operating Officer & Chief Financial Officer	72,884
C. Frank Bennett Senior Vice President, Antisense Research	27,250
Richard S. Geary Senior Vice President, Development	33,444
All Executive Officers as a Group	255,674

Equity Compensation Plan Information

Securities Authorized for Issuance Under Equity Compensation Plans

The following table sets forth information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of December 31, 2011.

Plan Category	Number of Shares to be Issued Upon Exercise of Outstanding Options	Weighted Average Exercise Price of Outstanding Options	Number of Shares Remaining Available for Future Issuance
Equity compensation plans approved by stockholders(a)	8,165,400	\$ 10.62	5,667,733(c)
Equity compensation plans not approved by stockholders(b)	2,556,537	\$ 13.82	—
Total	10,721,937	\$ 11.39	5,667,733

(a) Consists of four Isis plans: 1989 Plan, Directors' Plan, 2011 Equity Incentive Plan (the "2011 Plan") and Employee Stock Purchase Plan ("ESPP").

(b) Consists of the 2000 Broad-Based Equity Incentive Plan, more fully described below. The 2000 Broad-Based Equity Incentive Plan expired on January 5, 2010.

(c) Of these shares, 191,088 remained available for purchase under the ESPP as of December 31, 2011. The ESPP incorporates an evergreen formula pursuant to which on January 1 of each year, we automatically increase the aggregate number of shares reserved for issuance under the plan by 150,000 shares.

Description of 2000 Broad-Based Equity Incentive Plan

We adopted the 2000 Broad-Based Equity Incentive Plan (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 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 were made, to designate the number of shares 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, 2011, the 2000 Plan had 5,990,000 shares authorized for issuance, options to purchase an aggregate of 2,556,537 shares were granted and outstanding under the 2000 Plan, optionholders had exercised options to purchase an aggregate of 3,170,502 shares under the 2000 Plan, and no shares remained available for grant thereunder. The 2000 Plan expired on January 5, 2010, so we may no longer grant new options under the 2000 Plan.

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 percent per year after the first year and then at the rate of 2.08 percent per month thereafter during the optionholder's employment or service as a consultant, employee or Director. 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 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.

If we dissolve or liquidate, all outstanding stock awards will terminate immediately prior to such event.

If there is a:

- sale, lease or other disposition of all or substantially all of our assets;
- 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). If 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.

PROPOSAL 4

ADVISORY VOTE ON EXECUTIVE COMPENSATION

The Dodd-Frank Wall Street Reform and Consumer Protection Act of 2010, called the “Dodd-Frank Act,” enables Isis’ stockholders to vote to approve, on an advisory (nonbinding) basis, the compensation of our Chief Executive Officer, Chief Financial Officer and our two other executive officers, called our “named executive officers” as disclosed in this Proxy Statement in accordance with the SEC’s rules.

We are asking our stockholders to indicate their support for our named executive officer compensation as described in this Proxy Statement. This proposal, commonly known as a “say on pay” proposal, gives our stockholders the opportunity to express their views on the compensation paid to our named executive officers. This vote is not intended to address any specific item of compensation, but rather the overall compensation of our named executive officers and the philosophy, policies and practices described in this Proxy Statement. Accordingly, we are asking our stockholders to vote “FOR” the following resolution at the Annual Meeting:

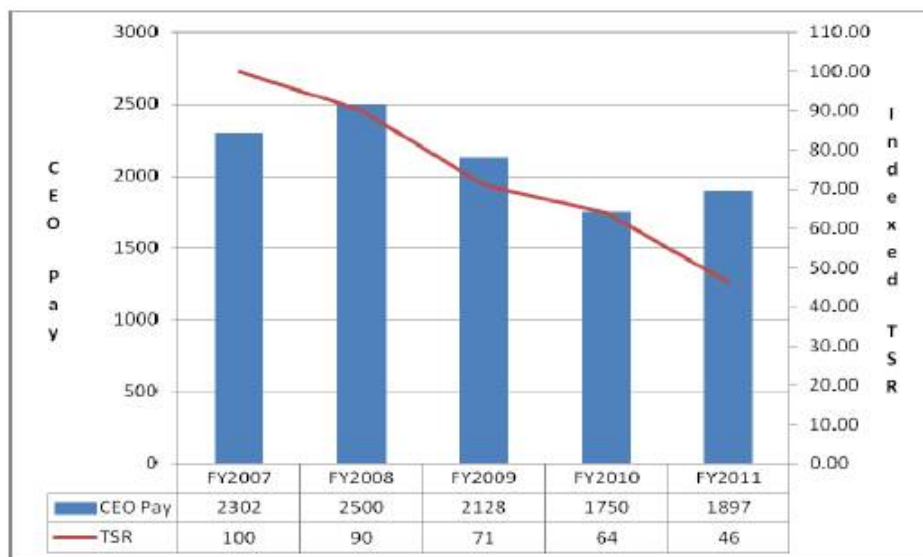
“RESOLVED, that Isis’ stockholders approve, on an advisory basis, the compensation of the named executive officers, as disclosed in this Proxy Statement for the 2012 Annual Meeting of stockholders pursuant to the compensation disclosure rules of the Securities and Exchange Commission.”

We recommend you carefully review the EXECUTIVE COMPENSATION section of this Proxy Statement located on pages 39 through 46. Below is a high-level summary of some of our compensation practices. This summary is qualified by the detailed disclosure contained in the EXECUTIVE COMPENSATION section of this Proxy Statement.

- we use a combination of compensation vehicles that provide a balanced mix of fixed and variable cash incentives, and long-term equity incentives;
- our cash bonuses are not guaranteed, meaning that they are 100% at risk, and include a multiplier based on both individual and Isis’ performance where the multiple can be less than one;
- our Compensation Committee sets a strict budget for equity awards and salary increases given to all employees under the annual merit review;
- our change of control agreements require a “double trigger” before we make a cash payment to an eligible executive officer;
- our policies do not provide for “gross-up” payments, except for relocation which applies equally to all eligible employees;
- our policies do not provide for perquisites for any employees, including our executive officers;
- we have a progressive contribution premium for our health care benefits, which means the more money an Isis employee makes, the more he or she contributes to the costs of his/her family’s health care;
- we incorporate a number of features into our compensation philosophy and objectives to mitigate the risk that our compensation policies and practices could encourage unnecessary or imprudent business risk taking;
- the 1989 Plan and the 2011 Plan prohibit the repricing of any options outstanding under such plans, unless approved by our stockholders;
- the 1989 Plan and the 2011 Plan require minimum vesting periods, except in the case of death, disability, retirement, or a change of control; and
- our ESPP requires employees to hold shares they purchase under the ESPP for a minimum of six months.

The following graphs show the relationship of our Chief Executive Officer’s compensation (\$ in thousands) compared to the total return (TSR) on \$100 invested on December 31, 2007 in our common stock through December 31, 2011. Although stock price is only one of the measures of Isis’ performance we use to set the compensation for our executive officers, including our CEO, as illustrated our CEO’s compensation generally decreased when our TSR declined.(6)

Regarding the year ended December 31, 2011, Dr. Crooke’s compensation was still over 17% less than his compensation for the year ended December 31, 2007. However, due to the significant achievements in 2011 (see “Evaluation of 2011: Business Highlights” on pages 45 through 46), Dr. Crooke’s compensation increased from 2010.



The affirmative vote of a majority of the holders of shares present or represented by proxy at the Annual Meeting and entitled to vote on the matter is required to adopt the resolution. If you indicate on your proxy to “Abstain” from voting, it will have the same effect as a vote “Against” this Proposal 4. Brokers do not have discretion to vote uninstructed shares with respect to this Proposal 4. Accordingly, if brokers do not receive voting instructions from beneficial owners of the shares, they cannot vote the shares. However, broker non-votes will not affect the outcome of the voting on this Proposal 4.

The “say on pay” vote is advisory, and therefore is not binding on Isis, the Compensation Committee or the Board of Directors. However, the Board and the Compensation Committee value the opinions of the stockholders. As such, if there is any significant vote against the named executive officer compensation as disclosed in this Proxy Statement, the Board will consider the stockholders’ concerns and the Board and Compensation Committee will evaluate whether any actions are necessary to address those concerns.

We currently hold the “say on pay” vote every year. As such, following the 2012 Annual Meeting, the next scheduled “say on pay” vote will be at the 2013 Annual Meeting of stockholders.

THE BOARD UNANIMOUSLY RECOMMENDS A VOTE “FOR” APPROVAL OF PROPOSAL 4.

(6) This table is not “soliciting material,” is not deemed “filed” with the SEC, is not subject to the liabilities of Section 18 of the Exchange Act and is not to be incorporated by reference in any of our filings under the Securities Act of 1933 (the “Securities Act”) or the Exchange Act, whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.

PROPOSAL 5

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 2012 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 2012 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 2012 Annual Meeting will be required to ratify the selection of Ernst & Young LLP. If you indicate on your proxy to “Abstain” from voting, it will have the same effect as an “Against” vote for this Proposal 5.

As of December 31, 2011, 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. The Audit Committee may pre-approve services as part of its approval of the scope of the engagement of the independent auditor or on an individual explicit case-by-case basis before the Audit Committee engages the independent registered public accounting firm to provide each service. As an additional measure to ensure auditor independence, beginning in 2004, the Audit Committee engaged Deloitte Tax LLP as our primary tax advisor. The Audit Committee pre-approved the fees described below.

Audit Fees

For the fiscal years ended December 31, 2011 and 2010, 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 \$470,000 and \$491,000, respectively. In addition, Ernst & Young LLP billed us \$26,000 and \$66,000 in 2011 and 2010, respectively, related to accounting consultations for implementing new accounting standards. Furthermore, the additional fees in 2010 also include consultations related to the accounting for the lease agreement associated with the construction of our new 176,000 square foot research facility.

Audit Related Fees

For the years ended December 31, 2011 and 2010, there were no audit related fees billed by Ernst & Young LLP that were reasonably related to the performance of the audit or review of our financial statements that are not included under “Audit Fees” above.

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Tax Fees

For the years ended December 31, 2011 and 2010, there were no tax fees billed by Ernst & Young LLP for tax related matters that were not part of the integrated audit fees. In 2011 and 2010, 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, 2011 and 2010, there were no fees billed by Ernst & Young LLP for information technology consulting.

All Other Fees

During the fiscal years ended December 31, 2011 and 2010, all other fees billed by Ernst & Young LLP were \$2,000 in each year. 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, 2011, none of the total hours expended on our financial audit by Ernst & Young LLP were provided by persons other than Ernst & Young LLP’s employees.

THE BOARD UNANIMOUSLY RECOMMENDS A VOTE “FOR” APPROVAL OF PROPOSAL 5.

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SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

This table outlines the ownership of our common stock as of March 30, 2012 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	12,698,141	12.7
BB Biotech AG (4) Vordergasse 3 CH-8200 Schaffhausen, Switzerland	7,233,800	7.2
BlackRock, Inc. (5) 40 East 52 nd Street New York, NY 10022	5,710,296	5.7
ClearBridge Advisors, LLC (6) 620 8 th Avenue New York, NY 10018	5,669,640	5.7
Columbia Wanger Asset Management, LLC (7) 227 West Monroe Street, Suite 3000 Chicago, IL 60606	5,083,000	5.1

Spencer R. Berthelsen (8)	136,870	*
Stanley T. Crooke (9)	1,848,632	1.8
Joseph Klein, III (10)	75,600	*
Frederick T. Muto (11)	89,000	*
B. Lynne Parshall (12)	467,924	*
John C. Reed (13)	87,500	*
Joseph H. Wender (14)	128,500	*
C. Frank Bennett (15)	186,324	*
Richard S. Geary (16)	135,376	*
All Directors and executive officers as a group (ten persons) (17)	3,284,627	3.2

*Less than one percent.

- (1) We base this table upon information supplied by officers, Directors, principal stockholders and Form 3s, Form 4s, Form 5s, 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 100,183,182 shares of common stock outstanding on March 30, 2012, 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 (the “Investment Advisers Act”), is the beneficial owner of 12,697,930 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 9,957,871 shares. Edward C. Johnson 3d and FMR LLC, through its control of Fidelity, and the funds each has sole power to dispose of the 12,697,930 shares owned by the Funds. Neither FMR LLC nor Edward C. Johnson 3d, Chairman of FMR LLC, has the sole power to vote or direct the voting of the shares owned directly by the Fidelity funds, which power resides with the funds’ Boards of Trustees. Fidelity carries out the voting of the shares under written guidelines established by the funds’ Boards of Trustees. Pyramis Global Advisors Trust Company (“PGATC”), an indirect wholly-owned subsidiary of FMR LLC and a bank as defined in Section 3(a)(6) of the Exchange Act, is the beneficial owner of 211 shares of our outstanding Common Stock as a result of its serving as investment manager of institutional accounts owning such shares. Edward C. Johnson 3d and FMR LLC, through its control of Pyramis Global Advisors Trust Company, each has sole dispositive power over 211 shares and sole power to vote or to direct the voting of 211 shares of Common Stock owned by the institutional accounts managed by PGATC as reported above.
- (4) BB Biotech shares voting and dispositive powers for these shares with Biotech Target N.V., a wholly-owned subsidiary of BB Biotech AG.
- (5) Various persons at BlackRock, Inc. have the right to receive or the power to direct the receipt of dividends from, or the proceeds from the sale of shares of our common stock. No one person’s interest in the shares of our common stock was more than five percent of the total outstanding common shares on December 31, 2011.
- (6) ClearBridge Advisors, LLC, is an investment adviser registered under the Investment Advisers Act. ClearBridge Advisors has sole voting power to direct the vote of 3,889,920 shares and sole power to dispose or direct the disposition of 5,669,640 shares.
- (7) Columbia Wanger Asset Management, LLC, an investment adviser registered under the Investment Advisers Act. Columbia Wanger Asset Management, LLC has sole voting power or to direct the vote of 4,585,000 shares and sole power to dispose or direct the disposition of 5,083,000 shares.
- (8) Includes 70 shares owned by Dr. Berthelsen’s daughter for which he disclaims beneficial ownership. Includes 107,500 shares of common stock issuable upon exercise of options held by Dr. Berthelsen that are exercisable on or before May 29, 2012.
- (9) Includes 913,369 shares of common stock issuable upon exercise of options held by Dr. Crooke that are exercisable on or before May 29, 2012. Also includes 59,872 shares of common stock issuable upon exercise of options held by Rosanne Crooke, Dr. Crooke’s wife, that are exercisable on or before May 29, 2012. Dr. Crooke disclaims beneficial ownership of the shares of common stock owned and issuable upon exercise of options held by his wife.
- (10) Includes 67,500 shares of common stock issuable upon exercise of options which Mr. Klein transferred to his three children that are exercisable on or before May 29, 2012 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 LLP Salary Deferral and Profit Sharing Plan and 87,500 shares of common stock issuable upon exercise of options held by Mr. Muto that are exercisable on or before May 29, 2012.

- (12) Includes 415,939 shares of common stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before May 29, 2012, and an aggregate of 50,000 shares of common stock issuable upon exercise of options which Ms. Parshall transferred to her two daughters that are exercisable on or before May 29, 2012.
- (13) Includes 87,500 shares of common stock issuable upon exercise of options held by Dr. Reed that are exercisable on or before May 29, 2012.
- (14) Includes 87,500 shares of common stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before May 29, 2012.
- (15) Includes 185,695 shares of common stock issuable upon exercise of options held by Dr. Bennett that are exercisable on or before May 29, 2012.
- (16) Includes 129,473 shares of common stock issuable upon exercise of options held by Dr. Geary that are exercisable on or before May 29, 2012.
- (17) Includes an aggregate of 2,315,089 shares issuable upon exercise of options held by all current Directors and executive officers as a group that are exercisable on or before May 29, 2012.

Section 16(a) Beneficial Ownership Reporting Compliance

Section 16(a) of the Exchange Act requires our Directors, executive officers, and persons who own more than ten percent of a registered class of our equity securities, to file with the SEC initial reports of ownership and reports of changes in ownership of our common stock and other equity securities. 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, 2011, all Section 16(a) filing requirements applicable to our officers, Directors and greater than ten percent beneficial owners were complied with.

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 our 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 stock compensation arrangements;
- reviewing and approving compensation arrangements for our executive officers, including our Chief Executive Officer;
- reviewing and approving compensation arrangements for our Directors;
- administering our benefit plans, including stock-based awards and employee stock purchase plans;
- evaluating risks associated with the compensation policies and assessing whether risks arising from our compensation policies and practices are reasonably likely to have a material adverse effect on us;
- 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.

Since the SEC will continue to adopt the final rules implementing and defining the recent Dodd Frank legislation, as part of the Compensation Committee responsibilities, Isis' management and the Compensation Committee will:

- monitor the SEC's adoption of the final rules and definitions; and
- adjust Isis' compensation policies as necessary to satisfy the new rules.

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. We designed our system to be fair and reward

individuals based on their contributions. As a result, we do not institute artificial limits on rewards. We consistently try to target actual total annual cash compensation at the 75th percentile of the biotech/pharmaceutical market to attract and retain individuals that perform in the top 25%. 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, stock options and restricted stock unit awards ("RSUs"). 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.

We incorporate a number of features into our compensation philosophy and objectives to mitigate the risk that our compensation policies and practices could encourage unnecessary or imprudent business risk taking. We use a combination of compensation vehicles that provide a balanced mix of fixed and variable cash incentives, and long-term stock incentives. Our cash bonuses are not guaranteed (i.e. are 100% at risk) and include a multiplier based on Isis' performance. Therefore, if Isis does not perform well, the cash bonus can be, and has been, zero. When setting our Company objectives, which then become our CEO's individual objectives, we structure the objectives so that they are results driven rather than task driven. For example, we typically include a number of objectives based on positive data in the clinic, such as in 2011 we had a Company objective of achieving positive pharmacological data in the clinic for at least three drugs. This type of objective only rewards our executives if the data are positive, because we must encourage the prudent spending of stockholder money on development decisions. In other words, we do not want to structure our objectives to reward "bad bets." We also align our Company objectives and individual objectives with our long term strategy and use little or no metric-based objectives such as earnings per share. This way, we avoid the temptation to deviate from Isis' long-term strategy just to meet a short-term metric. In addition, all of our stock compensation vests over a period of four years, with no vesting during the first year, and we set the option exercise price at the fair market value of our stock on the date of grant. This practice ensures that our stock compensation does not reward short term imprudent risk taking at the expense of long term stockholder value, because if stockholder value declines over time, so too will the value of the stock compensation. We cover the specific elements of our compensation policy and practices in more detail below.

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 Isis and of individuals. We pay our senior management team for results and their use of judgment in executing the strategies they have established. Therefore, the more senior a person becomes, the more the employee's cash compensation will be "at risk." We compensate the more junior employees for accomplishing their work well and, therefore, a lower portion of their cash compensation is "at risk."

The executive officers' annual compensation consists of three elements: base salary, a cash incentive bonus, no portion of which is guaranteed, and stock-based compensation. We have historically awarded stock-based compensation through stock option grants. Beginning in 2012, we broadened our stock-based compensation vehicles to include RSUs. The cash incentive bonus is the only element of these three that does not apply to all employees. The cash incentive bonus is available only to employees at the director level and above. We provide all other benefits, including 401(k) matching, to all employees. We describe these benefits in more detail later.

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 our objectives;
- Increased efficiencies and process improvements;
- Effective collaboration and teamwork;
- Individual expertise, skills and knowledge;
- The need to retain and motivate; and
- The magnitude of the impact a judgment by the individual can have on our success or failure.

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 Isis, but the scope of responsibility and accountability an employee may assume is broad. We do not have salary ranges, and therefore we do not set salary minimums or 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 ranges 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 Isis 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 Global Life Sciences Survey to obtain this information targeting the 50th - 75th percentile. Examples of other participating public companies in the San Diego area are: Arena Pharmaceuticals, Ligand Pharmaceuticals, and Neurocrine Biosciences. We then look at the salary required to attract a particular candidate. In the third step, we 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 as a result of 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 Isis' performance. The Company-wide merit increase budget percentage serves as the basis for each individual salary increase. The actual merit increase award for each employee, including our executive officers, will vary, higher or lower, from the Company-wide budget percentage depending upon the respective individual's contributions to Isis. However, regardless of individual employee variances, we do not exceed the Company-wide approved merit budget.

The Compensation Committee evaluates each executive officer's performance to set his or her annual merit increase. As part of this process, the Compensation Committee reviews the written reports prepared by the CEO evaluating the performance of each individual executive officer. The Compensation Committee carefully considers these reports since our CEO 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 officers' 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 2012 salary of \$735,169 was calculated as follows:

<u>2011 Base Salary</u>	(x)	<u>Merit Increase</u>	=	<u>Increase to Base Salary</u>
\$735,169	(x)	0%	=	\$0

The Compensation Committee approved a Company-wide merit increase budget for the entire Company equal to 3.7% of total salaries. Actual merit increases per individual ranged from 0% - 7.62% with an average of 3.6%. However, the Compensation Committee approved a 0% increase to executive officer salaries resulting in an actual aggregate merit increase of 3.42% which was 0.28 percentage points below the approved budget.

The Compensation Committee did not base this decision on the performance of the executive officers. Instead the Compensation Committee noted the following when recommending no salary increases for executive officers:

- base salary is guaranteed compensation and once established is not tied to company or individual performance,
- other than the CEO, executive officers' salaries were at the top of, or exceeded, the most comparable Radford category at the 90th percentile (in many cases the Radford categories were not considered to be reflective of the job scope),
- the MBO company success factor, and individual success factors for the executive officers, were above 100%, and
- the stock price decreased in 2011.

The 2011 merit budget increased 0.2 percentage points from the 2010 merit budget of 3.5%. This increase was driven by the general increase we observed in the market as well as Isis' strong performance in 2011. The Compensation Committee believed the level of increase was in line with comparable companies and was deserved based on company performance. The Compensation Committee approved this budget based on Isis' accomplishments in 2011, as noted in the section entitled "Evaluation of 2011: 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 Global Life Sciences.

Dr. Crooke's base salary is above the 75th percentile of Radford (\$584,500) and below the 90th percentile of Radford (\$800,000). The Compensation Committee annually reviews a report of peer group companies obtained by utilizing the most recent data available from Equilar's Executive Insight research database, a resource for benchmarking executive compensation and analyzing CEO and executive pay trends. Using the search criteria of: 1) CEO tenure of 14+ years; 2) Biotech/Biopharmaceuticals industry; and 3) market capitalization between \$1 billion and \$3 billion, we identified seven peer group CEOs.(7) This information illustrated that Dr. Crooke's base salary was below the CEO average base salary of \$778,713 for these seven companies. The results show that we pay our executives, on average, above the 75th percentile. The Compensation Committee recognizes the strong performance of our executive officers across multiple functions as well as their significant tenure in the company. However, as noted above, the Compensation Committee did not approve base salary increases for any executive officers for 2012. The average tenure of our executive officers, excluding our CEO, is 19.7 years. The average tenure of our executive officers, including our CEO, is 20.5 years. Dr. Crooke has been the CEO for 22 years.

The next component of an executive officer's compensation, as well as the compensation of our employees at the director level and above, 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 not guaranteed and is totally at risk. As such, a cash 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.

We calculate the actual amount of each officer's respective cash bonus based on the following formula:

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

(7) These companies were Acorda Therapeutics, Inc.; Charles River Laboratories International, Inc.; Medicis Pharmaceuticals Corporation; Myriad Genetics, Inc.; Regeneron Pharmaceuticals, Inc.; Techne Corporation; and United Therapeutics Corporation.

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The multipliers in this formula ensure we award bonuses based on both Isis' performance, and individual performance. For example, in 1999, the Company Success Factor was 0% due to the failures Isis 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 we reward our employees proportionately to Isis' success.

Target MBO percentages are based on position levels within Isis. The Target MBO percentages are as follows: Directors 15%; Executive Directors 20%; Vice Presidents 25% or 30%; COO 35%; and CEO 40%. An individual's Target MBO percentage does not change unless he or she changes level.

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 Isis' overall performance. The Committee measures Isis' 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 the prior 10 years to form a comparison for our current year's successes and/or failures.

Finally, the Compensation Committee approves each executive officer's Individual Success Factor based on the same elements it used to evaluate performance.

Once the Compensation Committee has determined the elements of the formula above, we calculate each executive officer's cash bonus in accordance with the following formula, as further demonstrated in the table below:

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

Name	Base Salary	Target MBO %	Company Success Factor	Individual Success Factor	Resulting Cash Bonus	Key Results Considered When Setting Individual Success Factor*
Stanley T. Crooke	\$ 735,169	40%	135%	135%	\$ 535,938	a through j
B. Lynne Parshall	\$ 641,574	35%	135%	135%	\$ 409,244	a through j
C. Frank Bennett	\$ 397,077	30%	135%	125%	\$ 201,020	b, c, d, e, g, h, i
Richard Geary	\$ 398,444	30%	135%	140%	\$ 225,918	a, b, c, d, g

* The letters in the table correspond to the applicable highlight under "Evaluation of 2011: Business Highlights" on pages 45 and 46.

The Compensation Committee set the Company Success Factor for the 2011 MBO at 135% due to our strong achievements for the year, including positive pharmacological data in the clinic for EXC001, CRP, FactorXI, ApoCIII and TTR. The section entitled "Evaluation of 2011: Business Highlights" below provides a full review of our accomplishments. This MBO target reflects an increase of 30 percentage points from the 2010 Company Success Factor of 105%. The Committee agreed that this increase was a fair reflection of an exceptional year with successes across the board and very few disappointments, with the only significant one being our stock price.

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 on average 21.41 times that of the average cash compensation for our lowest level employees and 1.62 times greater than the average of our other executive officers. Shareholder advocate organizations, such as ISS, consider 3x's and lower an appropriate ratio when measuring CEO compensation against all Executive Officers and Vice Presidents.

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Stock Compensation

We use stock options and RSUs 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 and RSUs on an annual basis to provide a continuing financial incentive and stock in Isis' growth.

Each year the Compensation Committee approves a budget that sets the number of stock options and RSUs we can grant our employees for annual merit awards. We do not grant options or RSUs that exceed this budget without the Compensation Committee's approval. Over the past five years, the average merit award stock budget set by the Compensation Committee has been approximately 1.6% of our outstanding common stock on an issued and outstanding

basis. We believe this stock budget is an important tool to balance our compensation objectives with stockholder interests. For 2011, the Compensation Committee set the merit stock option budget at 1.35 million shares, and the RSU budget at 150,000 shares which together represented 1.5% of our outstanding common stock on an issued and outstanding basis for that year. We believe awarding a combination of stock options and RSUs provides a number of benefits as RSUs are a strong retention vehicle for employees as they vest annually and retain their value but at the same time require fewer shares than option awards to deliver competitive value. This overall maximum, plus each employee's position and performance in the previous year, ultimately determines the size of the individual annual stock grant.

For each stock option and RSU, the Compensation Committee sets a vesting schedule. The stock option vesting schedule is typically over a 4-year period at the rate of 25% at the end of the first year and then at the rate of 2.08% per month for 36 months thereafter during the optionee's employment or services as a consultant or director. The RSU vesting schedule is typically over a 4-year period at the rate of 25% per year. 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. For example, our executive officers received merit stock options in January of 2001, but each officer held these options until at least the last 15 days of the 10-year term of such options, even though our stock price had traded significantly higher earlier in the life of these options. 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 with the exception of our Employee Stock Purchase Plan (ESPP) which has a six month minimum hold period for shares purchased under the ESPP.

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. We do not allow our executive officers to buy or sell our stock outside of the Rule 10b5-1 trading program except for purchases of our stock under our ESPP (but not subsequent sales of the stock).

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, EAP/WorkLife, basic life insurance, short-term disability/sick pay, long term disability, 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, which means the more money an Isis employee makes, the more he or she contributes to the costs of his/her family's health care.

Say on Pay

In 2011, Isis asked stockholders to provide a non-binding approval regarding our executive officer compensation for the previous year. This proposal, commonly known as a "Say on Pay" proposal, gave our stockholders the opportunity to express their views on the compensation paid to our named executive officers (NEOs). We are pleased to report that our stockholders overwhelmingly approved our executive officer's compensation. We are committed to providing our stockholders the opportunity for a "Say on Pay" annually.

Retention and Change of Control Agreements

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

Change in Control: As part of our normal course of business and as a result of our business strategy, 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. Occasionally, a transaction in the Biotech/Biopharmaceutical industry may start as a licensing transaction, but ultimately result in an acquisition. In certain scenarios, the potential for merger or being acquired may be in the best interests of our stockholders. As further described on pages 51 and 52 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.

Evaluation of 2011: Business Highlights

Operationally, 2011 was a strong year with successes across the board. Isis ended the year in a strong financial position and all the discovery programs made great progress. Isis met its aggressive goals for initiation of clinical development and the identification of new development candidates. Most importantly, Genzyme submitted a marketing application for KYNAMRO in Europe, made significant progress preparing the marketing application for KYNAMRO in the United States, and initiated the FOCUS FH study as further detailed below.

Drug Development Highlights

- a. KYNAMRO continued to advance in clinical development and moved closer to the market for patients with severe forms of FH, at high cardiovascular risk, who cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies.

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- Genzyme submitted a marketing application for KYNAMRO in Europe for patients with homozygous FH and severe heterozygous FH. Genzyme and Isis also made significant progress preparing to file for marketing approval in the United States.
 - Genzyme initiated the FOCUS FH study in FH patients that is designed to support potentially broadening the FH patient population beyond the first indication and support an alternative dosing regimen of three times a week dosing. Genzyme reached an agreement with the Food and Drug Administration on the design of the FOCUS FH study via a Special Protocol Assessment.
 - A clinical investigator presented data from an open-label extension study in patients treated with KYNAMRO for longer than one year, which demonstrated sustained reductions in all measured atherogenic lipids with a safety profile consistent with the Phase 3 studies.
 - Clinical investigators presented data from two studies of KYNAMRO at the 79th European Atherosclerosis Society Congress. The data highlight the potential of KYNAMRO in lowering lipoprotein a (Lp(a)), and potentially reducing the necessity for lipid-apheresis.
- b. Isis received more than \$23 million from partners in 2011 as its partners advanced drugs in development, including \$10 million from GSK for advancing ISIS-TTR_{Rx} and selecting ISIS-AAT_{Rx} as a development candidate.
- c. Isis and its partners reported positive clinical data on eight drugs and added six new drugs to its pipeline.
- d. Isis and its partners initiated Phase 1 clinical studies on eight drugs and initiated Phase 2 studies on three drugs.

Corporate Highlights

- e. Isis formed a new strategic alliance with Biogen Idec to develop and commercialize ISIS-SMN_{Rx} to treat spinal muscular atrophy. Isis received a \$29 million upfront payment and is eligible to receive up to an additional \$270 million in a license fee and milestone payments and double-digit royalties on sales of ISIS-SMN_{Rx}.
- f. Isis received \$4.4 million and is eligible to receive up to an additional \$9.6 million in milestone payments from the sale of Isis' equity ownership in Excaliard Pharmaceuticals, Inc. to Pfizer, Inc.
- g. Isis received Orphan Drug Designation in the United States and Europe and Fast Track Status in the United States for ISIS-SMN_{Rx} for the treatment of spinal muscular atrophy.
- h. Isis and CHDI Foundation, Inc. renewed their collaboration to discover and develop an antisense drug for the treatment of Huntington's Disease.
- i. Isis and GSK expanded their collaboration by initiating a sixth program to discover and develop drugs to treat rare and infectious diseases for which Isis received a \$3 million payment from GSK.
- j. Isis filed a patent infringement lawsuit against Santaris Pharma based upon Santaris' commercial activities selling antisense drugs and antisense drug discovery services to several pharmaceutical companies.

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Compensation of Executive Officers

The following table shows for the fiscal years ended December 31, 2011, 2010 and 2009 compensation awarded to or paid to, or earned by, our Chief Executive Officer, Chief Financial Officer and our two other executive officers at December 31, 2011, called our "Named Executive Officers."

In 2011, 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

Name and Principal Position	Year	Salary (\$)	Bonus(1) (\$)	Option Awards(2) (\$)	All Other Compensation(3) (\$)	Total (\$)
Stanley T. Crooke Chairman, President, Chief Executive Officer	2011	\$ 735,169	\$ 535,938	\$ 611,305	\$ 14,920	\$ 1,897,332
	2010	\$ 710,995	\$ 343,411	\$ 681,324	\$ 14,111	\$ 1,749,841
	2009	\$ 683,649	\$ 361,650	\$ 1,069,879	\$ 13,258	\$ 2,128,436
B. Lynne Parshall Director, Chief Operating Officer, Chief Financial Officer	2011	\$ 641,574	\$ 409,244	\$ 364,913	\$ 19,088	\$ 1,434,819
	2010	\$ 620,478	\$ 262,230	\$ 363,374	\$ 17,813	\$ 1,263,895
	2009	\$ 596,613	\$ 276,157	\$ 557,971	\$ 16,567	\$ 1,447,308
C. Frank Bennett Senior Vice President, Antisense	2011	\$ 397,077	\$ 201,020	\$ 136,434	\$ 17,398	\$ 751,929
	2010	\$ 384,020	\$ 133,063	\$ 158,977	\$ 17,178	\$ 693,238

Research	2009	\$	369,250	\$	146,500	\$	234,725	\$	16,226	\$	766,701
Richard S. Geary	2011	\$	398,444	\$	225,918	\$	167,446	\$	14,125	\$	805,933
Senior Vice President,	2010	\$	379,470	\$	161,370	\$	186,622	\$	14,087	\$	741,549
Development	2009	\$	364,000	\$	169,533	\$	206,559	\$	12,328	\$	752,420

- (1) We present bonuses in the years they were earned, not in the year paid. Bonuses represent compensation for achievements and are not necessarily paid in the year they are earned; for example, in January 2012 we paid bonuses for 2011 performance.
- (2) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with FASB Topic ASC 718 ("ASC 718") for stock options granted to the Named Executive Officers. ASC 718 expense for the stock options is based on the fair value of the options on the date of grant using the Black-Scholes option-valuation model. For more information, please see Note 6 of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2011 regarding assumptions underlying valuation of equity awards.
- (3) Includes AD&D, Basic Life, Medical, Dental, Vision, and 401(k) matching contributions which are available to all employees.

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Grants of Plan-Based Awards

The following table shows for the fiscal year ended December 31, 2011, certain information regarding grants of plan-based awards to the Named Executive Officers:

Grants of Plan-Based Awards in Fiscal 2011

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	1/3/11	122,096	\$ 10.29	\$ 611,305
B. Lynne Parshall	1/3/11	72,884	\$ 10.29	\$ 364,913
C. Frank Bennett	1/3/11	27,250	\$ 10.29	\$ 136,434
Richard S. Geary	1/3/11	33,444	\$ 10.29	\$ 167,446

- (1) Amounts represent the aggregate expense that will be recognized for financial statement reporting purposes in accordance with ASC 718 for stock options granted to the Named Executive Officers. ASC 718 expense for the stock options is based on the fair value of the options on the date of grant using the Black-Scholes option-valuation model. For more information, please see Note 6 of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2011 regarding assumptions underlying valuation of equity awards.

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 3, 2011, the same date on which the committee granted stock options to our other employees.

All of these stock options were granted out of our 1989 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.

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

The following table shows for the fiscal year ended December 31, 2011, 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, 2011. In addition, there were no stock awards outstanding for the individuals named below at December 31, 2011.

Outstanding Option Awards At December 31, 2011

Name	Number of Securities Underlying Unexercised Options (#) Exercisable	Number of Securities Underlying Unexercised Options (#) Unexercisable	Full(1) Vest Date	Option Exercise Price (\$)	Option Expiration Date
Stanley T. Crooke	50,000	0	1/2/2007	\$ 6.84	1/1/2013
	128,924	0	1/3/2010	\$ 5.25	1/2/2013
	50,000	0	9/21/2010	\$ 7.26	9/20/2013
	178,740	0	1/2/2011	\$ 11.12	1/1/2014
	80,000	0	1/2/2008	\$ 6.81	1/1/2014
	186,526	3,969	1/2/2012	\$ 15.38	1/1/2015

	109,375	40,625	1/2/2013	\$	14.47	1/1/2016
	57,099	62,064	1/4/2014	\$	11.27	1/3/2017
	0	122,096	1/3/2015	\$	10.29	1/2/2018
	(2)25,000	0	1/2/2007	\$	6.84	1/1/2013
	(2)49,506	0	1/3/2010	\$	5.25	1/2/2013
	30,000	0	9/21/2010	\$	7.26	9/20/2013
	77,454	0	1/2/2011	\$	11.12	1/1/2014
B. Lynne Parshall	38,400	0	1/2/2008	\$	6.81	1/1/2014
	89,613	1,907	1/2/2012	\$	15.38	1/1/2015
	24,375	5,625	9/16/2012	\$	16.45	9/15/2015
	57,042	21,187	1/2/2013	\$	14.47	1/1/2016
	30,453	33,101	1/4/2014	\$	11.27	1/3/2017
	0	72,884	1/3/2015	\$	10.29	1/2/2018
	19,000	0	1/2/2006	\$	21.05	1/1/2012
	11,500	0	1/2/2007	\$	6.84	1/1/2013
	10,322	0	1/3/2010	\$	5.25	1/2/2013
C. Frank Bennett	36,145	0	1/2/2011	\$	11.12	1/1/2014
	28,800	0	1/2/2008	\$	6.81	1/1/2014
	45,237	963	1/2/2012	\$	15.38	1/1/2015
	23,996	8,913	1/2/2013	\$	14.47	1/1/2016
	13,323	14,482	1/4/2014	\$	11.27	1/3/2017
	0	27,250	1/3/2015	\$	10.29	1/2/2018
	8,000	0	1/2/2006	\$	21.05	1/1/2012
	11,686	0	1/3/2010	\$	5.25	1/2/2013
	19,042	0	1/2/2011	\$	11.12	1/1/2014
	1,049	0	1/2/2008	\$	6.81	1/1/2014
Richard S. Geary	9,791	209	1/1/2012	\$	15.75	12/31/2014
	23,500	500	1/2/2012	\$	15.38	1/1/2015
	8,333	1,667	8/16/2012	\$	19.08	8/15/2015
	21,116	7,844	1/2/2013	\$	14.47	1/1/2016
	15,640	17,000	1/4/2014	\$	11.27	1/3/2017
	0	33,444	1/3/2015	\$	10.29	1/2/2018

- (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 50,000 shares of common stock issuable upon exercise of options which Ms. Parshall transferred to her two daughters.

Option Exercises

The following table shows for the fiscal year ended December 31, 2011, certain information regarding option exercises during the last fiscal year with respect to the Named Executive Officers:

Option Exercises in Fiscal 2011(1)

Name	Option Awards	
	Number of Shares Acquired on Exercise (2) (3) (#)	Value Realized on Exercise (\$)
Stanley T. Crooke	16,720	\$ 18,726
	5,000	\$ 5,600
	22,000	\$ 22,440
	15,178	\$ 15,482
	1,822	\$ 2,004
B. Lynne Parshall(4)	15,000	\$ 14,850
	6,763	\$ 7,575
	2,100	\$ 2,352
	8,500	\$ 8,670
	6,162	\$ 6,285
C. Frank Bennett	738	\$ 812
	6,000	\$ 5,940
	1,555	\$ 1,742
	2,000	\$ 2,040
	500	\$ 560
	1,340	\$ 1,367
	160	\$ 176
	1,500	\$ 1,485

	10,000	\$	23,706
	1,144	\$	1,281
	1,500	\$	1,530
Richard S. Geary	300	\$	336
	982	\$	1,002
	118	\$	130
	1,000	\$	990

- (1) We did not utilize stock awards as part of our compensation plan prior to 2012. As such, we do not include information regarding stock awards that would otherwise appear as blank columns in this table.
- (2) Each individual executed each option exercise and resulting sales pursuant to the individual's Rule 10b5-1 trading plan.
- (3) Each exercised option would have expired on 1/1/12, except the 10,000 shares exercised by Dr. Bennett were subject to an option that would have expired on 1/2/13.
- (4) Includes options exercised by Ms. Parshall's daughters.

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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 2011, the maximum matching contribution was \$3,675. We do not provide any nonqualified defined contribution or other deferred compensation plans.

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 severance agreements, the details of which are provided below.

Retention and Change of Control Agreements

In December 2008, we amended and restated our severance agreements with Stanley T. Crooke and B. Lynne Parshall to clarify the provisions of such agreements in light of Section 409A of the 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, regarding Dr. Crooke and Ms. Parshall, the Compensation Committee has approved that in the event of a change of control, the vesting and exercisability of their then outstanding and unvested stock options and restricted stock unit awards will be accelerated in full, to the extent permitted by the applicable stock option plan.

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 our property and information and sign an agreement releasing Isis from liability.

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Potential Payments Upon Termination or Change-Of-Control

The following table estimates the lump sum payments that would be required under the agreements described above that were effective as of December 31, 2011. This table estimates the lump sum payments based upon either a termination without cause or a termination in connection with a change of control assuming either occurred on December 31, 2011. The estimates in this table are forward-looking statements. Please see the special note regarding forward-looking statements on page 57 of this Proxy Statement.

Name	Termination Event	
	Termination Without Cause	Termination in a Change of Control
Stanley T. Crooke	—	\$ 2,205,507
B. Lynne Parshall	\$ 962,361	\$ 1,603,935

Director Compensation

We paid our non-employee Directors a fee of \$30,000 per year until September 20, 2011 when the fee was increased to \$45,000 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, 2011, we paid total fees of \$33,750 to each of our non-employee Directors except for Dr. DiMarchi who received total fees paid of \$15,000 due to his resignation from the Board on June 16, 2011.

In 2011, each non-employee Director also received automatic stock option grants under our Directors' Plan. On July 1, 2011, under the Directors' 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 \$9.30 per share, the fair market value of the common stock on the date of the grant, based on the closing sales price reported on Nasdaq. The options vest over a four-year period in equal annual installments.

The following table shows for the fiscal year ended December 31, 2011 certain information with respect to the compensation of all our non-employee Directors:

Director Compensation for Fiscal 2011

Name	Fees Earned or Paid in Cash (\$)	Option Awards(1) (\$)	All Other Compensation (\$)	Total (\$)
Spencer R. Berthelsen	\$ 33,750	\$ 82,130	—	\$ 115,880
Richard D. DiMarchi(2)	\$ 15,000	—	—	\$ 15,000
Joseph Klein	\$ 33,750	\$ 82,130	—	\$ 115,880
Frederick T. Muto(3)	\$ 33,750	\$ 82,130	—	\$ 115,880
John C. Reed	\$ 33,750	\$ 82,130	—	\$ 115,880
Joseph H. Wender(3)	\$ 33,750	\$ 82,130	—	\$ 115,880

(1) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with FASB Topic ASC 718 ("ASC 718") for stock options granted to the Directors. ASC 718 expense for the stock options is based on the fair value of the options on the date of grant using the Black-Scholes option-valuation model. For more information, please see Note 6 of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2011 regarding assumptions underlying valuation of equity awards.

(2) Dr. DiMarchi resigned from the Board on June 16, 2011.

(3) Mr. Muto and Mr. Wender had 22,000 and 4,000 stock options, respectively, expire last year due to the option price being less than the trading price of our stock on the date of expiration.

Outstanding Equity Awards at Fiscal Year-End — Directors

The following table shows for the fiscal year ended December 31, 2011, certain information regarding outstanding awards at fiscal year-end of all our non-employee Directors (none of our non-employee Directors exercised options in 2011):

Name	Number of Securities Underlying Unexercised Options (#)	
	Exercisable	Unexercisable
Spencer R. Berthelsen	107,500	37,500
Joseph Klein	67,500	37,500
Frederick T. Muto	87,500	37,500
John C. Reed	107,500	37,500
Joseph H. Wender	87,500	37,500

Certain Relationships and Related Transactions

We have provided some of the information below because our stockholders may find it useful when evaluating the proposals contained in this Proxy Statement. When we include a transaction in this section, we do not necessarily mean that the transaction qualifies as a related party transaction under the securities laws.

Dr. Rosanne Crooke, the wife of Dr. Stanley Crooke, our Chairman and Chief Executive Officer, is a non-executive officer of Isis working part time at 30 hours per week. The Compensation Committee approves Dr. Rosanne Crooke's compensation. Her compensation is commensurate with the compensation of other employees at the same level at Isis. For the fiscal years ended 2011, 2010, and 2009, she received the following compensation:

Name	Year	Salary (\$)	Bonus(1) (\$)	Option Awards(2) (\$)	All Other Compensation(3) (\$)	Total (\$)
Rosanne Crooke,	2011	\$ 189,778	\$ 80,063	\$ 75,102	\$ 3,710	\$ 348,653
Vice President,	2010	\$ 160,600	\$ 55,446	\$ 120,977	\$ 3,394	\$ 340,417
Cardiovascular	2009	\$ 147,002	\$ 42,263	\$ 49,929	\$ 336	\$ 239,530
Diseases Drug						
Discovery Research						

- (1) We present bonuses in the years they were earned, not in the year paid. Bonuses represent compensation for achievements and are not necessarily paid in the year they are earned; for example, in January 2012 we paid bonuses for 2011 performance.
- (2) These amounts represent the estimated fair values of stock option grants we recognized as share-based compensation expense. The estimated fair value amounts were determined using the Black-Scholes option-valuation model and are not indicative of whether Dr. Rosanne Crooke will realize the estimated fair value or any financial benefits from the award. The applicable amounts represent:
 - 7,000 shares at \$14.47 per share received on January 2, 2009;
 - 6,600 shares at \$11.27 per share received on January 4, 2010;
 - 18,750 shares at \$9.22 per share received on July 19, 2010 for her promotion to Vice President; and
 - 15,000 shares at \$10.29 per share received on January 3, 2011.
- (3) Includes AD&D, Basic Life, Medical, Dental, Vision, and 401(k) company contributions which are available to all employees.

One of our Directors, Mr. Muto, who was elected to the Board in March 2001, is a partner at Cooley LLP, our outside legal counsel. We paid Cooley LLP an aggregate of \$70,000 in fees in 2011 for legal services, which amount is substantially less than five percent of Cooley's gross revenues for its 2011 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

A committee of the Board composed entirely of independent Directors approves transactions with related persons, as defined under SEC regulations. The Compensation Committee of the Board approves all compensation we pay to employees that may qualify as a related person and the Audit Committee approves all other related party transactions, as specified in its charter. The committees only approve related-party transactions at committee meetings, or by unanimous written consent in lieu of a meeting, and record the approvals 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 Chief Executive Officer or Chief Operating Officer (for non-executive officers) to determine that no conflict of interest exists.

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

COMPENSATION COMMITTEE REPORT*

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 our Proxy Statement relating to the 2012 Annual Meeting of stockholders.

The Compensation Committee
Spencer R. Berthelsen, *Chairman*
John C. Reed
Joseph H. Wender

AUDIT COMMITTEE REPORT*

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 financial 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, 2011 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, 2011 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 for 2012.

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 our stockholders will be "householding" our proxy materials. A single notice of internet availability of proxy materials 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 notice of internet availability of proxy materials, please notify your broker and direct your written request to Isis Pharmaceuticals, Inc., Attn: Linda Powell, Assistant Corporate Secretary, 2855 Gazelle Court, Carlsbad, California 92010, or contact Linda Powell at (760) 603-2471, and we will promptly provide you a separate notice of internet availability of proxy materials. 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.

* 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 Securities Act or the Exchange Act.

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, 2011 that we filed with the SEC, and is available free of charge. Please send written requests to:

B. Lynne Parshall, Secretary
Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

You may also visit our website (www.isispharm.com(8)) to view our 2011 Annual Report. The Annual Report is not incorporated into this Proxy Statement and is not considered solicitating material.

By Order of the Board of Directors,

B. Lynne Parshall
Secretary

April 23, 2012

Special Note Regarding Forward-Looking Statements

This Proxy Statement includes forward-looking statements regarding Isis Pharmaceuticals' business, the financial position and outlook for Isis and the therapeutic and commercial potential of our technologies and products in development. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs, including the planned commercialization of KYNAMRO, 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 drugs. 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, 2011, which is on file with the SEC. Copies of this and other documents are available from the Company.

Isis Pharmaceuticals® is a registered trademark of Isis Pharmaceuticals, Inc. KYNAMRO™ is a trademark of Genzyme Corporation.

(8) 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.

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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 be comprised of 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 submitted to 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 review and evaluate and, if appropriate, make recommendations to Board of Directors on any matters related to stockholder protection and takeover preparedness, equity or debt financing plans and opportunities, and the selection and evaluation of money managers or investment advisors for the Company.
15. 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.
16. 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.
17. The Audit Committee shall have adequate resources and authority to discharge its responsibilities and duties including the following:
- 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.
 - The Audit Committee will have the authority to review all aspects of the Company's financial operations on a planned basis.
 - 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.
18. 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.
2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN
ADOPTED BY THE BOARD OF DIRECTORS SEPTEMBER 11, 2001
APPROVED BY STOCKHOLDERS MAY 31, 2002
EFFECTIVE DATE: MAY 31, 2002**

**AMENDED: APRIL 20, 2006 (Amendment approved by Board on
December 12, 2005 and April 20, 2006 and by the Stockholders on May 3, 2006)**

**AMENDED: JUNE 5, 2008 (Amendment approved by Board on
September 13, 2007 and February 22, 2008 and by the Stockholders on June 5, 2008)**

**AMENDED: JUNE 2, 2010 (Amendment and Restatement approved by Board on
February 26, 2010 and by the Stockholders on June 2, 2010)**

1. PURPOSES.

(a) Amendment and Restatement. This Plan was originally an amendment and restatement of the Isis Pharmaceuticals, Inc. 1992 Non-Employee Directors' Stock Option Plan, and is an amendment and restatement of the Isis Pharmaceuticals, Inc. 2002 Non-Employee Director's Stock Option Plan, as amended through June 7, 2012. The amendment and restatement of the Plan shall not amend or cancel any options granted and outstanding under this Plan as of the amendment and restatement date.

(b) Eligible Recipients. The persons eligible to receive Stock Awards are the Non-Employee Directors of the Company.

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

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

2. DEFINITIONS.

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

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

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

(d) **“Capitalization Adjustment”** has the meaning ascribed to that term in Section 12(a).

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

(i) any Exchange Act Person becomes the Owner, directly or indirectly, of securities of the Company representing more than 50% of the combined voting power of the Company’s then outstanding securities

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other than by virtue of a merger, consolidation or similar transaction and other than by a purchase of securities directly from the Company;

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

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

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

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

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

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

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

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

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

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

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payment of a director's fee by the Company for services as a Director shall not cause a Director to be considered a "Consultant" for purposes of the Plan.

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

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

(i) a sale or other disposition of all or substantially all, as determined by the Board in its discretion, of the consolidated assets of the Company and its Subsidiaries;

(ii) a sale or other disposition of at least 90% of the outstanding securities of the Company;

(iii) a merger, consolidation or similar transaction following which the Company is not the surviving corporation; or

(iv) a merger, consolidation or similar transaction following which the Company is the surviving corporation but the shares of Common Stock outstanding immediately preceding the merger, consolidation or similar transaction are converted or exchanged by virtue of the merger, consolidation or similar transaction into other property, whether in the form of securities, cash or otherwise.

(l) **"Director"** means a member of the Board of Directors of the Company.

(m) **"Disability"** means the permanent and total disability of a person within the meaning of Section 22(e)(3) of the Code.

(n) **"Employee"** means any person employed by the Company or an Affiliate. Service as a Director or payment of a director's fee by the Company or an Affiliate shall not be sufficient to constitute "employment" by the Company or an Affiliate.

(o) **"Entity"** means a corporation, partnership or other entity.

(p) **"Exchange Act"** means the Securities Exchange Act of 1934, as amended.

(q) **"Exchange Act Person"** means any natural person, Entity or "group" (within the meaning of Section 13(d) or 14(d) of the Exchange Act), except that "Exchange Act Person" shall not include (A) the Company or any Subsidiary of the Company, (B) any employee benefit plan of the Company or any Subsidiary of the Company or any trustee or other fiduciary holding securities under an employee benefit plan of the Company or any Subsidiary of the Company, (C) an underwriter temporarily holding securities pursuant to an offering of such securities, or (D) an Entity Owned, directly or indirectly, by the stockholders of the Company in substantially the same proportions as their Ownership of stock of the Company.

(r) **"Fair Market Value"** means, as of any date, the value of the Common Stock determined as follows:

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(i) If the Common Stock is listed on any established stock exchange or traded on the Nasdaq National Market or the Nasdaq SmallCap Market, the Fair Market Value of a share of Common Stock shall be the closing sales price for such stock (or the closing bid, if no sales were reported) as quoted on such exchange or market (or the exchange or market with the greatest volume of trading in the Common Stock) on the last market trading day prior to the day of determination, as reported in The Wall Street Journal or such other source as the Board deems reliable.

(ii) In the absence of such markets for the Common Stock, the Fair Market Value shall be determined in good faith by the Board.

(s) **"Holder"** means a person to whom an Option or RSU Award is granted pursuant to the Plan or, if applicable, such other person who holds an outstanding Option or RSU Award.

(t) **"Initial Grant"** means an Option and/or RSU granted to a Non-Employee Director who meets the criteria specified in subsection 6(a) of the Plan.

(u) **"Non-Employee Director"** means a Director who is not an Employee.

(v) **"Nonstatutory Stock Option"** means an Option not intended to qualify as an incentive stock option within the meaning of Section 422 of the Code and the regulations promulgated thereunder.

(w) **"Officer"** means a person who is an officer of the Company within the meaning of Section 16 of the Exchange Act and the rules and regulations promulgated thereunder.

(x) **"Option"** means a Nonstatutory Stock Option granted pursuant to the Plan.

(y) **"Option Agreement"** means a written agreement between the Company and a Holder evidencing the terms and conditions of an individual Option grant. Each Option Agreement shall be subject to the terms and conditions of the Plan.

(z) **“Option Allocation Percentage”** means the percentage (ranging from 0% to 100%) that was attributable to stock options which the Compensation Committee of the Board most recently approved before the date of grant hereunder when it set the allocation of equity compensation for the Company’s employees between stock options and restricted stock unit awards.

(aa) **“Own,” “Owned,” “Owner,” “Ownership”** A person or Entity shall be deemed to “Own,” to have “Owned,” to be the “Owner” of, or to have acquired “Ownership” of securities if such person or Entity, directly or indirectly, through any contract, arrangement, understanding, relationship or otherwise, has or shares voting power, which includes the power to vote or to direct the voting, with respect to such securities.

(bb) **“Plan”** means this Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors’ Stock Option Plan, which is an amendment and restatement of the Isis Pharmaceuticals, Inc. 1992 Non-Employee Directors’ Stock Option Plan.

(cc) **“RSU Award”** means a right to receive shares of Common Stock which is granted pursuant to the terms and conditions of Section 8.

(dd) **“RSU Award Agreement”** means a written agreement between the Company and a holder of a RSU Award evidencing the terms and conditions of a RSU Award grant. Each RSU Award Agreement shall be subject to the terms and conditions of the Plan.

(ee) **“RSU Allocation Percentage”** means the percentage that was attributable to restricted stock units which the Compensation Committee of the Board approved before the date of grant hereunder when it set the

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allocation of equity compensation for the Company’s employees between stock options and restricted stock unit awards. The RSU Allocation Percentage will always equal one *minus* the Option Allocation Percentage.

(ff) **“RSU:Option Valuation Ratio”** means the ratio, represented as a percentage, comparing the value (as determined by the Compensation Committee of the Board) of (i) a restricted stock unit to receive one share of the Company’s common stock to (ii) an option to purchase shares of the Company’s common stock at fair market value at the time of grant, as most recently approved by the Compensation Committee of the Board in connection with setting the equity compensation for the Company’s employees; *provided*, such ratio can never be more than 100%. For example, if the Compensation Committee of the Board determines that a restricted stock unit to receive one share of the Company’s common stock has a value that is equal to an option to purchase three shares of the Company’s common stock at fair market value, then the RSU:Option Valuation Ratio would be 33.33% (i.e 1:3).

(gg) **“Rule 16b-3”** means Rule 16b-3 promulgated under the Exchange Act or any successor to Rule 16b-3, as in effect from time to time.

(hh) **“Securities Act”** means the Securities Act of 1933, as amended.

(ii) **“Stock Award”** means an Option or RSU Award, as applicable.

(jj) **“Subsidiary”** means, with respect to the Company, (i) any corporation of which more than 50% of the outstanding capital stock having ordinary voting power to elect a majority of the board of directors of such corporation (irrespective of whether, at the time, stock of any other class or classes of such corporation shall have or might have voting power by reason of the happening of any contingency) is at the time, directly or indirectly Owned by the Company, and (ii) any partnership in which the Company has a direct or indirect interest (whether in the form of voting or participation in profits or capital contribution) of more than 50%.

3. ADMINISTRATION.

(a) **Administration by Board.** The Board shall administer the Plan. The Board may not delegate administration of the Plan to a committee.

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

(i) To determine the provisions of each Stock Award to the extent not specified in the Plan.

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

(iii) To amend the Plan or a Stock Award as provided in Section 13.

(iv) To terminate or suspend the Plan as provided in Section 14.

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

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

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

4. SHARES SUBJECT TO THE PLAN.

(a) **Share Reserve.** Subject to the provisions of Section 12(a) relating to Capitalization Adjustments, the Common Stock that may be issued pursuant to Stock Awards shall not exceed in the aggregate **1,200,000** shares of Common Stock.

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

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

5. ELIGIBILITY.

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

6. NON-DISCRETIONARY GRANTS.

(a) **Initial Grants.** Without any further action of the Board, each person who is elected or appointed for the first time after the effective date of this amendment and restatement of the Plan to be a Non-Employee Director automatically shall, upon the date of his or her initial election or appointment to be a Non-Employee Director by the Board or stockholders of the Company, as applicable, be granted, on the terms and conditions set forth herein, an Initial Grant of Option and RSU Awards calculated as follows (in each case rounding down to the nearest whole share):

(i) An Option to purchase a number of shares of Common Stock equal to 30,000 multiplied by the then applicable Option Allocation Percentage; and

(ii) An RSU Award to receive a number of shares of Common Stock equal to 30,000 multiplied by the then applicable RSU Allocation Percentage and multiplied by the then applicable RSU:Option Valuation Ratio.

(b) **Annual Grants.** Without any further action of the Board, after the effective date of this amendment and restatement of the Plan, a Non-Employee Director shall be granted an Annual Grant as follows: On July 1 of each year, beginning on July 1, 2012, each person who is then a Non-Employee Director automatically shall be granted, on the terms and conditions set forth herein, an Annual Grant of Option and RSU Awards calculated as follows (in each case rounding to the nearest whole share):

(i) An Option to purchase a number of shares of Common Stock equal to 15,000 multiplied by the then applicable Option Allocation Percentage; and

(ii) An RSU Award to receive a number of shares of Common Stock equal to 15,000 multiplied by the then applicable RSU Allocation Percentage and multiplied by the then applicable RSU:Option Valuation Ratio.

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For example, if the Option Allocation Percentage is 75%, the RSU Allocation Percentage is 25%, and the RSU:Option Valuation Ratio is 33.33%, then the Annual Grant would be an Option to purchase 11,250 shares of Common Stock (i.e., 15,000 x 75%), and an RSU Award to receive 1,250 shares of Common stock (i.e., 15,000 x 25% x 33.33%). Should the date of grant set forth above be a legal holiday, then such grant shall be made on the next business day.

7. OPTION PROVISIONS.

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

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

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

(c) **Consideration.** The purchase price of Common Stock acquired pursuant to the exercise of an Option shall be paid, to the extent permitted by applicable law, by any combination of the following methods of payment:

(i) by cash, check, bank draft or money order payable to the Company; or

(ii) pursuant to a program developed under Regulation T as promulgated by the Federal Reserve Board that, prior to the issuance of the stock subject to the Option, results in either the receipt of cash (or check) by the Company or the receipt of irrevocable instructions to pay the aggregate exercise price to the Company from the sales proceeds.

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

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

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

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

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

(g) **Termination of Continuous Service.** In the event that an Holder's Continuous Service terminates (other than upon the Holder's death or Disability), the Holder may exercise his or her Option (to the

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

(h) **Extension of Termination Date.** An Holder's Option Agreement may also provide that if the exercise of the Option following the termination of the Holder's Continuous Service (other than upon the Holder's death or Disability) would be prohibited at any time solely because the issuance of shares of Common Stock would violate the registration requirements under the Securities Act, then the Option shall terminate on the earlier of (i) the expiration of the term of the Option set forth in subsection 7(a) or (ii) the expiration of a period of 3 months after the termination of the Holder's Continuous Service during which the exercise of the Option would not be in violation of such registration requirements. In addition, unless otherwise provided in an Holder's Option Agreement, if the immediate sale of any Common Stock received upon exercise of an Option following the termination of the Holder's Continuous Service would violate the Company's insider trading policy, then the Option shall terminate on the earlier of (i) the expiration of a period equal to the applicable post-termination exercise period after the termination of the Holder's Continuous Service during which the sale of Common Stock received upon exercise of the Option would not be in violation of the Company's insider trading policy, or (ii) the expiration of the term of the Option as set forth in the applicable Option Agreement.

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

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

8. RESTRICTED STOCK UNIT PROVISIONS.

Each Restricted Stock Unit Award Agreement shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. The terms and conditions of Restricted Stock Unit Award Agreements may change from time to time, and the terms and conditions of separate Restricted Stock Unit Award Agreements need not be identical; *provided, however*, that each Restricted Stock Unit Award Agreement shall conform to (through incorporation of the provisions hereof by reference in the Agreement or otherwise) the substance of each of the following provisions:

(a) **Consideration.** At the time of grant of a Restricted Stock Unit Award, the Board will determine the consideration, if any, to be paid by the Holder upon delivery of each share of Common Stock subject to the Restricted Stock Unit Award. The consideration to be paid (if any) by the Holder for each share of Common Stock subject to a Restricted Stock Unit Award may be paid in any form of legal consideration that may be acceptable to the Board, in its sole discretion, and permissible under applicable law.

(b) **Vesting.** Each RSU Award under this Plan shall vest as follows: one-fourth of the shares subject to the RSU shall vest on each annual anniversary of the date of grant provided that the Holder has, during the entire

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year prior to such vesting date, continuously served as a Non-Employee Director or as an Employee of or Consultant to the Company or any Affiliate.

(c) **Payment.** A Restricted Stock Unit Award may be settled by the delivery of shares of Common Stock, their cash equivalent, any combination thereof or in any other form of consideration, as determined by the Board and contained in the Restricted Stock Unit Award Agreement.

(d) **Additional Restrictions.** At the time of the grant of a Restricted Stock Unit Award, the Board, as it deems appropriate, may impose such restrictions or conditions that delay the delivery of the shares of Common Stock (or their cash equivalent) subject to a Restricted Stock Unit Award to a time after the vesting of such Restricted Stock Unit Award.

(e) **Dividend Equivalents.** Dividend equivalents may be credited in respect of shares of Common Stock covered by a Restricted Stock Unit Award, as determined by the Board and contained in the Restricted Stock Unit Award Agreement. At the sole discretion of the Board, such dividend equivalents may be converted into additional shares of Common Stock covered by the Restricted Stock Unit Award in such manner as determined by the Board. Any additional shares covered by the Restricted Stock Unit Award credited by reason of such dividend equivalents will be subject to all of the same terms and conditions of the underlying Restricted Stock Unit Award Agreement to which they relate.

(f) **Termination of Holder's Continuous Service.** Except as otherwise provided in the applicable Restricted Stock Unit Award Agreement, such portion of the Restricted Stock Unit Award that has not vested will be forfeited upon the Holder's termination of Continuous Service.

9. COVENANTS OF THE COMPANY.

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

(b) **Securities Law Compliance.** The Company shall seek to obtain from each regulatory commission or agency having jurisdiction over the Plan such authority as may be required to grant Stock Awards and to issue and sell shares of Common Stock upon exercise of the Stock Awards; provided, however, that this undertaking shall not require the Company to register under the Securities Act the Plan, any Stock Award or any Common Stock issued or issuable pursuant to any such Stock Award. If, after reasonable efforts, the Company is unable to obtain from any such regulatory commission or agency the authority which counsel for the Company deems necessary for the lawful issuance and sale of Common Stock under the Plan, the Company shall be relieved from any liability for failure to issue and sell Common Stock upon exercise of such Stock Awards unless and until such authority is obtained. A Non-Employee Director shall not be eligible for the grant of a Stock Award or the subsequent issuance of Common Stock pursuant to the Stock Award if such grant or issuance would violate any applicable securities law.

(c) **No Obligation to Notify or Minimize Taxes.** The Company shall have no duty or obligation to any Holder to advise such Holder (or the estate of, or transferee of, such Holder) as to the time or manner of exercising such Stock Award. Furthermore, the Company shall have no duty or obligation to warn or otherwise advise such Holder (or the estate of, or transferee of, such Holder) of a pending termination or expiration of a Stock Award or a possible period in which the Stock Award may not be exercised. The Company has no duty or obligation to minimize the tax consequences of a Stock Award to the Holder of such Stock Award.

10. USE OF PROCEEDS FROM STOCK.

Proceeds from the sale of Common Stock pursuant to Options or RSU Awards (if any) shall constitute general funds of the Company.

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11. MISCELLANEOUS.

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

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

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

(d) **Investment Assurances.** The Company may require a Holder, as a condition of exercising or acquiring Common Stock under any Award, (i) to give written assurances satisfactory to the Company as to the Holder's knowledge and experience in financial and business matters and/or to employ a purchaser representative reasonably satisfactory to the Company who is knowledgeable and experienced in financial and business matters and that he or she is capable of evaluating, alone or together with the purchaser representative, the merits and risks of exercising the Stock Award; and (ii) to give written assurances satisfactory to the Company stating that the Holder is acquiring the Common Stock subject to the Stock Award for the Holder's own account and not with any present intention of selling or otherwise distributing the Common Stock. The foregoing requirements, and any assurances given pursuant to such requirements, shall be inoperative if (1) the issuance of the shares of Common Stock upon the exercise or acquisition of Common Stock under the Stock Award has been registered under a then currently effective registration statement under the Securities Act or (2) as to any particular requirement, a determination is made by counsel for the Company that such requirement need not be met in the circumstances under the then applicable securities laws. The Company may, upon advice of counsel to the Company, place legends on stock certificates issued under the Plan as such counsel deems necessary or appropriate in order to comply with applicable securities laws, including, but not limited to, legends restricting the transfer of the Common Stock.

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

(f) **Electronic Delivery.** Any reference herein to a "written" agreement or document shall include any agreement or document delivered electronically or posted on the Company's intranet (or other shared electronic medium controlled by the Company to which the Holder has access).

12. ADJUSTMENTS UPON CHANGES IN STOCK.

(a) **Capitalization Adjustments.** If any change is made in, or other event occurs with respect to, the Common Stock subject to the Plan, or subject to any Stock Award, without the receipt of consideration by the Company (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by the Company) (each, a “Capitalization Adjustment”), the Plan will be appropriately adjusted in the class(es) and maximum number of securities subject both to the Plan pursuant to subsection 4(a) and to the nondiscretionary Stock Awards specified in Section 6, and the outstanding Stock Awards will be appropriately adjusted in the class(es) and number of securities and price per share of Common Stock subject to such outstanding Stock Awards. The Board shall make such adjustments, and its determination shall be final, binding and conclusive. (The conversion of any convertible securities of the Company shall not be treated as a transaction “without receipt of consideration” by the Company.)

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

(c) **Corporate Transaction.** In the event of a Corporate Transaction, any surviving corporation or acquiring corporation may assume any or all Stock Awards outstanding under the Plan or may substitute similar stock awards for Stock Awards outstanding under the Plan (it being understood that similar stock awards include, but are not limited to, options to acquire, or restricted stock unit rights to receive, the same consideration paid to the stockholders or the Company, as the case may be, pursuant to the Corporate Transaction). In the event that any surviving corporation or acquiring corporation does not assume any or all such outstanding Stock Awards or substitute similar stock awards for such outstanding Stock Awards, then with respect to Stock Awards that have been neither assumed nor substituted and that are held by Holders whose Continuous Service has not terminated prior to the effective time of the Corporate Transaction, the vesting of such Stock Awards (and, if applicable, the time at which such Stock Awards may be exercised) shall (contingent upon the effectiveness of the Corporate Transaction) be accelerated in full to a date prior to the effective time of such Corporate Transaction as the Board shall determine (or, if the Board shall not determine such a date, to the date that is 5 days prior to the effective time of the Corporate Transaction), and the Stock Awards shall terminate if not exercised at or prior to such effective time. With respect to Stock Awards outstanding under the Plan that have been neither assumed nor substituted and that are held by Holders whose Continuous Service has terminated prior to the effective time of the Corporate Transaction, the vesting of such Stock Awards (and, if applicable, the time at which such Stock Award may be exercised) shall not be accelerated unless otherwise provided in a written agreement between the Company or any Affiliate and the holder of such Stock Award, and such Stock Awards shall terminate if not exercised prior to the effective time of the Corporate Transaction.

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

(e) **Parachute Payments.** If any payment or benefit the Holder would receive pursuant to a Change in Control from the Company or otherwise (“Payment”) would (i) constitute a “parachute payment” within the meaning of Section 280G of the Code, and (ii) but for this sentence, be subject to the excise tax imposed by Section 4999 of the Code (the “Excise Tax”), then such Payment shall be reduced to the Reduced Amount. The “Reduced Amount” shall be either (x) the largest portion of the Payment that would result in no portion of the Payment being subject to the Excise Tax or (y) the largest portion, up to and including the total, of the Payment, whichever amount, after taking into account all applicable federal, state and local employment taxes, income taxes, and the Excise Tax (all computed at the highest applicable marginal rate), results in the Holder’s receipt, on an after-tax basis, of the

greater amount of the Payment notwithstanding that all or some portion of the Payment may be subject to the Excise Tax. If a reduction in a Payment is required pursuant to the preceding sentence and the Reduced Amount is determined pursuant to clause (x) of the preceding sentence, the reduction shall occur in the manner (the “**Reduction Method**”) that results in the greatest economic benefit for Holder. If more than one method of reduction will result in the same economic benefit, the items so reduced will be reduced pro rata (the “**Pro Rata Reduction Method**”). Notwithstanding the foregoing, if the Reduction Method or the Pro Rata Reduction Method would result in any portion of the Payment being subject to taxes pursuant to Section 409A of the Code that would not otherwise be subject to taxes pursuant to Section 409A of the Code, then the Reduction Method and/or the Pro Rata Reduction Method, as the case may be, shall be modified so as to avoid the imposition of taxes pursuant to Section 409A of the Code as follows: (A) as a first priority, the modification shall preserve to the greatest extent possible, the greatest economic benefit for Holder as determined on an after-tax basis; (B) as a second priority, Payments that are contingent on future events (e.g., being terminated without cause), shall be reduced (or eliminated) before Payments that are not contingent on future events; and (C) as a third priority, Payments that are “deferred compensation” within the meaning of Section 409A of the Code shall be reduced (or eliminated) before Payments that are not deferred compensation within the meaning of Section 409A of the Code.

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

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

13. AMENDMENT OF THE PLAN AND STOCK AWARDS.

- (a) **Amendment of Plan.** The Board at any time, and from time to time, may amend the Plan. However, except as provided in Section 12(a) relating to Capitalization Adjustments, no amendment shall be effective unless approved by the stockholders of the Company to the extent stockholder approval is necessary to satisfy the requirements of Rule 16b-3 or any Nasdaq or securities exchange listing requirements.
- (b) **Stockholder Approval.** The Board, in its sole discretion, may submit any other amendment to the Plan for stockholder approval.
- (c) **No Impairment of Rights.** Rights under any Stock Award granted before amendment of the Plan shall not be impaired by any amendment of the Plan unless (i) the Company requests the consent of the Holder and (ii) the Holder consents in writing.
- (d) **Amendment of Stock Awards.** The Board at any time, and from time to time, may amend the terms of any one or more Stock Awards; *provided, however*, that the rights under any Stock Award shall not be impaired by any such amendment unless (i) the Company requests the consent of the Holder and (ii) the Holder consents in writing.
- (e) **Option Repricing Prohibited.** The Board will not have the authority, at any time, without obtaining the approval of a majority of the shares present or represented and entitled to vote at a duly convened meeting of stockholders, to (1) reduce the exercise price of any Options under the Plan that are currently outstanding; or (2) cancel any outstanding Options under the Plan and grant in substitution therefore new Options

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under the Plan at a lower exercise price (including entering into any “6 month and 1 day” cancellation and re-grant scheme), regardless of whether or not the cancelled Options revert to and again become available for issuance under the Plan This Section 13(e) may not be amended without the affirmative vote of the holders of a majority of the shares present or represented and entitled to vote at a duly convened meeting of the stockholders of the Company. Notwithstanding the foregoing, this paragraph will not be construed to apply to “issuing or assuming a stock option in a transaction to which section 424(a) applies,” within the meaning of Section 424 of the Code.”

14. TERMINATION OR SUSPENSION OF THE PLAN.

- (a) **Plan Term.** The Board may suspend or terminate the Plan at any time. Unless sooner terminated, the Plan shall terminate on June 1, 2020. No Stock Awards may be granted under the Plan while the Plan is suspended or after it is terminated.
- (b) **No Impairment of Rights.** Suspension or termination of the Plan shall not impair rights and obligations under any Stock Award granted while the Plan is in effect except with the written consent of the Holder.

15. EFFECTIVE DATE OF PLAN.

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

16. CHOICE OF LAW.

The law of the State of California shall govern all questions concerning the construction, validity and interpretation of this Plan without regard to such state’s conflict of laws rules.

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Appendix C

**AMENDMENT
TO
ISIS PHARMACEUTICALS, INC.
1989 STOCK OPTION PLAN
ADOPTED BY THE BOARD OF DIRECTORS MARCH 27, 2012**

SUBJECT TO APPROVAL BY STOCKHOLDERS

The Amendment to the Isis Pharmaceuticals, Inc. 1989 Stock Option Plan (the “Amendment”), is effective as of June 7, 2012.

- A. WHEREAS, subject to approval by Isis’ stockholders, the Board of Directors of Isis approved an amendment and restatement to the Isis Pharmaceuticals, Inc. 1989 Stock Option Plan (the “Plan”), as more fully described below.

NOW THEREFORE, the Plan is hereby amended and restated as follows:

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

ARTICLE 1. AMENDMENT

- 1.1 Amendment of Section 12(a). Section 12(a) of the Plan is hereby amended, restated and replaced in its entirety by the following language:

12. TERMINATION OR SUSPENSION OF THE PLAN.

(a) The Committee may suspend or terminate the Plan at any time. Unless sooner terminated, the Plan will terminate on January 31, 2024. No Options may be granted under the Plan while the Plan is suspended or after it is terminated.

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ISIS PHARMACEUTICALS, INC.
1989 STOCK OPTION PLAN

As Amended September 5, 1991
As Amended September 4, 1992
As Amended January 4, 1993
As Amended December 2, 1993 and January 20, 1994
As Amended December 7, 1994
As Amended February 27, 1995 and December 14, 1995
As Amended September 6, 1996
As Amended February 27, 1998
As Amended March 29, 2004
As Amended June 5, 2008
As Amended February 27, 2009
As Amended February 26, 2010

1. PURPOSE.

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

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

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

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

2. ADMINISTRATION.

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

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

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

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

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

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

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

3. SHARES SUBJECT TO THE PLAN.

(a) Subject to the provisions of paragraph 10 relating to adjustments upon changes in stock, the stock that may be issued pursuant to Options granted under the Plan will not exceed in the aggregate 20,000,000 shares of the Company's common stock. If any Option granted under the Plan will for any reason expire or otherwise terminate without having been exercised in full, the stock not purchased under such Option will again become available for the Plan.

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

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

4. ELIGIBILITY.

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

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

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

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5. OPTION PROVISIONS.

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

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

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

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

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

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

(f) The Company may require any optionee, or any person to whom an Option is transferred under subparagraph 5(d), as a condition of exercising any such Option, (1) to give written assurances satisfactory to the Company as to the optionee's knowledge and experience in financial and business matters and/or to employ a purchaser representative reasonably satisfactory to the Company who is knowledgeable and experienced in financial and business matters, and that he or she is capable of evaluating, alone or together with the purchaser representative, the merits and risks of exercising the Option; and (2) to give written assurances satisfactory to the Company stating that such person is acquiring the stock subject to the Option for such person's own account and not with any present intention of selling or otherwise distributing the stock. These requirements, and any assurances given pursuant to such requirements, will be inoperative as to any particular requirement, if a determination is made by counsel for the Company that such requirement need not be met in the circumstances under the then applicable securities laws.

(g) An Option will terminate 3 months after termination of the optionee's employment or relationship as a consultant or director with the Company or an Affiliate, unless (i) such termination is due to such person's permanent and total disability, within the meaning of Section 422(c)(6) of the Code, in which case the Option may, but need not, provide that it may be exercised at any time within 1 year following such termination of employment or relationship as a consultant or director; or (ii) the optionee dies while in the employ of or while serving as a consultant or director to the Company or an Affiliate, or within not more than 3 months after termination of such relationship, in which case the Option may, but need not, provide that it may be exercised at any time within 18 months following the death of the optionee by the person or persons to whom the optionee's rights under such Option pass by will or by the laws of descent and distribution; or (iii) the Option by its terms specifies either (a) that it will terminate sooner than 3 months after termination

with the Company or an Affiliate. This subparagraph 5(g) will not be construed to extend the term of any Option or to permit anyone to exercise the Option after expiration of its term, nor will it be construed to increase the number of shares as to which any Option is exercisable from the amount exercisable on the date of termination of the optionee's employment or relationship as a consultant or director.

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

6. COVENANTS OF THE COMPANY.

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

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

7. USE OF PROCEEDS FROM STOCK.

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

8. MISCELLANEOUS.

(a) Subject to the limitation set forth in Section 5(e), and *solely* in connection with (i) an optionee's death, permanent and total disability within the meaning of Section 422(c)(6) of the Code or retirement from the Company; or (ii) a Change in Control, the Committee will have the power to accelerate the time during which an Option may be exercised or the time during which an Option or any part thereof will vest, notwithstanding the provisions in the Option stating the time during which it may be exercised or the time during which it will vest. For purposes of this Section 8(a), Change in Control means: (i) a sale of all or substantially all of the assets of the Company; (ii) a merger or consolidation in which the Company is not the surviving corporation and in which beneficial ownership of securities of the Company representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of Directors has changed; (iii) 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, and in which beneficial ownership of securities of the Company representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of the Company's Board of Directors has changed; or (iv) an acquisition by any person, entity or group within the meaning of Section 13(d) or 14(d) of the Exchange Act, or any comparable successor provisions (excluding any employee benefit plan, or related trust, sponsored or maintained by the Company or subsidiary of the Company or other entity controlled by the Company) of the beneficial ownership (within the meaning of Rule 13d-3 promulgated under the Exchange Act, or comparable successor rule) of securities of the Company representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of the Company's Board of Directors."

(b) Neither an optionee nor any person to whom an Option is transferred under subparagraph 5(d) will be deemed to be the holder of, or to have any of the rights of a holder with respect to, any shares subject to

such Option unless and until such person has satisfied all requirements for exercise of the Option pursuant to its terms.

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

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

9. OPTION REPRICING PROHIBITED.

The Board will not have the authority, at any time, without obtaining the approval of a majority of the shares present or represented and entitled to vote at a duly convened meeting of stockholders, to (1) reduce the exercise price of any Options under the Plan that are currently outstanding; or

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

10. ADJUSTMENTS UPON CHANGES IN STOCK.

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

(b) In the event of: (1) a dissolution or liquidation of the Company; (2) a merger or consolidation in which the Company is not the surviving corporation; or (3) a reverse merger in which the Company is the surviving corporation but the shares of the Company's common stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise then to the extent permitted by applicable law: (i) any surviving corporation will assume any Options outstanding under the Plan or will substitute similar Options for those outstanding under the Plan, or (ii) such Options will continue in full force and effect. In the event any surviving corporation refuses to assume or continue such Options, or to substitute similar Options for those outstanding under the Plan, then, with respect to Options held by persons then performing services as employees or as consultants or directors for the Company, as the case may be, the time during which such Options become vested or may be exercised will be accelerated and the Options terminated if not exercised prior to such event.

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11. AMENDMENT OF THE PLAN.

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

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

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

12. TERMINATION OR SUSPENSION OF THE PLAN.

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

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

13. EFFECTIVE DATE OF PLAN.

The Plan is effective April 19, 1991.

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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 PROXY MATERIALS

If you would like to reduce the costs incurred by our company 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 proxy materials 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 Vote Processing, c/o Broadridge, 51 Mercedes Way, Edgewood, NY 11717.

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

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

THIS PROXY CARD IS VALID ONLY WHEN SIGNED AND DATED.

	For All	Withhold All	For All Except
The Board of Directors recommends you vote FOR the following nominee to be elected for a term expiring 2015:	o	o	o

**1. Election of Directors
Nominees**

01 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.

The Board of Directors recommends you vote FOR proposals 2, 3, 4 and 5.	For	Against	Abstain
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2. Approve an amendment and restatement of the Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan.	o	o	o
3. Approve an extension to the term of the Isis Pharmaceuticals, Inc. Amended and Restated 1989 Stock Option Plan.	o	o	o
4. To approve, by non-binding vote, executive compensation.	o	o	o
5. Ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for the 2012 fiscal year.	o	o	o

NOTE: Such other business as may properly come before the meeting or any adjournment thereof.

Please sign exactly as your name(s) appear(s) hereon. When signing as attorney, executor, administrator, or other fiduciary, please give full title as such. Joint owners should each sign personally. All holders must sign. If a corporation or partnership, please sign in full corporate or partnership name, by authorized officer.

Signature [PLEASE SIGN WITHIN BOX]	Date	Signature (Joint Owners)	Date
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Important Notice Regarding the Availability of Proxy Materials for the Annual Meeting: The Form 10-K, Notice & Proxy Statement is/are available at www.proxyvote.com.

PROXY

THIS PROXY IS SOLICITED ON BEHALF OF THE BOARD OF DIRECTORS OF ISIS PHARMACEUTICALS, INC.

The undersigned hereby appoints B. Lynne Parshall and Stanley T. Crooke, and each of them, with power to act without the other and with power of substitution, as proxies and attorneys-in-fact and hereby authorizes them to represent and vote, as provided on the other side, all the shares of Isis Pharmaceuticals, Inc. Common Stock which the undersigned is entitled to vote and, in their discretion, to vote upon such other business as may properly come before the Annual Meeting of Stockholders of the Company to be held June 7, 2012 or any adjournment thereof with all powers which the undersigned would possess if present at the Meeting.

THIS PROXY CARD, WHEN PROPERLY EXECUTED, WILL BE VOTED IN THE MANNER DIRECTED HEREIN BY THE UNDERSIGNED. IF NO DIRECTION IS MADE BUT THE CARD IS SIGNED, THIS PROXY CARD WILL BE VOTED FOR THE ELECTION OF THE NOMINEE UNDER PROPOSAL 1, FOR PROPOSAL 2, FOR PROPOSAL 3, FOR PROPOSAL 4 AND FOR PROPOSAL 5 AND IN THE DISCRETION OF THE PROXIES WITH RESPECT TO SUCH OTHER BUSINESS AS MAY PROPERLY COME BEFORE THE MEETING.

Continued and to be signed on reverse side