

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

**SCHEDULE 14A**

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

Filed by the Registrant

Filed by a Party other than the Registrant

Check the appropriate box:

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

**Isis Pharmaceuticals, Inc.**

(Name of Registrant as Specified In Its Charter)

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

Payment of Filing Fee (Check the appropriate box):

- No fee required.
- 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:  
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ISIS PHARMACEUTICALS, INC.  
2855 Gazelle Court  
Carlsbad, CA 92010

NOTICE OF

2014 ANNUAL MEETING OF STOCKHOLDERS

Dear Stockholders,

I am pleased to invite you to Isis Pharmaceuticals, Inc.'s 2014 Annual Meeting of Stockholders. We will host the meeting at our offices in Carlsbad, California on Tuesday, June 10, 2014, at 2:00 p.m. Pacific Time. This booklet includes the agenda for this year's Annual Meeting and the Proxy Statement. We will cover the formal items on the agenda during the Annual Meeting. Following the formal Annual Meeting, we will review the major developments of the past year and our plans for 2014, and answer your questions. The Proxy Statement explains the matters we will discuss in the meeting and provides additional information about us.

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 proxy materials under a Securities and Exchange Commission rule that allows us to furnish such material to our stockholders over the Internet rather than in paper form. We believe this method of distribution reduces our environmental impact and costs without hindering our stockholders' timely access to such important material. As a result, if you are a stockholder of record (that is, if your stock is registered with us in your own name) you will receive a Notice Regarding the Availability of Proxy Materials in the mail, which contains a control number and instructions that allow you to access our proxy materials and vote electronically through the Internet or to request printed proxy materials so you may vote by telephone or mail.

If your shares are registered in the name of a broker or other nominee, that nominee will forward the Notice Regarding the Availability of Proxy Materials to you and you can direct that nominee to vote your shares. Alternatively, if your nominee participates in a program provided through Broadridge Financial Solutions, Inc. that allows you to vote by telephone or through the Internet, your nominee will send you a voting form with 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. In this document, unless the context requires otherwise, the words "Isis," "Company," "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

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

NOTICE OF 2014 ANNUAL MEETING OF STOCKHOLDERS

Date: Tuesday, June 10, 2014  
Time: 2:00 p.m., Pacific Time  
Place: Isis Pharmaceuticals, Inc.  
2855 Gazelle Court  
Carlsbad, CA 92010

Dear Stockholders,

At our 2014 Annual Meeting, we will ask you to:

- Proposal 1: elect Spencer R. Berthelsen, B. Lynne Parshall and Joseph H. Wender to serve as Directors for a three-year term;
- Proposal 2: make an advisory vote, ratifying the appointment of Breau B. Castleman to fill a vacancy on our Board of Directors for a one-year term;
- Proposal 3: make an advisory vote, ratifying the appointment of Joseph Loscalzo to fill a vacancy on our Board of Directors for a two-year term;
- Proposal 4: approve an amendment to the Company's Restated Certificate of Incorporation to increase the authorized number of shares of Common Stock from 200,000,000 to 300,000,000 shares;
- Proposal 5: approve an amendment and restatement of our 2002 Non-Employee Directors' Stock Option Plan to (i) increase the non-discretionary stock option grants for new Directors to 32,000 shares and non-discretionary annual grants to all non-employee Directors to 16,000 shares, with a corresponding RSU award, and (ii) update the provision prohibiting our Board of Directors from repricing or cancelling outstanding options in exchange for cash or other stock awards without obtaining the approval of our stockholders;
- Proposal 6: make an advisory vote on executive compensation;
- Proposal 7: ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2014 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 11, 2014 you may vote at the Annual Meeting.

By order of the Board of Directors,

B. Lynne Parshall  
Secretary

Carlsbad, California  
April 29, 2014

**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.**

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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 (the "Board") is soliciting your proxy to vote at the 2014 Annual Meeting of Stockholders, including at any adjournments or postponements of 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 (the "SEC"). As a result, you received in the mail the Notice Regarding the Availability of Proxy Materials (the "Notice"). 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 to 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 29, 2014 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 9, 2014.

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

We will hold the meeting on Tuesday, June 10, 2014, at 2:00 p.m. Pacific Time at our offices located at 2855 Gazelle Court, Carlsbad, California 92010. You may find directions to the Annual Meeting at [www.isispharm.com](http://www.isispharm.com).<sup>1</sup> 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 that follows the Annual Meeting available on the day of the meeting and for a limited time following the meeting at [www.isispharm.com](http://www.isispharm.com).<sup>1</sup>

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 11, 2014 may vote at the Annual Meeting. On this record date, there were 117,555,909 shares of common stock outstanding and entitled to vote.

*Stockholder of Record: Shares Registered in Your Name*

If on April 11, 2014 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 over the telephone or the Internet as instructed under the section below titled "How do I vote?" Whether or not you plan to attend the meeting, we urge you to fill out and return the proxy card or vote over the telephone or Internet to ensure your vote is counted.

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<sup>1</sup> 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.

If on April 11, 2014 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 in person.

**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 seven matters scheduled for a vote:

- Proposal 1: elect Spencer R. Berthelsen, B. Lynne Parshall and Joseph H. Wender to serve as Directors for a three-year term;
- Proposal 2: make an advisory vote, ratifying the appointment of Breaux B. Castleman to fill a vacancy on our Board of Directors for a one-year term;
- Proposal 3: make an advisory vote, ratifying the appointment of Joseph Loscalzo to fill a vacancy on our Board of Directors for a two-year term;
- Proposal 4: approve an amendment to the Company’s Restated Certificate of Incorporate to increase the authorized number of shares of Common Stock from 200,000,000 to 300,000,000 shares;
- Proposal 5: approve an amendment and restatement of our 2002 Non-Employee Directors’ Stock Option Plan to (i) increase the non-discretionary stock option grants for new Directors to 32,000 shares and non-discretionary annual grants to all non-employee Directors to 16,000 shares, with a corresponding RSU award, and (ii) update the provision prohibiting our Board from repricing or cancelling outstanding options in exchange for cash or other stock awards without obtaining the approval of our stockholders;
- Proposal 6: make an advisory vote on executive compensation; and
- Proposal 7: ratify the Audit Committee’s selection of Ernst & Young LLP as independent auditors for our 2014 fiscal year.

#### **What if another matter is properly brought before the meeting?**

The Board 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 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 2014 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](http://www.proxyvote.com) to vote your shares through the Internet. The votes represented by your proxy will be displayed 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. 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 1-6 regarding the election of Directors, ratification, on an advisory basis, of the appointment of each of Mr. Castleman and Dr. Loscalzo to fill vacancies on the Board, approval of an amendment to our Restated Certificate of Incorporation to increase the authorized number of shares of Common Stock, approval of an amendment and restatement of the 2002 Non-Employee Directors’ Stock Option Plan and approval, on an advisory basis, of our 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 nominees for Director named in the Proxy Statement;
- “For” the ratification, on an advisory basis, of the appointment of Mr. Castleman to fill a vacancy on our Board for a one-year term;
- “For” the ratification, on an advisory basis, of the appointment of Dr. Loscalzo to fill a vacancy on our Board for a two-year term;
- “For” the approval of the amendment to our Restated Certificate of Incorporation to increase the authorized number of shares of Common Stock;
- “For” the approval of the amendment and restatement of the 2002 Non-Employee Directors’ Stock Option Plan;
- “For” the approval, on an advisory basis, of executive compensation; and
- “For” the ratification of the Audit Committee’s selection of Ernst & Young LLP as independent auditors for our 2014 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 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 our common stock in "street name" on behalf of beneficial owners of such shares. We may reimburse persons representing beneficial owners of our 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, officers or employees any additional compensation for soliciting proxies. We have engaged Alliance Advisors LLC to render solicitation services, and will pay Alliance its customary fee, which we estimate to be about \$14,000. However, please be aware that you must bear any costs associated with your Internet service, 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 or proxy card, your shares are registered in more than one name or are registered in different accounts. Please complete, sign, 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 2015 Annual Meeting of Stockholders, you must send the proposal to us by no later than December 30, 2014. 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 10, 2015. 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 and proxy card indicates the number of shares of our common stock that you owned at the close of business on April 11, 2014. The inspector of elections will count votes for the meeting, and will separately count “For” and “Against” votes, abstentions, and broker non-votes. With respect to Proposal 1, the election of Directors, stockholders do not affirmatively vote “Against” nominees. Instead, if you do not want to elect a particular nominee, you should choose to “Withhold” a vote in favor of the applicable nominee for Director and the inspector of elections will count each “Withhold” for each nominee. Abstentions will have no effect on Proposal 1. Abstentions will count towards the vote total for Proposals 2-7 and, in each case, will have the same effect as “Against” votes. Broker non-votes have no effect and the inspector of elections will not count them towards the vote total for any proposal, except for Proposal 4, the amendment to our Restated Certificate of Incorporation, in which case broker non-votes will have the same effect as an “Against” vote.

## 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 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 1-6 regarding the election of Directors, ratification, on an advisory basis, of the appointment of each of Mr. Castleman and Dr. Loscalzo to fill vacancies on the Board, approval of an amendment to our Restated Certificate of Incorporation to increase the authorized number of shares of Common Stock, approval of an amendment and restatement of the 2002 Non-Employee Directors’ Stock Option Plan and approval, on an advisory basis, of our 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?

- Proposal 1: For the election of Directors 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.
- Proposal 2: We will consider the advisory vote on the ratification of the appointment of Mr. Castleman to fill a vacancy on the Board to be approved if such ratification 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.
- Proposal 3: We will consider the advisory vote on the ratification of the appointment of Dr. Loscalzo to fill a vacancy on the Board to be approved if such ratification 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.
- Proposal 4: To be approved, the amendment to our Restated Certificate of Incorporation to increase the authorized number of shares of Common Stock must receive “For” votes from the holders of a majority of our shares outstanding as of the record date. If you mark your proxy to “Abstain” from voting, it will have the same effect as an “Against” vote. Broker non-votes will also have the same effect as “Against” votes.
- Proposal 5: To be approved, the amendment of our 2002 Non-Employee Directors’ Stock Option Plan must receive “For” votes from the holders of a majority of shares either present in person or represented by proxy and entitled to vote. 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.
- Proposal 6: We will consider the 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.
- Proposal 7: To be approved, the ratification of the selection of Ernst & Young LLP as our independent auditors for our 2014 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. Broker non-votes will have no effect.



**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 with 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](http://www.proxyvote.com).

ELECTION OF DIRECTORS

**Information about our Board**

The Board is divided into three classes. Presently, the Board has eight members with two classes consisting of three Directors each and one class consisting of two Directors. Each class serves a three-year term and we hold elections each year at the Annual Meeting to elect the Directors whose terms are expiring.

In addition, the Board may elect a new Director to fill any vacant spot, including a vacancy caused by an increase in the size of the Board. However, the Board believes it is important for our stockholders to ratify any member of the Board who the Board appoints. As a result, whenever the Board appoints a new member, the Board will submit such new member's directorship for ratification at the next regularly scheduled Annual Meeting of Stockholders.

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 Isis' management on our stockholders' behalf.

**Information about the 2014 Elections**

The Board has nominated three individuals for election at the 2014 Annual Meeting. Each of the nominees currently serves as one of our Directors. Dr. Berthelsen, Ms. Parshall and Mr. Wender have served as a Director since May 2002, September 2000 and January 1994, respectively, and have been re-elected by our stockholders each successive term. If re-elected, Dr. Berthelsen, Ms. Parshall and Mr. Wender will serve until the 2017 Annual Meeting or, in each case, until his or her successor is elected and has qualified, or until his or her earlier death, resignation or removal.

On December 13, 2011, the Board, 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 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.

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. 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 delivered its report to the Board on February 11, 2014. Following that report, the Board determined it would be in the best interests of Isis and its stockholders to nominate Dr. Berthelsen, Ms. Parshall, and Mr. Wender to be elected as Directors at the Annual Meeting. We provide below a short biography for each nominee. Dr. Berthelsen, Ms. Parshall, and Mr. Wender have agreed to serve if elected, and we have no reason to believe that they cannot serve. However, if they cannot serve, we may vote your proxy for another nominee proposed by the Board, or the Board may reduce the number of authorized Directors.

## **Biographies of the Nominees for Election for a Three-Year Term Expiring at the 2017 Annual Meeting**

**Spencer R. Berthelsen**, M.D., age 62, 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 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 multi-specialty group practice and 32 years of experience as a practicing physician.

**B. Lynne Parshall**, age 59, 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 Chief Financial Officer from June 1994 through December 31, 2012. She also serves as our Corporate Secretary, and has served with the Company in various executive roles since November 1991. 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. Ms. Parshall serves on the board of directors of Regulus Therapeutics, Inc. and Cytokinetes Inc., two biopharmaceutical companies. 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 69, 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. Mr. Wender also is a managing partner and owns, with his wife, Colgin Cellars. As of March 2014, Mr. Wender is a director of CBS Outdoors America Inc., lessors of advertising space on out-of-home advertising structures.

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 Isis 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.

**THE BOARD UNANIMOUSLY RECOMMENDS A VOTE “FOR” THE ELECTION OF THE ABOVE NOMINEES.**

## **Biographies of the Directors Whose Terms Expire at the 2015 Annual Meeting**

**Frederick T. Muto**, age 60, 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 and a founding partner of Cooley LLP’s San Diego office.

The Board believes Mr. Muto is uniquely suited to serve on the Board primarily because, with nearly 35 years of 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.

**Breaux B. Castleman**, age 73, has served as a Director of Isis since June 2013. Since August 2001, Mr. Castleman has been president and chief executive officer of Syntiro Healthcare Services, Inc., a health care investment company, which recently sold its operations as a service provider of integrated care management and disease management. Mr. Castleman has been a director of USMD Holdings, Inc., a physician-led integrated healthcare system, since September 2009 and was a director of MELA Sciences, Inc., a medical device company, from 2003 until 2011.

The Board believes that Mr. Castleman is uniquely suited to serve on the Board and the Audit Committee because he has significant experience in strategic planning and financial engineering for Fortune 1000 companies and has financial advisory expertise in the life sciences industry.

#### **Biographies of the Directors Whose Terms Expire at the 2016 Annual Meeting**

**Stanley T. Crooke**, M.D., Ph.D., age 69, 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 nearly 25 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 53, 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.

**Joseph Loscalzo**, age 62, is Hersey Professor of the Theory and Practice of Medicine at Harvard Medical School, Chairman of the Department of Medicine, and Physician-in-Chief at Brigham and Women's Hospital. Dr. Loscalzo received his A.B. degree, summa cum laude, his Ph.D. in biochemistry, and his M.D. from the University of Pennsylvania. His clinical training was completed at Brigham and Women's Hospital and Harvard Medical School, where he served as Resident and Chief Resident in medicine and Fellow in cardiovascular medicine. Post-training, Dr. Loscalzo joined the Harvard faculty and staff at Brigham and Women's Hospital in 1984. He rose to the rank of Associate Professor of Medicine, Chief of Cardiology at the West Roxbury Veterans Administration Medical Center, and Director of the Center for Research in Thrombolysis at Brigham and Women's Hospital. He joined the faculty of Boston University in 1994, first as Chief of Cardiology and, in 1997, Wade Professor and Chair of Medicine, Professor of Biochemistry, and Director of the Whitaker Cardiovascular Institute. He returned to Harvard and Brigham and Women's Hospital in 2005.

The Board believes Dr. Loscalzo is uniquely suited to serve on the Board primarily because of his extensive scientific expertise, including 25 years of research in the areas of vascular biology, thrombosis, and atherosclerosis, and practical knowledge as a practicing physician. Dr. Loscalzo's expertise and role as a leading cardiologist is particularly valuable as we mature and grow our cardiovascular franchise.

## PROPOSAL 2

### ADVISORY VOTE TO RATIFY THE APPOINTMENT OF MR. CASTLEMAN

This Proposal 2 vote is to ratify the appointment of Mr. Castleman to the Board. Mr. Castleman was nominated to join the Board by our Nominating, Governance and Review Committee and was unanimously appointed to the Board on June 25, 2013. Mr. Castleman was appointed to fill a vacancy in a class of Directors whose term expires at the 2015 Annual Meeting because our Certificate of Incorporation requires that as nearly as possible, each class is to consist of one third of the number of Directors. However, the Board believes that, in keeping with our commitment to good corporate governance practices, it is important for our stockholders to ratify, on an advisory basis, any member of the Board who the Board appoints. As a result, the Board submitted Mr. Castleman's directorship for ratification, on an advisory basis, at the Annual Meeting.

This Proposal 2 vote is advisory and therefore is not binding on Isis or the Board. However, the Board and Nominating, Governance and Review Committee value the opinions of the stockholders. As such, if less than a majority of shares either present in person or represented by proxy and entitled to vote at the Annual Meeting approve the ratification of Mr. Castleman's appointment to the Board, then the Nominating, Governance and Review Committee will make a recommendation to the Board on whether to request Mr. Castleman to tender his resignation or take other action. The Board will act on the Nominating, Governance and Review 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. If the Nominating, Governance and Review Committee recommends that the Board request Mr. Castleman's resignation, Mr. Castleman will not participate in the recommendation of the Nominating, Governance and Review Committee or in the Board's decision.

**THE BOARD UNANIMOUSLY RECOMMENDS A VOTE "FOR" THE RATIFICATION OF THE APPOINTMENT OF MR. CASTLEMAN.**

## PROPOSAL 3

### ADVISORY VOTE TO RATIFY THE APPOINTMENT OF DR. LOSCALZO

This Proposal 3 vote is to ratify the appointment of Dr. Loscalzo to the Board. Dr. Loscalzo was nominated to join the Board by our Nominating, Governance and Review Committee and was unanimously appointed to the Board on February 3, 2014. Dr. Loscalzo was appointed to fill a vacancy in a class of Directors whose term expires at the 2016 Annual Meeting because our Certificate of Incorporation requires that as nearly as possible, each class is to consist of one third of the number of Directors. However, the Board believes that, in keeping with our commitment to good corporate governance practices, it is important for our stockholders to ratify, on an advisory basis, any member of the Board who the Board appoints. As a result, the Board submitted Dr. Loscalzo's directorship for ratification, on an advisory basis, at the Annual Meeting.

This Proposal 3 vote is advisory and therefore is not binding on Isis or the Board. However, the Board and Nominating, Governance and Review Committee value the opinions of the stockholders. As such, if less than a majority of shares either present in person or represented by proxy and entitled to vote at the Annual Meeting approve the ratification of Dr. Loscalzo's appointment to the Board, then the Nominating, Governance and Review Committee will make a recommendation to the Board on whether to request Dr. Loscalzo to tender his resignation or take other action. The Board will act on the Nominating, Governance and Review 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. If the Nominating, Governance and Review Committee recommends that the Board request Dr. Loscalzo's resignation, Dr. Loscalzo will not participate in the recommendation of the Nominating, Governance and Review Committee or in the Board's decision.

**THE BOARD UNANIMOUSLY RECOMMENDS A VOTE "FOR" THE RATIFICATION OF THE APPOINTMENT OF DR. LOSCALZO.**

## Independence of the Board

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 our Nominating, Governance and Review Committee of the Board. Our 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 applicable 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. Croke 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 or other disqualifying relationship with us. With respect to Mr. Muto who is a partner of Cooley LLP, our outside legal counsel, he is independent for purposes other than serving on the Audit Committee or Compensation Committee, of which he is not a member.

## Information Regarding the Board and its Committees

### *Leadership Structure*

Our Chief Executive Officer is the Chairman of the Board. The Board believes that Isis’ CEO is best suited to serve as Chairman because he has served as CEO since Isis was formed 25 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. Our independent Directors bring experience, oversight and expertise from outside Isis 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, Dr. Loscalzo and Mr. Muto (who are both independent Board members) are part of the Agenda Committee, which 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 of these committees and its respective roles and responsibilities on pages 13 through 18 of this Proxy Statement. While each of these committees is responsible for evaluating certain risks and overseeing the management of such risks, these committees regularly inform the entire Board 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, the Nominating, Governance and Review Committee and the Scientific/Medical Committee periodically ask our executives to discuss the most likely sources of material future risks and how we are addressing any significant potential vulnerability.

#### Board Committees

The Board has five committees: an Audit Committee, a Compensation Committee, a Nominating, Governance and Review Committee, an Agenda Committee and a Scientific/Medical 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 our Audit Committee, Compensation Committee, and Nominating, Governance and Review 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.

#### Meetings and Attendance; Committee Members

The Board met five times in 2013. During 2013, all Directors attended 100% of the meetings of the Board except Dr. Berthelsen and Mr. Klein who attended 80% of the meetings. 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 2013 for each of the Board committees. Our Scientific/Medical Committee was formally established in 2014 and, therefore, did not meet during fiscal 2013.

Name	Audit	Compensation	Nominating, Governance and Review	Agenda	Attended 2013 Annual Meeting
Dr. Spencer R. Berthelsen	--	X*	X*	--	X
Mr. Breaux B. Castleman	X <sup>(1)</sup>	--	--	--	X
Dr. Stanley T. Crooke	--	--	--	X	X
Mr. Joseph Klein	X	--	--	--	X
Dr. Joseph Loscalzo <sup>(2)</sup>	--	--	--	--	N/A
Mr. Frederick T. Muto <sup>(3)</sup>	--	--	--	X	--
Ms. B. Lynne Parshall	--	--	--	X	X
Dr. John C. Reed <sup>(4)</sup>	--	X	--	--	--
Mr. Joseph H. Wender	X*	X	X	X	--
Total meetings in fiscal year 2013	4	5 <sup>(5)</sup>	3	4	

\* Committee Chairperson

- (1) Mr. Castleman was appointed to the Audit Committee, replacing Dr. Berthelsen, at the September 2013 Board meeting.
- (2) Dr. Loscalzo was appointed to the Board on February 3, 2014.
- (3) Mr. Muto serves as counsel, in a non-voting capacity, to the Nominating, Governance and Review Committee and as an advisor to the Compensation Committee.
- (4) On February 12, 2013, Dr. Reed resigned as a member of the Board due to his commitments as Head of Roche Pharma Research and Early Development and as a member of Roche’s Corporate Executive Committee. Mr. Wender replaced Dr. Reed as a member of the Nominating, Governance and Review Committee.
- (5) The Compensation Committee also acted by written consent 12 times. Our Compensation Committee acts by unanimous written consent each month to confirm stock options and RSUs granted in connection with new hires and promotions.



The table below identifies our current Board and committee members.

Name	Audit	Compensation	Nominating, Governance and Review	Agenda	Science/ Medical
Dr. Spencer R. Berthelsen	--	X*	X*	--	X
Mr. Breaux B. Castleman	X	--	X	--	--
Dr. Stanley T. Crooke	--	--	--	X	X*
Mr. Joseph Klein	X	--	--	--	--
Dr. Joseph Loscalzo	--	--	--	X	X
Mr. Frederick T. Muto	--	--	--	X	--
Ms. B. Lynne Parshall	--	--	--	X	--
Mr. Joseph H. Wender	X*	X	X	--	--

\* Committee Chairperson

#### Audit Committee

The Audit Committee of the Board 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 sessions with the auditors in which 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 changes to our investment policy;
- receiving and considering our independent auditors' comments as to the audit of the financial statements and 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 35 years of experience as an investment banker with Goldman, Sachs & Co. We provide the Audit Committee with the funding it needs to perform its duties.

In 2013, the Audit Committee met four times. You can find the Audit Committee charter on our corporate website at [www.isispharm.com](http://www.isispharm.com).<sup>2</sup> 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 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 40 through 60 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 consultants’ 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 RSUs 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 five times in 2013 and acted by unanimous written consent 12 times. You can find our Compensation Committee charter on our corporate website at [www.isispharm.com](http://www.isispharm.com).<sup>2</sup>

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.

### **Compensation Committee Interlocks and Insider Participation**

As noted above, during the fiscal year ended December 31, 2013, our Compensation Committee was composed of Drs. Berthelsen and Reed and Mr. Wender. On February 12, 2013, Dr. Reed resigned as a member of the Board due to his commitments as Head of Roche Pharma Research and Early Development and as a member of Roche’s Corporate Executive Committee. 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 or Compensation Committee.

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

## Nominating, Governance and Review Committee

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

- interviewing, evaluating, nominating and recommending individuals for membership on our Board, and 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 three times during 2013. You can find our Nominating, Governance and Review Committee charter on our corporate website at [www.isispharm.com](http://www.isispharm.com).<sup>3</sup>

### *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.

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
- being committed to rigorously represent the long-term interests of our stockholders.

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<sup>3</sup> 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 considering Director nominations, the Nominating, Governance and Review 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 gender, 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. 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. 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 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. During the fiscal year ended December 31, 2013, the Nominating, Governance and Review Committee engaged the services of a third party search firm to help it identify, screen, interview and check the references of potential 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 to include in our Proxy Statement for our 2015 Annual Meeting of Stockholders 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 30, 2014. 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 nomination set forth above is qualified in its entirety by reference to our full and complete Amended and Restated Bylaws, which is an exhibit to our Current Report on Form 8-K filed with the SEC on December 14, 2011 a copy of which is available by contacting our Corporate Secretary. To date, the Board has not received or rejected a timely Director nominee for election at the upcoming stockholder meeting from a stockholder or stockholders holding more than 5% of our voting stock.

#### **Agenda Committee**

The primary function of the Agenda Committee of the Board is to determine the matters to be considered by the Board at each of its meetings and prepare an agenda accordingly. The Agenda Committee met four times in 2013.

#### **Scientific/Medical Committee**

The Scientific/Medical Committee was formally established in 2014 and primarily focuses on the key scientific and development issues facing our technology and drugs in development, and help set our strategy in such areas.

#### **Stockholder Communications with the Board**

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 relate 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](http://www.isispharm.com).<sup>4</sup>

## Corporate Governance Guidelines

In 2003, the Board 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 for Board committees and compensation, "clawbacks" of executive compensation, and share retention guidelines for our executive officers and Directors. 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 the Audit, Compensation and Nominating, Governance and Review committees at [www.isispharm.com](http://www.isispharm.com).<sup>4</sup>

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<sup>4</sup> 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 4

### APPROVAL OF AN AMENDMENT TO THE COMPANY'S RESTATED CERTIFICATE OF INCORPORATION TO INCREASE THE NUMBER OF AUTHORIZED SHARES OF COMMON STOCK

The Board has adopted, subject to stockholder approval, an amendment to Isis' Restated Certificate of Incorporation to increase the authorized number of shares of our Common Stock from 200,000,000 shares to 300,000,000 shares. To maintain Isis' flexibility to structure future strategic transactions, which may include a significant equity component, we believe it is in the interests of Isis' stockholders to increase the authorized number of shares of Common Stock now.

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

In addition to the 117,541,860 shares of Common Stock outstanding on March 31, 2014, there were 8,554,745 shares of Common Stock issuable upon exercise of outstanding options or subject to vesting of outstanding RSUs granted under our equity plans and 3,954,656 shares of Common Stock available for future grants under our equity plans. Additionally, the Board has reserved 12,102,531 shares of Common Stock for issuance under our convertible notes. This means Isis currently has approximately 58 million shares available for future use (i.e. shares that are not already outstanding or reserved for future issuance under our convertible notes or equity plans).

Although the Board has no present plans to issue the additional shares of common stock, it believes that it is important that we maintain the flexibility to issue additional shares of Common Stock in connection with raising capital, acquisitions and other strategic transactions, equity incentives to employees and other proper corporate purposes, should our Board deem any of those actions to be in the best interests of our company and our stockholders. For example, in May 2013, we successfully completed a public offering of approximately 9.6 million shares of our Common Stock, raising \$173.2 million in net proceeds, which we are using to support Phase 3 development of ISIS-APOCIII<sub>Rx</sub>, retain other drugs longer in development and advance the rest of our pipeline. If our stockholders do not approve this Proposal 4, we may not be able to complete strategic transactions, access the capital markets, retain employees and pursue other business opportunities important to our success.

If the Board determines that a hostile takeover attempt or a change in Isis' control or management is not in the best interest of Isis' stockholders, Isis could use the additional shares of Common Stock that would become available for issuance if this Proposal 4 is approved to oppose, delay or prevent such attempted takeover or change, which could discourage certain transactions in which our stockholders might otherwise receive a premium for their shares over the then current market prices.

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

**THE BOARD UNANIMOUSLY RECOMMENDS A VOTE "FOR" APPROVAL OF PROPOSAL 4**

**APPROVAL OF AN AMENDMENT AND RESTATEMENT OF OUR 2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN**

In this Proposal 5, we are requesting our stockholders approve an amendment and restatement of our 2002 Non-Employee Directors' Stock Option Plan (the "Directors' Plan") which the Board adopted on February 11, 2014, subject to stockholder approval. The primary purpose of the amendment and restatement is to (i) increase the non-discretionary stock option grants for new Directors to 32,000 shares and non-discretionary annual grants to all non-employee Directors to 16,000 shares, with a corresponding RSU award based on a ratio determined by our Compensation Committee, which the Directors' Plan refers to as the RSU/Option Factor, and (ii) update the provision prohibiting the Board from repricing any outstanding options by reducing the exercise price of the stock award or cancelling any outstanding options in exchange for cash or other stock awards without obtaining the approval of our stockholders within 12 months prior to the repricing or cancellation and re-grant event.

**Background for the Current Request and Expected Future Grant Practices**

We believe increasing the non-discretionary stock option grants for new Directors to 32,000 shares and non-discretionary annual grants to all non-employee Directors to 16,000 shares, with a corresponding RSU award based on a then current RSU/Option Factor will improve our ability to attract and retain unique and highly qualified talent. Additionally, we believe updating the prohibitions against repricing outstanding options or cancelling any outstanding options in exchange for cash or other stock awards better aligns the Directors' Plan with the most current accepted best practices related to equity compensation.

The affirmative vote of a majority of the shares present in person or represented by proxy and entitled to vote at the Annual Meeting 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 5, 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 5. Broker non-votes will not have any effect on the outcome of this Proposal 5.

**THE BOARD UNANIMOUSLY RECOMMENDS A VOTE "FOR" APPROVAL OF PROPOSAL 5.**



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; and
- incentivize our non-employee Directors to exert maximum efforts to promote our success.

## Administration

Our Board administers the Directors' Plan. Our Board may not delegate administration of the Directors' Plan to a committee. The Board 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 and was approved by the stockholders at the June 7, 2012 Annual Meeting. As of March 31, 2014, there were RSUs and options to purchase 465,310 shares of common stock issued and outstanding under the Directors' Plan, our Directors had exercised options to purchase 449,563 shares and 283,875 shares were available for future grants, which we expect to last until at least the 2015 Annual Meeting of Stockholders. Assuming stockholder approval of this Proposal 5, we expect to grant options to purchase a total of 96,000 shares and RSUs worth 16,002 shares under the Directors' Plan on July 1, 2014.

On March 31, 2014 the last reported sales price of our common stock on the NASDAQ Global Select Market was \$43.21 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 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. Six of our eight 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").

The Directors' Plan currently provides for nondiscretionary grants of stock options and RSU awards to the non-employee Directors as follows:

- *Initial Grants*
  - o 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
  - o 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.
  - o For example, using the Option Allocation Percentage of 75%, RSU Allocation Percentage of 25%, and the RSU:Option Value Ratio of 50% that were approved for 2013 by the Compensation Committee, a new non-employee Director who joined the Board in 2013 received an initial stock option to purchase 22,500 shares of common stock (i.e. 30,000 x 75%) and an RSU award worth 3,750 shares of common stock (i.e. 30,000 x 25% x 50%).

· *Annual Grants*

- o 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
- o 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.
- o For example, using the Option Allocation Percentage of 75%, RSU Allocation Percentage of 25%, and the RSU:Option Value Ratio of 50% that were approved for 2013 by the Compensation Committee, on July 1, 2013, each non-employee Director received a stock option to purchase 11,250 shares of common stock (i.e. 15,000 x 75%) and an RSU award worth 1,875 shares of common stock (i.e. 15,000 x 25% x 50%).

Under the proposed amendments to the Directors' Plan under this Proposal 5, the initial nondiscretionary grants are for options to purchase 32,000 shares with an RSU award equal to 32,000 multiplied by the then applicable RSU/Option Factor and the annual nondiscretionary grants are for options to purchase 16,000 shares with an RSU award equal to 16,000 multiplied by the then RSU/Option Factor.

The RSU/Option Factor is a ratio, represented by a fraction, as approved by the Compensation Committee when it sets the allocation of equity compensation for our employees between Options and RSU awards. ***The RSU/Option Factor can be as low as zero and as high as one.*** The RSU/Option Factor approved by the Compensation Committee as of the date the Board approved the amendment and restatement of the Directors' Plan was 1/6.

Therefore, if our stockholders approve this Proposal 5, the Directors' Plan will provide for nondiscretionary grants of stock options and RSU awards to the non-employee Directors as follows:

· *Initial Grants*

- o an initial grant of a stock option to purchase 32,000 shares of common stock to each person when he or she first becomes a non-employee Director, and
- o an initial grant of an RSU award to each person when he or she first becomes a non-employee Director in an amount equal to 32,000 *multiplied by* the then applicable RSU/Option Factor.
- o For example, using the RSU/Option Factor of 1/6 that was approved by the Compensation Committee and is currently in place, a new non-employee Director joining the Board after the 2014 Annual Meeting of Stockholders would receive an initial stock option to purchase 32,000 shares of common stock and an RSU award worth 5,333 shares of common stock (i.e. 32,000 x 1/6).

· *Annual Grants*

- o 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 16,000 shares of common stock to each non-employee Director, and
- o 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 16,000 *multiplied by* the then applicable RSU/Option Factor.
- o For example, using the RSU/Option Factor of 1/6 that was approved by the Compensation Committee and is currently in place, on July 1, 2014, each non-employee Director would receive a stock option to purchase 16,000 shares of common stock and an RSU award worth 2,667 shares of common stock (i.e. 16,000 x 1/6).

## Terms of Options

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

*Vesting Schedule and 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 is replaced by individuals who are not nominated by members of our current Board or members nominated by our current Board 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.

#### **No Repricing, "Cash-Out," or Cancellation and Re-Grant of Options without Stockholder Approval**

Under the Directors' Plan, as amended by this Proposal 5, the Board cannot reprice any outstanding options by reducing the exercise price of the stock award or cancel any outstanding options in exchange for cash or other stock awards without obtaining the approval of our stockholders within 12 months prior to the repricing or cancellation and re-grant event. Without the amendment proposed in this Proposal 5, the Directors' Plan currently does not expressly prohibit the cancellation of outstanding stock options in exchange for cash or other stock awards.

#### **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/"cashing-out". 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, 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, 2014 to our non-employee Directors, assuming stockholder approval of this Proposal 5. 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.

<b>NEW PLAN BENEFITS AMENDED AND RESTATED 2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN</b>		
<b>Name of Non-Employee Director</b>	<b>Number of Option Shares (16,000)</b>	<b>Number of Restricted Stock Unit Awards (16,000 x 1/6)</b>
Spencer R. Berthelsen	16,000	2,667
Breaux B. Castleman	16,000	2,667
Joseph Klein, III	16,000	2,667
Joseph Loscalzo	16,000	2,667
Frederick T. Muto	16,000	2,667
Joseph H. Wender	16,000	2,667
<b>Non-Employee Directors as a Group</b>	<b>96,000</b>	<b>16,002</b>

## 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, 2013.

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)	7,078,280	\$12.11	5,715,176(c)
Equity compensation plans not approved by stockholders(b)	630,086	\$14.84	—
Total	7,708,366	\$12.33	5,715,176

(a) Consists of four Isis plans: 1989 Stock Option Plan, Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, 2011 Equity Incentive Plan and 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, 264,275 remained available for purchase under the ESPP as of December 31, 2013. 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, or the 2000 Plan, to provide our employees, officers, Directors and consultants an opportunity to benefit from increases in the value of our common stock through the granting of non-statutory stock options, stock bonuses and rights to purchase restricted stock. At the time we adopted the 2000 Plan, we were not required to seek the approval of our stockholders. The Board has delegated administration of the 2000 Plan to the Compensation Committee of the Board, and the Compensation Committee has delegated administration of the 2000 Plan to the Non-Management Stock Option Committee with respect to certain option grants to employees who are not our executive officers. The Board has the power to construe and interpret the 2000 Plan and, subject to the provisions of the 2000 Plan, to select the persons to whom stock awards are to be made, to designate the number of shares to be covered by each stock award, to establish vesting schedules, to specify the exercise price and the type of consideration to be paid to us upon exercise or purchase.

As of December 31, 2013, the 2000 Plan had 5,990,000 shares authorized for issuance, options to purchase an aggregate of 630,086 shares were granted and outstanding under the 2000 Plan, option holders had exercised options to purchase an aggregate of 4,906,111 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 option holder'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 of Directors will make such adjustments, and its determination will be final, binding and conclusive. We will not treat the conversion of any of our convertible securities as a transaction without receipt of consideration.

In the event of our dissolution or liquidation, all outstanding stock awards will terminate immediately prior to such event.

In the event of:

- a sale, lease or other disposition of all or substantially all of our assets;
- a merger or consolidation in which we are not the surviving corporation; or
- reverse merger in which we are the surviving corporation but the shares of common stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise;

then any surviving corporation or acquiring corporation will assume any stock awards outstanding under the 2000 Plan or will substitute similar stock awards (including an award to acquire the same consideration paid to the stockholders in the transaction for those outstanding under the 2000 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar stock awards for those outstanding under the 2000 Plan, then with respect to stock awards held by participants whose continuous service has not terminated, we will accelerate the vesting of such stock awards in full and the stock awards will terminate if not exercised (if applicable) at or prior to such event.



ADVISORY VOTE ON EXECUTIVE COMPENSATION

The Dodd-Frank Wall Street Reform and Consumer Protection Act of 2010, called the “Dodd-Frank Act,” entitles Isis’ stockholders to vote to approve, on an advisory (nonbinding) basis, the compensation of our Chief Executive Officer, Chief Financial Officer and our three other most highly compensated executive officers (at December 31, 2013), 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 6, 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 2014 Annual Meeting of Stockholders pursuant to the compensation disclosure rules of the Securities and Exchange Commission.”**

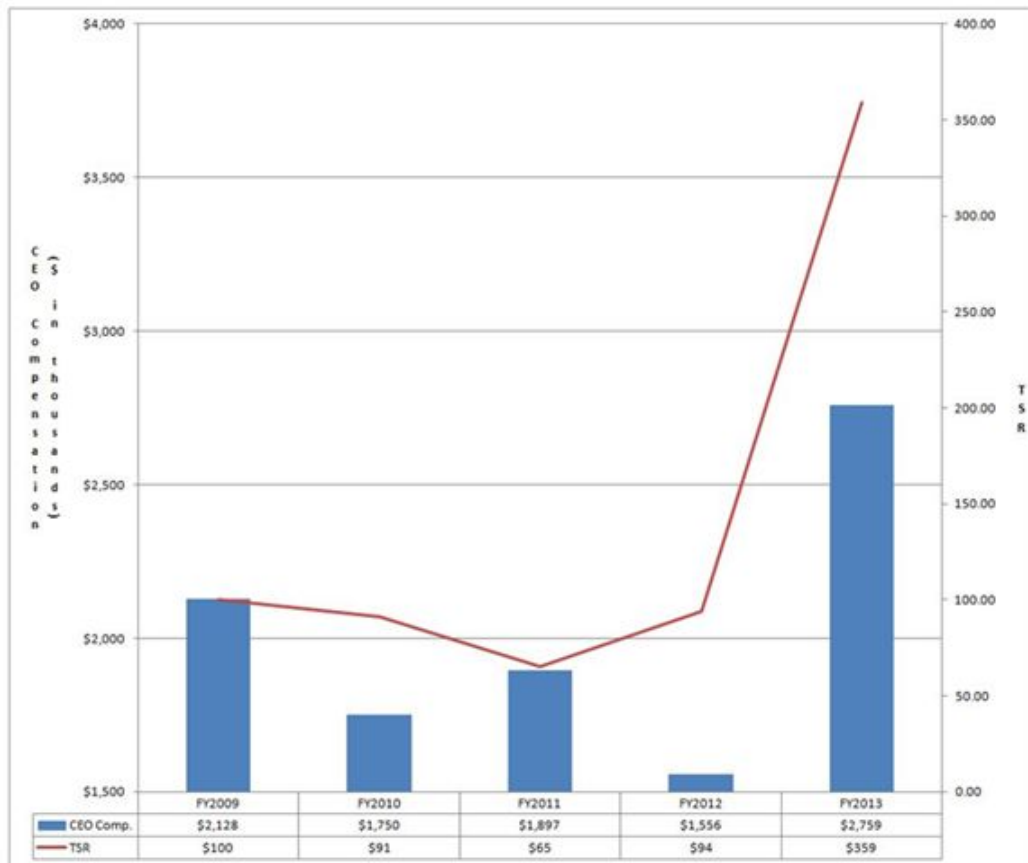
We recommend you carefully review the EXECUTIVE COMPENSATION section of this Proxy Statement located on pages 40 through 60. Below is a high-level summary of some of our compensation practices. This summary is qualified by the detailed disclosure contained in the EXECUTIVE COMPENSATION section of this Proxy Statement.

The table below summarizes some of our executive compensation practices, both the practices we implement because we believe they are consistent with our vision and long-term stockholder value (see “What We Do” below), and those that we choose not to implement as we believe they are counter to our vision and long-term stockholder value (see “What We Don’t Do” below):

What We Do	What We Don't Do
ü Demand more of every employee: more commitment, more knowledge, more intensity, more innovation	û Do not guarantee a cash bonus – cash bonuses can, and have been, zero
ü Reward productivity and performance	û Do not provide perquisites for any employees
ü Recognize the value of long-term employees and low turnover	û Do not provide “gross-up” payments, other than for relocation
ü Use a balanced mix of fixed and variable cash incentives and long-term equity	û Do not allow shorting and hedging against our stock
ü Evaluate compensation compared to the 50 <sup>th</sup> percentile of our peer group	û Do not reprice or “cash-out” stock options without stockholder approval
ü Design our compensation philosophy and objectives to mitigate unnecessary or imprudent business risk taking	
ü Set explicit and demanding objectives at the beginning of each year from which we measure performance for the year	
ü Place a maximum limit on Performance MBOs	
ü Set a strict budget for equity awards and salary increases	
ü Set the size of equity awards based on individual and company performance	
ü Require minimum vesting periods for equity awards	
ü Require our executive officers and non-employee Board members to hold shares received from their RSUs until they meet certain ownership thresholds or no longer serve the company	
ü Require our employees to hold ESPP shares for a minimum of six months	
ü Require our executive officers, VPs and many other employees to trade Isis’ stock through Rule 10b5-1 trading plans	
ü Use a “double trigger” for cash payments for change of control	
ü Use an executive “claw-back” policy	
ü Use an independent compensation consultant engaged by the Compensation Committee	

**CEO Compensation vs. Total Return  
(Over Five Years)**

The following graphs show the relationship of our Chief Executive Officer’s compensation (\$ in thousands) as calculated pursuant to SEC rules compared to the total return (TSR) on \$100 invested on December 31, 2009 in our common stock through December 31, 2013. 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 below, our CEO’s compensation is generally in alignment with our stock performance over the period shown.<sup>5</sup>



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 6. Brokers do not have discretion to vote uninstructed shares with respect to this Proposal 6. 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 6.

The “say on pay” vote is advisory, and therefore is not binding on Isis, the Compensation Committee or the Board. However, Isis’ management, the Board and the Compensation Committee value the opinions of the stockholders. As such, if there is any significant vote against the named executive officers’ 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.

**THE BOARD UNANIMOUSLY RECOMMENDS A VOTE “FOR” APPROVAL OF PROPOSAL 6.**

<sup>5</sup> This graph 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, as amended (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.

**RATIFICATION OF SELECTION OF INDEPENDENT AUDITORS**

The Audit Committee of the Board has selected Ernst & Young LLP as our independent registered public accounting firm for our 2014 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 2014 Annual Meeting to answer any questions and make a statement should they desire to do so.

Although our bylaws do not require stockholders to ratify 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 do not ratify the selection of 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 2014 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 7.

As of December 31, 2013, 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 procedure 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, we do not use Ernst & Young LLP as our primary tax advisor. The Audit Committee pre-approved the fees described below.

**Audit Fees**

For the fiscal years ended December 31, 2013 and 2012, 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 \$552,000 and \$480,000, respectively. The increase in audit fees was primarily due to additional audit procedures that Ernst & Young LLP performed for the 2013 audit based on new guidance from the Public Company Accounting Oversight Board. In addition, Ernst & Young LLP billed us \$87,000 in 2012 for audit fees related to our partnership activities. Furthermore, Ernst & Young LLP billed us \$96,000 in 2013 in connection with our public offering of Common Stock in May 2013 and \$135,000 in 2012 related to our convertible debt offering in August 2012.

**Audit Related Fees**

For the years ended December 31, 2012 Ernst & Young LLP billed us \$10,000 for accounting consultations for our partnership activities that were reasonably related to the performance of the audit or review of our financial statements that are not included under "Audit Fees" above. For the year ended December 31, 2013, there were no audit related fees billed by Ernst & Young.

## **Tax Fees**

For the years ended December 31, 2013 and 2012, there were no tax fees billed by Ernst & Young LLP for tax related matters that were not part of the integrated audit fees. In 2013 and 2012, we utilized Deloitte Tax LLP for our tax services.

## **All Other Fees**

During the fiscal years ended December 31, 2013 and 2012, 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, 2013, 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 7.**

## SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

This table outlines the ownership of our common stock as of March 31, 2014 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 <sup>(1)</sup>	
	Number of Shares	Percent of Total <sup>(2)</sup>
FMR LLC <sup>(3)</sup> 245 Summer Street Boston, MA 02210	17,679,361	15.0
Artisan Partners Holdings LP <sup>(4)</sup> 875 East Wisconsin Avenue, Suite 800 Milwaukee, WI 53202	9,778,160	8.3
BlackRock, Inc. <sup>(5)</sup> 40 East 52 <sup>nd</sup> Street New York, NY 10022	8,844,551	7.5
The Vanguard Group <sup>(6)</sup> 100 Vanguard Boulevard Malvern, PA 19355	7,681,946	6.5
ClearBridge Investment, LLC <sup>(7)</sup> 620 8 <sup>th</sup> Avenue New York, NY 10018	7,197,661	6.1
BB Biotech AG <sup>(8)</sup> Vordergasse 3 CH-8200 Schaffhausen, Switzerland	6,417,548	5.5
Spencer R. Berthelsen <sup>(9)</sup>	136,246	*
Breaux B. Castleman	0	*
Stanley T. Crooke <sup>(10)</sup>	1,220,849	1.0
Joseph Klein, III <sup>(11)</sup>	2,413	*
Joseph Loscalzo	0	*
Frederick T. Muto <sup>(12)</sup>	98,376	*
B. Lynne Parshall <sup>(13)</sup>	36,000	*
Joseph H. Wender <sup>(14)</sup>	107,998	*
C. Frank Bennett <sup>(15)</sup>	129,882	*
Richard S. Geary <sup>(16)</sup>	13,163	*
Elizabeth L. Hougen <sup>(17)</sup>	71,330	*
All Directors and executive officers as a group (thirteen persons) <sup>(18)</sup>	1,892,647	1.6

\*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 117,541,860 shares of common stock outstanding on March 31, 2014, adjusted as required by rules promulgated by the SEC.
- (3) Fidelity Management & Research Company ("Fidelity"), a wholly-owned subsidiary of FMR LLC and an investment adviser registered under Section 203 of the Investment Advisers Act of 1940, is the beneficial owner of 14,704,780 shares or 12.590% of the Common Stock outstanding of Isis as a result of acting as investment adviser to various investment companies registered under Section 8 of the Investment Company Act of 1940. The number of shares of Common Stock of Isis owned by the investment companies at December 31, 2013 included 481,095 shares of Common Stock resulting from the assumed conversion of \$8,000,000 principal amount of ISIS PHARMA CV 2.75% 10/01/19 (60.1368 shares of Common Stock for each \$1,000 principal amount of debenture).

Edward C. Johnson 3d and FMR LLC, through its control of Fidelity, and the funds each has sole power to dispose of the 14,704,780 shares owned by the Funds.

Fidelity SelectCo, LLC ("SelectCo"), 1225 17th Street, Suite 1100, Denver, Colorado 80202, a wholly-owned subsidiary of FMR LLC and an investment adviser registered under Section 203 of the Investment Advisers Act of 1940, is the beneficial owner of 2,651,034 shares or 2.270% of the Common Stock outstanding of Isis as a result of acting as investment adviser to various investment companies registered under Section 8 of the Investment Company Act of 1940 (the "SelectCo Funds").

Edward C. Johnson 3d and FMR LLC, through its control of SelectCo, and the SelectCo Funds each has sole power to dispose of the 2,651,034 owned by the SelectCo Funds.

The ownership of one investment company, Fidelity Growth Company Fund, amounted to 9,613,220 shares or 8.231% of the Common Stock outstanding. Fidelity Growth Company Fund has its principal business office at 245 Summer Street, Boston, Massachusetts 02210.

Members of the family of Edward C. Johnson 3d, Chairman of FMR LLC, are the predominant owners, directly or through trusts, of Series B voting common shares of FMR LLC, representing 49% of the voting power of FMR LLC. The Johnson family group and all other Series B shareholders have entered into a shareholders' voting agreement under which all Series B voting common shares will be voted in accordance with the majority vote of Series B voting common shares. Accordingly, through their ownership of voting common shares and the execution of the shareholders' voting agreement, members of the Johnson family may be deemed, under the Investment Company Act of 1940, to form a controlling group with respect to FMR LLC.

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, LLC ("PGALLC"), 900 Salem Street, Smithfield, Rhode Island, 02917, an indirect wholly-owned subsidiary of FMR LLC and an investment adviser registered under Section 203 of the Investment Advisers Act of 1940, is the beneficial owner of 240,547 shares or 0.206% of the outstanding Common Stock of Isis as a result of its serving as investment adviser to institutional accounts, non-U.S. mutual funds, or investment companies registered under Section 8 of the Investment Company Act of 1940 owning such shares. The number of shares of Common Stock of Isis owned by the institutional account(s) at December 31, 2013 included 240,547 shares of Common Stock resulting from the assumed conversion of \$4,000,000 principal amount of ISIS PHARMA CV 2.75% 10/01/19 (60.1368 shares of Common Stock for each \$1,000 principal amount of debenture).

Edward C. Johnson 3d and FMR LLC, through its control of PGALLC, each has sole dispositive power over 240,547 shares and sole power to vote or to direct the voting of 240,547 shares of Common Stock owned by the institutional accounts or funds advised by PGALLC as reported above.

Pyramis Global Advisors Trust Company ("PGATC"), 900 Salem Street, Smithfield, Rhode Island, 02917, 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 83,000 shares or 0.071% of the outstanding Common Stock of the Isis 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 PGATC, each has sole dispositive power over 83,000 shares and sole power to vote or to direct the voting of 83,000 shares of Common Stock owned by the institutional accounts managed by PGATC as reported above.

- (4) The shares reported herein have been acquired on behalf of discretionary clients of Artisan Partners Limited Partnership ("APLP"), Artisan Investments GP LLC ("Artisan Investments") Artisan Partners Holdings LP ("Artisan Holdings") Artisan Partners Asset Management Inc. ("APAM") Artisan Partners Funds, Inc. ("Artisan Funds"). Artisan Holdings is the sole limited partner of APLP and the sole member of Artisan Investments; Artisan Investments is the general partner of APLP; APAM is the general partner of Artisan Holdings. APLP holds 9,778,160 shares, including 5,597,870 shares on behalf of Artisan Funds. Persons other than APLP are entitled to receive all dividends from, and proceeds from the sale of, those shares.
- (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.
- (6) The Vanguard Group has sole voting power to direct the vote of 159,970 shares, sole power to dispose or direct the disposition of 7,529,476 shares, shared dispositive power for 152,470 shares. Vanguard Fiduciary Trust Company, a wholly-owned subsidiary of The Vanguard Group, Inc., is the beneficial owner of 152,470 shares or 0.13% of the Common Stock outstanding of Isis as a result of its serving as investment manager of collective trust accounts. Vanguard Investments Australia, Ltd., a wholly-owned subsidiary of The Vanguard Group, Inc., is the beneficial owner of 7,500 shares of Isis' Common Stock outstanding as a result of its serving as investment manager of Australian investment offerings.
- (7) ClearBridge Advisors, LLC, is an investment adviser registered under the Investment Advisers Act. ClearBridge Advisors has sole voting power to direct the vote of 7,005,575 shares and sole power to dispose or direct the disposition of 7,197,661 shares.
- (8) BB Biotech shares voting and dispositive powers for its shares with Biotech Target N.V., a wholly-owned subsidiary of BB Biotech AG.
- (9) Includes 70 shares owned by Dr. Berthelsen's daughter for which he disclaims beneficial ownership. Includes 96,563 shares of common stock issuable upon exercise of options held by Dr. Berthelsen that are exercisable on or before May 30, 2014.
- (10) Includes shares of common stock held by Dr. Crooke and 437,837 shares of common stock issuable upon exercise of options held by Dr. Crooke that are exercisable on or before May 30, 2014. Also includes 50,053 shares of common stock issuable upon exercise of options held by Rosanne Crooke, Dr. Crooke's wife, which are exercisable on or before May 30, 2014. Dr. Crooke disclaims beneficial ownership of the shares of common stock owned and issuable upon exercise of options held by his wife.
- (11) Includes 100 shares of common stock beneficially owned by Mr. Klein's son.
- (12) Includes 1,500 shares of common stock beneficially owned through the Cooley LLP Salary Deferral and Profit Sharing Plan and 96,563 shares of common stock issuable upon exercise of options held by Mr. Muto that are exercisable on or before May 30, 2014.
- (13) Includes 31,978 shares of common stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before May 30, 2014.



- (14) Includes 71,563 shares of common stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before May 30, 2014.
- (15) Includes 125,546 shares of common stock issuable upon exercise of options held by Dr. Bennett that are exercisable on or before May 30, 2014.
- (16) Includes 8,208 shares of common stock issuable upon exercise of options held by Dr. Geary that are exercisable on or before May 30, 2014.
- (17) Includes 70,098 shares of common stock issuable upon exercise of options held by Ms. Hougen that are exercisable on or before May 30, 2014.
- (18) Includes an aggregate of 1,059,633 shares issuable upon exercise of options held by all current Directors and executive officers as a group that are exercisable on or before May 30, 2014.

**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, 2013, all Section 16(a) filing requirements applicable to our officers, Directors and greater than ten percent beneficial owners were complied with.

## Compensation Discussion and Analysis

### Overview

Since inception, the Isis mission has been to create a new, more efficient technology for drug discovery and development, antisense technology, and exploit that technology to create a pipeline of first-in-class medicines to treat a wide range of diseases. Today, thanks to the innovation and perseverance of Isis, we believe antisense technology is taking its place as the third platform for drug discovery alongside small molecules and protein therapeutics.

Isis is focused on innovation. Based on the efficiency of antisense technology, Isis has implemented a unique business strategy that is intended to assure long-term innovation. Isis has created a unique innovation-focused, science-driven, culture that couples with its technology and business model to assure long-term productivity and a commitment to the patients we serve.

Antisense technology exists today primarily because of the innovation at Isis. Isis has more than 1,200 issued patents and approximately 690 patent applications that should assure substantial control of key elements of the technology for many years to come. This intellectual property has been critical in the completion of partnerships that have resulted in over \$2 billion in cash to date and the development of a consortium of companies who advance the technology alongside us, and thereby increase our reach. We should continue to realize the value of the partnerships and the consortium of companies for many years to come in the form of milestone payments, license fees and royalties. Isis has been recognized as one of the top ten most innovative companies in the Biotechnology industry, based on number of granted patents, scientific strength, industry impact, technology strength and research intensity. Our nearly 1,900 issued patents and applications are all the more remarkable given that Isis has fewer than 370 employees. This means Isis has produced more than five issued patents and applications per employee.

A key component of our business and organizational strategy is to maintain an optimal size to foster innovation. We believe the optimal size is 350-400 employees. To maintain this optimal size we license our medicines at key value inflection points during development, thus avoiding the need to build the large, complex, inefficient organizations associated with fully integrated pharmaceutical companies. We also demand more of every employee at Isis and do not tolerate mediocrity. We have been remarkably successful in achieving these goals. Today we have 32 new medicines in development; one medicine in development per 12 employees. And we believe this productivity is sustainable. We plan to add three to five new medicines to the pipeline every year without significant increases in the number of employees.

By design, Isis demands more of every employee, particularly the middle and senior level leaders. This requires us to design our compensation system to recruit, motivate and retain outstanding individuals. Here too, we have been successful. Our average employee voluntary turnover rate over the last five years has been 3.2% per year, while the average voluntary turnover in the United States for biotech/pharmaceutical companies during the same period was 9.7%. Given the uniqueness and complexity of our technology, it is critical to retain the knowledge and experience of outstanding long service employees. The experience and seniority of our employees is as critical to our future success as it has been to the success we have enjoyed to date.

In summary, at Isis, our vision is clear and is designed to promote long-term creation of value through innovation, and bring benefit to generations of patients with many diseases. Our vision is to:

- create and constantly advance a new more efficient drug discovery platform, antisense technology;
- create a unique business model and culture committed to creating long-term value through innovation;
- broaden, deepen and advance our pipeline of antisense drugs;
- demand more of every employee - more commitment, more knowledge, more intensity, more innovation;
- aggressively manage average and below average performance so every employee produces more; and
- demand great performance and pay for that performance.

Through the efficiency of our technology platform and business strategy we have built a pipeline of 32 drugs in development with fewer than 370 employees, representing a ratio of 1 drug : 12 employees.

*Summary of Compensation Practices*

Below we summarize some of our compensation practices, both the practices we implement because we believe they are consistent with our vision and long-term stockholder value (see “What We Do” below), and those we choose not to implement as we believe they are counter to our vision and long-term stockholder value (see “What We Don’t Do” below):

What We Do	What We Don’t Do
ü Demand more of every employee: more commitment, more knowledge, more intensity, more innovation	û Do not guarantee a cash bonus – cash bonuses can, and have been, zero
ü Reward productivity and performance	û Do not provide perquisites for any employees
ü Recognize the value of long-term employees and low turnover	û Do not provide “gross-up” payments, other than for relocation
ü Use a balanced mix of fixed and variable cash incentives and long-term equity	û Do not allow shorting and hedging against our stock
ü Evaluate compensation compared to the 50 <sup>th</sup> percentile of our peer group	û Do not reprice or “cash-out” stock options without stockholder approval
ü Design our compensation philosophy and objectives to mitigate unnecessary or imprudent business risk taking	
ü Set explicit and demanding objectives at the beginning of each year from which we measure performance for the year	
ü Place a maximum limit on Performance MBOs	
ü Set a strict budget for equity awards and salary increases	
ü Set the size of equity awards based on individual and company performance	
ü Require minimum vesting periods for equity awards	
ü Require our executive officers and non- employee Board members to hold shares received from their RSUs until they meet certain ownership thresholds or no longer serve the company	
ü Require our employees to hold ESPP shares for a minimum of six months	
ü Require our executive officers, VPs and many other employees to trade Isis’ stock through Rule 10b5-1 trading plans	
ü Use a “double trigger” for cash payments for change of control	
ü Use an executive “claw-back” policy	
ü Use an independent compensation consultant engaged by the Compensation Committee	

We have designed our executive compensation program to attract and retain executives who can help us meet our business objectives and will motivate our executives to enhance long-term stockholder value. The Compensation Committee of the Board, with input from an independent compensation consultant, 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 reviews and ratifies the Compensation Committee's decisions regarding the compensation of executive officers.

The Compensation Committee's responsibilities include:

- reviewing and approving 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 stock-based awards and ESPP;
- evaluating risks associated with our compensation policies and practices and assessing whether these risks are reasonably likely to have a material adverse effect on us;
- selecting and retaining a qualified, independent compensation consultant;
- performing other functions as may be necessary or convenient in the efficient discharge of the foregoing; and
- reporting to the Board from time to time, or whenever it shall be called upon to do so.

As the SEC continues to adopt the final rules implementing and defining the Dodd-Frank legislation, 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.

*Independent Compensation Consultant*

The Compensation Committee has the authority and budget to hire an independent compensation consultant as it deems necessary. The Compensation Committee has retained Barney & Barney LLC as its independent compensation consultant. Barney & Barney LLC primarily provided the Compensation Committee advice in the following areas:

- selecting the 2013 Executive Peer Group;
- evaluating the pay mix for our executive officers;
- evaluating short-term and long-term incentives for our executive officers; and
- evaluating non-employee Director compensation.

Barney & Barney LLC did not provide any additional services to us or our affiliates.

Our compensation philosophy supports and rewards the characteristics and behaviors we believe will make us successful:



We incorporate a number of features into our compensation structure 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 Performance MBOs are not guaranteed (i.e. are 100% at risk) and include a multiplier, or performance factor, based on Isis' and the employee's performance. Therefore, if *either* Isis or the employee does not perform well, the Performance MBO can be, and has been, zero.

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 of compensation received by an employee. Dr. Crooke's total cash compensation is on average 20.06 times that of the average cash compensation for our lowest level employees and 1.76 times greater than the average of our other executive officers. Stockholder advocacy organizations consider 3 times and lower an appropriate ratio when measuring CEO compensation against all executive officers. We cover the specific elements of our compensation structure in more detail below.

#### Objectives

As noted above, our vision is clear and is designed to promote long-term creation of value through innovation, and bring benefit to generations of patients with many diseases. Our vision is to:

- create and constantly advance a new more efficient drug discovery platform, antisense technology;
- create a unique business model and culture committed to creating long-term value through innovation;
- broaden, deepen and advance our pipeline of antisense drugs;
- demand more of every employee - more commitment, more knowledge, more intensity, more innovation;
- aggressively manage average and below average performance so that every employee produces more; and
- demand great performance and pay for that performance.

Drug discovery and development across a portfolio of many drugs (currently 32 for Isis) is a long process that spans many years, where decisions we make today can have a positive or negative consequence five years, ten years, and even further into the future. As such, it is essential that we set goals that incentivize our employees to execute our long-term strategy, because we believe our long-term strategy should continue to reward our stockholders into the future.

For us to retain our technology leadership and effectively manage the technical complexity and broad scope of our development pipeline, our most senior executives must advance multiple drug strategies and collaborative partnerships in parallel and consistently over many years, versus emphasizing one or two at the expense of others that deserve attention. As a result, other than stock price, we do not use metric-based objectives such as earnings per share because metrics typically overly emphasize two or three annual business metrics and ignore the complexity of the tasks we are undertaking. By taking this approach, we avoid the temptation to deviate from creating fundamental long-term value to meet a short-term metric.

We structure our objectives so they are results driven rather than task driven. We typically include a number of objectives that are based on achieving positive data in the clinic. For example, in 2013 we had a corporate objective to mature our pipeline and as a measure to achieve positive data from seven Phase 2 studies. This type of objective only rewards our executives if the data are positive - we do this to encourage the prudent spending of stockholder money on development decisions. In other words, we want to structure our objectives to reward success based on judgment, rather than the making of “bad bets.”

At the beginning of each year, we set aggressive corporate objectives that our Board approves. On at least a quarterly basis, the Board evaluates our progress in achieving these objectives. We define excellent performance as a year in which we have met most of our objectives.

#### *Importance of Tenure; Our Investment in Knowledge-Rich Employees*

It takes a significant period of time and a substantial investment to recruit and develop executives who possess the experience and talent necessary to lead at Isis given our innovative technology, innovative business strategy and complex drug development pipeline. Senior executives must have experience with all aspects of our business to be effective leaders. Our drug technology is a “platform technology”, which means the more knowledge and experience an employee has with our technology platform, the better equipped he or she is to create value at Isis. Given the uniqueness and complexity of our technology, it is critical to retain the knowledge and experience of outstanding long service employees. The experience and seniority of our employees is critical to our future success. For these reasons, it is our objective to attract and retain the best talent available, and to invest in those individuals who deliver long-term productivity.

**Given the uniqueness and complexity of our technology, it is critical to retain the knowledge and experience of outstanding long service employees.**

- Long tenure among a dedicated and highly skilled workforce, combined with the highest performance standards, contributes to our leadership in the industry and serves the interests of stockholders.
- Our focus on retention is coupled to a strong belief that executive talent most often should be developed and promoted from within Isis.
- The long tenure of high-performing executive officers reflects this strategy at all levels of the organization.
  - o Our executive officers have tenures at Isis ranging from 13 years to more than 25 years.
- Each of the executive officers has been carefully evaluated and selected through a rigorous performance assessment process over a long career. In their current assignments, they remain subject to a challenging annual performance assessment in which they must continue to meet the highest standards or be reassigned or separated from the Company.

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 system to reflect accountability both for the successes and failures (both long-term and short-term) of Isis and our employees. 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 within Isis, the more the person'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 more senior role a person plays, the more that person's cash compensation will be "at risk."**

Our executive officers' total direct compensation consists of three elements:

- (1) base salary,
- (2) MBO – Performance Based – At Risk Cash Compensation, no portion of which is guaranteed, and
- (3) 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 MBO – Performance Based – At Risk Cash Compensation is the only element that does not apply to all employees. Individual Performance MBOs are 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 the above three compensation elements. These factors include:

- Company-wide performance, including achievement of corporate objectives;
- the Compensation Committee's assessment of our CEO's and executive officers' individual performance;
- competitive compensation practices;
- increased efficiencies and process improvements;
- effective collaboration and teamwork;
- individual expertise, skills and knowledge;
- the need to retain and motivate;
- the impact an individual's judgment has on our success or failure; and
- the advice of our independent compensation consultant.

The Compensation Committee relies on these and other factors such as general economic conditions, industry conditions, and the Compensation Committee's collective business judgment in setting and/or approving the appropriate increases. We do not have specific weightings assigned to these performance factors, as the importance of each factor can vary among the executive officers and from year to year.

#### *Peer Group*

The Compensation Committee considers relevant market pay practices when setting executive compensation to ensure our ability to recruit and retain high performing talent.

As part of setting the 2013 compensation, the Compensation Committee, in consultation with the independent compensation consultant, evaluated and selected a peer group of 24 life science companies (the "Executive Peer Group"). The Compensation Committee reviews the compensation of our executive officers against the Executive Peer Group's executive compensation to ensure that our compensation is competitive and to inform and shape its decision-making when setting compensation. However, the Compensation Committee does not strictly adhere to quantitative benchmarks.

The Executive Peer Group, which the Compensation Committee will review on an annual basis, consists of companies that generally:

- are similar to Isis in terms of certain factors, including one or more of the following: size (i.e., revenue, market capitalization), industry, and stage of development;
- have named executive officer positions that are comparable to ours in terms of breadth, complexity and scope of responsibilities; and
- compete with us for executive talent.

The Executive Peer Group does not include companies headquartered outside the United States (because compensation and benefit practices are generally different outside the United States, the comparable compensation data for the executive officers is not available and cost of living is different) or companies in industries whose compensation programs are not comparable to our programs, such as non-life science companies.

In June of 2013, the Compensation Committee reviewed the Executive Peer Group using the criteria listed above, noting that Isis' market capitalization was approximately \$2.5 billion and had more than doubled since the Compensation Committee last set the Executive Peer Group. As part of this process, the Compensation Committee looked at companies in Isis' industry with market capitalizations of between \$500 million and \$5 billion, including looking at companies that themselves identified Isis as a peer, so called "reverse peers". Based on this evaluation, the Compensation Committee added Ariad Pharmaceuticals, InterMune, Immunogen, Medivation, Seattle Genetics, United Therapeutics and ViroPharma to the Executive Peer Group, as these companies fell within the market capitalization range, were in Isis' sector, and many were reverse peers. Additionally, the Compensation Committee removed Affimax, Dynavax Technologies, and Spectrum Pharmaceuticals because they were below the market capitalization range, and removed Genomic Health because it is a laboratory testing services company rather than a drug discovery and development company like Isis.



The following table lists the companies in the 2013 Executive Peer Group, along with Isis' rankings among these companies, based on market capitalization, and financial data reported by each company for the most recently-reported fiscal year at the time the Compensation Committee selected the Executive Peer Group, June 2013.

Company (ticker)	Annual Revenues (in millions)	Market Capitalization (in millions)	Stage of Lead Drug
Accorda Therapeutics (ACOR)	\$305.8	\$1,378.0	Market
Alkermes (ALKS)	\$390.0	\$4,513.9	Market
Alnylam Pharmaceuticals (ALNY)	\$66.7	\$1,873.8	Phase II
Arena Pharmaceuticals (ARNA)	\$27.6	\$1,938.2	Market
Ariad Pharmaceuticals (ARIA)	\$0.6	\$3,501.7	Market
Array BioPharma (ARRY)	\$85.1	\$699.5	Phase II
Auxilium Pharmaceuticals (AUXL)	\$395.3	\$749.0	Market
Exelixis (EXEL)	\$47.5	\$885.9	Market
Halozyyme Therapeutics (HALO)	\$42.3	\$812.2	Market
ImmunoGen (IMGN)	\$16.4	\$1,554.6	Market
Incyte Corporation (INCY)	\$297.1	\$3,086.9	Market
Infinity Pharmaceuticals (INFI)	\$47.1	\$1,427.1	Phase II
InterMune (ITMN)	\$26.2	\$815.4	Phase III
Jazz Pharmaceuticals (JAZZ)	\$586.0	\$4,027.7	Market
Lexicon Pharmaceuticals (LXRX)	\$1.1	\$1,221.0	Phase III
MannKind (MNKD)	\$0.4	\$1,914.0	Phase III
Medivation (MDVN)	\$181.7	\$3,728.6	FDA Approved
Momenta Pharmaceuticals (MNTA)	\$63.9	\$695.8	FDA Approved
Nektar Therapeutics (NKTR)	\$81.2	\$1,094.0	FDA Approved
Seattle Genetics (SGEN)	\$210.8	\$4,326.8	Market
The Medicines Company (MDCO)	\$558.6	\$1,855.1	Market
Theravance (THRX)	\$135.8	\$3,582.3	NDA
United Therapeutics (UTHR)	\$916.1	\$3,442.6	Market
ViroPharma (VPHM)	\$427.9	\$1,817.6	Market
Isis Pharmaceuticals, Inc. (ISIS)	\$102.1	\$2,433.8 *	Market
Isis' Ranking	12	9	1
Isis' Percentile Rank	54%	67%	42%

\* Isis' market capitalization at March 31, 2014 was approximately \$5.08 billion.

The table below compares total cash compensation and the total direct compensation of our named executive officer's against that of the 50<sup>th</sup> percentile of the Executive Peer Group.

Name	2013 Total Cash Compensation		2013 Total Direct Compensation	
	Named Executive Officer	50 <sup>th</sup> Percentile of Executive Peer Group	Named Executive Officer	50 <sup>th</sup> Percentile of Executive Peer Group
Stanley T. Crooke	\$1,539,076	\$1,238,100	\$2,758,536	\$3,366,400
Elizabeth L. Hougen	\$581,367	\$575,900	\$769,865	\$1,373,000
B. Lynne Parshall	\$1,167,745	\$760,100	\$1,751,326	\$2,084,400
C. Frank Bennett	\$631,601	\$477,400	\$958,865	\$884,500
Richard S. Geary	\$624,362	\$380,400	\$942,223	\$655,100

All companies in all industries strive to be more productive than their peers. Leadership management and compensation systems are all focused on enhancing long term productivity. However, measurement of productivity is challenging, particularly in biotechnology.

Even for established R&D based pharmaceutical companies for which the comparator group is obvious, comparisons of productivity are challenging. While revenues and profits per employee may be good measures for a portion of the equation, they are inadequate because they provide little insight into potential for topline sales growth and no insight into innovation, which is the foundation for long-term sustainable growth. To provide insight into these attributes, measures of the size, maturity and potential value of the drug pipeline are necessary. Additionally, measures of innovation such as numbers of issued patents and patent applications per employee can be used.

Because biotechnology companies' business models vary, ranging from companies repurposing a single in-licensed commercial drug, to companies developing in-licensed novel drugs, to true research-based companies and a few companies pioneering broad new technology platforms, comparisons of productivity within the biotechnology industry are even more challenging. Such comparisons are even more difficult for development stage pre-commercial companies.

Nevertheless, it is as important to develop productivity metrics and compare productivity for biotechnology companies as it is for any other industry. As Isis matures and achieves revenues from the commercial sale of its products, we will use revenue and profit per employee as metrics, supplemented by metrics that measure the value of our drug pipeline and innovation. We analyze our productivity against the Executive Peer Group and other leaders in drug development using, among other measures, number of drugs in clinical development per employee and number of patents per employee. The table below measures Isis on these productivity metrics against the median for the Executive Peer Group, and the leading company in the peer group for each productivity metric (based on the most recent Annual Report of the companies in June 2013, when the Compensation Committee selected the Executive Peer Group):

**Total direct compensation for each of our CEO, CFO and COO was below the 50th percentile range of the Executive Peer Group.**

	<b>Drugs in Clinical Development per Employee</b>	<b>Patents per Employee</b>
Isis' Ranking	2nd	3rd
Executive Peer Group Median	1 drug for every 61 employees	0.02 patents per employee
Peer Leader for Drugs in Clinical Development per Employee (Exelixis)	1 drug for every 6 employees	NA
Peer Leader for Patents per Employee (Theravance)	NA	6 patents per employee
Isis Pharmaceuticals, Inc. (ISIS)	1 drug for every 12 employees	3 patents per employee

As illustrated, Isis' innovative culture and business strategy have made Isis incredibly productive in terms of the number of drugs in development per employee and patents per employee.

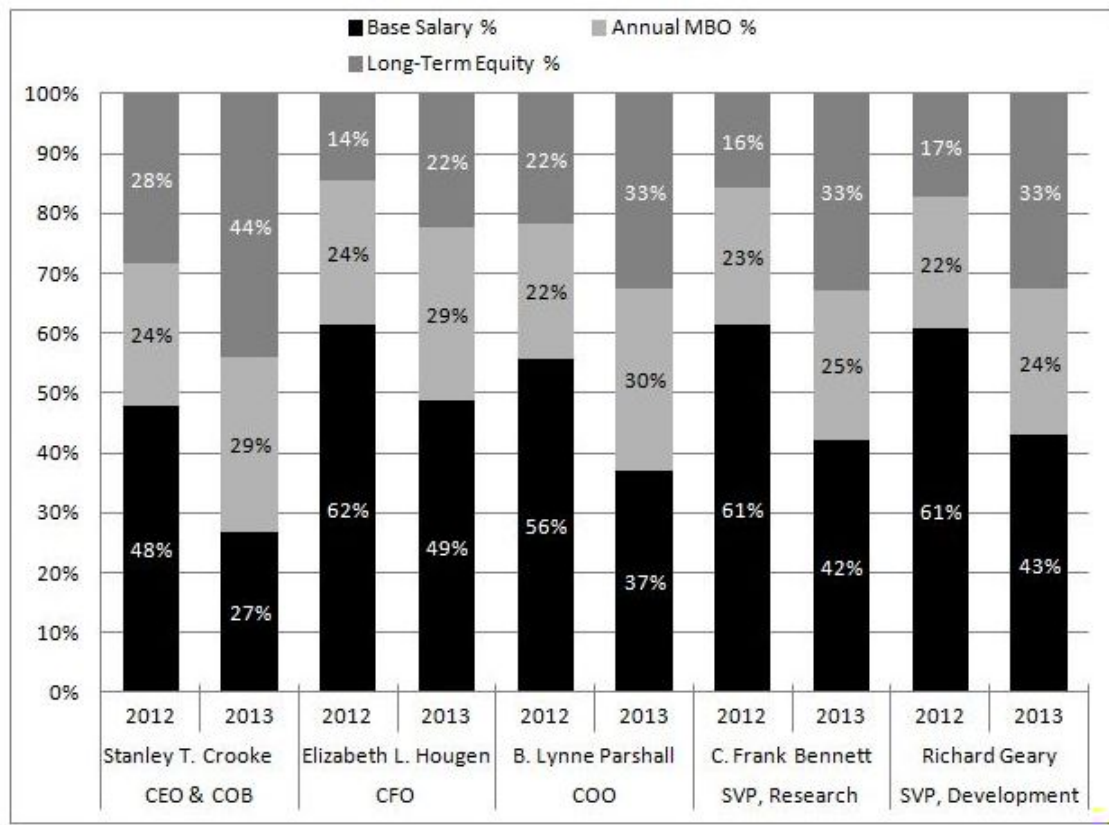
*Compensation Allocation/Pay Mix*

A key element of our compensation philosophy is to monitor and adjust our pay mix so the pay mix is weighted less heavily on fixed compensation (salary) with more weight on long-term incentive compensation (equity compensation). As part of the Compensation Committee's review of our total pay mix for executive officers, the Compensation Committee implemented the following:

- Salaries were frozen for named executive officers from 2011-2013. The Compensation Committee did not increase salaries for the CEO and applicable named executive officers for each of 2011, 2012 and 2013;
- More cash compensation is at risk. The Compensation Committee increased the proportion of our CEO's, COO's and other named executive officer's cash compensation that is at risk for 2013 and going forward; and
- More of total compensation is long-term equity. The Compensation Committee adjusted the total pay mix for our CEO and other executive officers such that more of their compensation is in the form of long-term equity compensation.

An annual review of our total pay mix helps Isis compete for talent in the competitive marketplace and maintain compensation equity and balance among positions with similar responsibilities. The target pay mix for our executive officers is a result of the compensation targets which emphasize long-term compensation versus short-term compensation. Actual salary levels, annual Performance MBO awards and long-term incentive awards will vary based on an individual's responsibilities, tenure in a particular position, experience, individual performance and Company performance.

The following chart illustrates the portions of actual total direct compensation for the named executive officers that are composed of base salary, annual MBO and long-term equity for 2012 and 2013:



Name	Year	Base Salary	Annual MBO	Long-Term Equity	Base Salary %	Annual MBO %	Long-Term Equity %
Stanley T. Crooke CEO & COB	2012	\$735,169	\$367,585	\$435,437	48%	24%	28%
	2013	\$735,169	\$803,907	\$1,203,708	27%	29%	44%
Elizabeth L. Hougen CFO	2012	\$337,036	\$131,444	\$79,203	62%	24%	14%
	2013	\$365,496	\$215,871	\$167,880	49%	29%	22%
B. Lynne Parshall COO	2012	\$641,574	\$256,630	\$250,811	56%	22%	22%
	2013	\$641,574	\$526,171	\$562,945	37%	30%	33%
C. Frank Bennett SVP, Research	2012	\$397,077	\$148,904	\$101,591	61%	23%	16%
	2013	\$397,077	\$234,524	\$307,226	42%	25%	33%
Richard S. Geary SVP, Development	2012	\$398,444	\$143,440	\$113,462	61%	22%	17%
	2013	\$398,444	\$225,918	\$303,166	43%	24%	33%

The fixed component of our compensation structure 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, specifically ten levels, 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 salary ranges because years of experience have shown that this approach often creates unnecessary bureaucracy and a loss of talented individuals. Our aim is to attract and retain the most highly qualified employees in an extremely competitive market.

We determine base compensation levels for all our employees primarily by market forces. Accordingly, the Compensation Committee believes that it is important when making its compensation decisions to be informed as to the current practices of comparable publicly held companies with which we compete for top talent. To this end, the Compensation Committee reviews market and peer company data, which includes competitive information relating to the mix and levels of compensation for executives in the life sciences industry. We obtain this information for the Executive Peer Group based on recent public filings with the SEC. In addition, we also review data from the Radford Global Life Sciences Survey, which is a summary of compensation data submitted by over 500 life sciences companies. The Committee uses these data to inform and shape its decision-making but does not strictly adhere to quantitative benchmarks. In addition, we assess whether the scope of job responsibilities and internal equity warrant a given base salary.

Base salaries for CEO and COO were *frozen* for 2011-2013.

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 Isis' performance and external factors such as the average merit budget of comparable companies. The actual merit increase award for each employee, including our executive officers, will vary depending upon the respective employee's contributions to Isis. For example, for 2013 performance the Company-wide merit increase budget was 3.3%, with a range of individual merit award increases of 0% to 5.0%. 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 or COO evaluating the performance of each individual executive officer. The Compensation Committee carefully considers these reports since our CEO and COO are 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 our company's 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. Our CEO has no role in determining his own compensation.

The executive officers' new salaries for each year are calculated as follows:

Performance MBOs can be, and have in the past been, zero.

Performance MBOs have a maximum limit.

- Current Base Salary (x) Merit Increase = Increase to Base Salary
- Current Base Salary (+) Increase to Base Salary = New Base Salary

For example, Dr. Crooke's 2014 salary of \$768,252 was calculated as follows:

<u>2013 Base Salary</u>	(x)	<u>Merit Increase</u>	=	<u>Increase to Base Salary</u>
\$735,169	(x)	4.5%	=	\$33,083
<u>Current Base Salary</u>	(+)	<u>Increase to Base Salary</u>	=	<u>New Base Salary in 2014</u>
\$735,169	(+)	\$33,083	=	\$768,252

When reviewing salaries, the Compensation Committee noted that our CEO's salary, and the salary for our other named executive officers, was greater than the 50<sup>th</sup> percentile of the Executive Peer Group. The Compensation Committee also noted its desired target mix of compensation is less weighted on salary and therefore did not increase base salaries for the CEO, COO and most of the other named executive officers for the previous three years (2011-2013). Given Isis' outstanding 2013 performance, and given that most salaries were fixed over the prior three years, the Compensation Committee approved merit increases to each of the named executive officer's salaries for 2014.

*MBO-Performance Based-At Risk Cash Compensation (Performance MBO)*

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 performance based cash payment through our Performance MBO program. Our Performance MBO rewards employees for reaching specific objectives and for the judgment they use in making decisions, while an employee's base salary compensates the employee for his or her continued service and performance. We do not guarantee a Performance MBO as compensation. It is totally at risk. As such, a Performance MBO 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 MBO bonuses differs from salary increases because, unlike salary increases, market forces do not impact bonus amounts.

We calculate the actual amount of each executive officer's respective Performance MBO based on the following formula:

$$\text{Base Salary (x) Target MBO \% (x) Company Performance Factor (x) Individual Performance Factor} = \text{Performance MBO Amount}$$

*Performance MBOs can be zero.* The multipliers in this formula ensure we award Performance MBOs based on *both* Isis' performance and individual performance. This means an employee may not receive a Performance MBO even if he or she performed well in a year in which the Company does not meet its corporate objectives. Similarly, if an employee performed poorly in a year in which the Company met its corporate objectives, he or she may not receive a Performance MBO.

For example, in 1999 no Performance MBOs for executive officers were paid due to the failures Isis faced at the time. In 2004 our CEO's Performance MBO was 64% of the Performance MBO he received in 2003 because of disappointing clinical trial results; the Company Performance Factor was 50% that year. Conversely, in 2007 Isis had a seminal year and we rewarded our executive officers consistent with Isis' success.

Performance MBOs have a maximum limit. Performance MBOs are limited by a maximum Company Performance Factor, maximum Individual Performance Factor and Target MBO Percentage:

- We have a maximum Company Performance Factor of 200% and a maximum Individual Performance Factor of 160%. This range represents the boundary conditions for our Performance Factors and ensures we reward our employees consistent with Isis' success.
- We base Target MBO Percentages on position levels within Isis. The Target MBO percentages for 2013 were: Directors 15%; Executive Directors 20%; Vice Presidents 25% or 30%; Senior Vice Presidents 35%, COO 45%; and CEO 60%.
- An individual's Target MBO percentage does not change unless he or she changes position level or the Compensation Committee sets a new target for that level.

The table below summarizes the minimum and maximum MBO for 2013 as a percentage of salary:

Name	Minimum MBO Percentage of Salary	Maximum MBO Percentage of Salary
Stanley T. Crooke	0%	192%
Elizabeth L. Hougen	0%	112%
B. Lynne Parshall	0%	144%
C. Frank Bennett	0%	112%
Richard S. Geary	0%	112%

The Compensation Committee sets the Company Performance Factor based on the following process:

- Isis' achievement of the approved corporate objectives for the year. At the end of each year, the Compensation Committee meets to evaluate Isis' overall performance. The Compensation 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 (Please see chart below);
- In addition, the Compensation Committee considers our one-, three- and five-year total stockholder returns, and based on these returns may reduce the Individual Performance Factors for our executive officers;
- The Compensation Committee then reviews the Company Performance Factor history from the prior 10 years to form a comparison for our current year's successes and/or failures; and
- Finally, the Compensation Committee approves each executive officer's Individual Performance Factor based on the individual's performance.

Once the Compensation Committee has determined the elements of the formula above, we use that formula to calculate each executive officer's Performance MBO.

Evaluation of 2013 Corporate Objectives. On December 5, 2013, the Compensation Committee completed its evaluation of the Company's performance against the 2013 Corporate Objectives.

The Compensation Committee also evaluated the Company's achievement of two unplanned accomplishments: (1) the completion of a successful equity offering and (2) the Company demonstrated ISIS-APOCIII<sub>Rx</sub> efficacy in patients with familial chylomicronemia syndrome, or FCS. The Compensation Committee considers significant unplanned accomplishments when setting MBO awards. Unplanned accomplishments are *not* in exchange for, or replacements for, missed Corporate Objectives. Rather, because Isis has a long-term strategy of discovering and developing drugs, and then licensing those drugs to corporate partners, we want to encourage our employees to capitalize on unplanned opportunities based on emerging scientific data, unplanned or accelerated interest from a corporate partner or favorable market conditions, even if such opportunities could not have been anticipated and as such were not part of the Corporate Objectives set at the beginning of the year.

The Compensation Committee set the Company Performance Factor for the 2013 MBO at 135% due to our strong achievements for the year across drug discovery, development and corporate development, including the significant increase in the stock price, advancing key programs into or towards Phase 3 studies, and seven positive efficacy studies for drugs in our pipeline, with only one significant disappointment; the failure to achieve marketing approval for Kynamro in Europe. The table below provides a detailed evaluation of each objective:

Evaluation of 2013 Corporate Objectives		
	Objective & Pre-Approved Measures	Evaluation
1	<p>Successfully advance Kynamro:</p> <ul style="list-style-type: none"> <li>· Approval and launch of Kynamro in the United States; and</li> <li>· Approval of Kynamro in Europe.</li> </ul>	<p>Isis <i>met substantial portions</i> of this objective:</p> <ul style="list-style-type: none"> <li>· Isis achieved the approval and launch for Kynamro in the US.</li> <li>· Isis did not achieve approval and launch of Kynamro in Europe.</li> </ul>
2	<p>Enhance corporate value:</p> <ul style="list-style-type: none"> <li>· End 2013 with greater than \$300 million in cash, cash equivalents and short-term investments;</li> <li>· Stock price increase greater than ten percentage points over percentage change in NASDAQ Biotechnology Index;</li> <li>· Meet net operating loss and cash guidance; and</li> <li>· Meet budget.</li> </ul>	<p>Isis <i>exceeded</i> this objective:</p> <ul style="list-style-type: none"> <li>· Isis ended 2013 with over \$655 million in cash, cash equivalents and short-term investments.</li> <li>· Isis' stock closed at \$39.84 per share on December 31, 2013, representing a nearly 270% increase from January 2, 2013 and over a 200 percentage point increase over the increase in the NASDAQ Biotechnology Index.</li> <li>· Isis greatly exceeded its guidance.</li> <li>· Isis met its budget.</li> </ul>
3	<p>Advance Pipeline:</p> <ul style="list-style-type: none"> <li>· Positive data from seven efficacy studies;</li> <li>· Initiate two Phase 3 studies;</li> <li>· Open specified sites and enroll target number of patients in TTR study;</li> <li>· Initiate Phase 2 studies on two new drugs;</li> <li>· Complete one positive Phase 1 study; and</li> <li>· Identify three new development candidates.</li> </ul>	<p>Isis <i>met</i> this objective:</p> <ul style="list-style-type: none"> <li>· Isis achieved positive data from seven efficacy studies.</li> <li>· Isis initiated the Phase 3 study for ISIS-TTR<sub>Rx</sub>, and made significant progress towards starting the Phase 3 studies for ISIS-SMN<sub>Rx</sub> and ISIS-ApoC-III<sub>Rx</sub>.</li> <li>· Isis exceeded opening the specified sites and made significant progress towards meeting the enrollment targets for the TTR study.</li> <li>· Isis initiated Phase 2 studies on four new drugs.</li> <li>· Isis completed a positive Phase 1 study on one drug.</li> <li>· Isis identified three new development candidates.</li> </ul>

	Objective & Pre-Approved Measures	Evaluation
4	<p>Make corporate partnerships successful:</p> <p><i>GlaxoSmithKline</i></p> <ul style="list-style-type: none"> <li>· Initiate Phase 3 Study ISIS-TTR<sub>Rx</sub></li> <li>· Identify at least one new Development Candidate</li> <li>· Initiate Phase 1 study for ISIS-GSK3<sub>Rx</sub></li> </ul> <p><i>Biogen Idec</i></p> <ul style="list-style-type: none"> <li>· Initiate infant study for ISIS-SMN<sub>Rx</sub> and meet enrollment</li> <li>· Complete enrollment in multi-dose in children with SMA and open-label studies for ISIS-SMN<sub>Rx</sub></li> <li>· Achieve breakthrough therapy status for ISIS-SMN<sub>Rx</sub></li> <li>· Identify DMPK Development Candidate (achieve milestone)</li> <li>· Expand relationship strategically</li> </ul> <p><i>AstraZeneca</i></p> <ul style="list-style-type: none"> <li>· Complete enrollment of lymphoma study for ISIS-STAT3<sub>Rx</sub></li> <li>· Complete studies required for AstraZeneca to select second development candidate</li> <li>· Initiate a second study in patients for STAT3 (AstraZeneca to initiate).</li> </ul>	<p>Isis <i>exceeded</i> this objective:</p> <p><i>GlaxoSmithKline</i></p> <ul style="list-style-type: none"> <li>· Isis initiated the Phase 3 study for ISIS-TTR<sub>Rx</sub>.</li> <li>· Isis identified ISIS-GSK4<sub>Rx</sub> earning a \$5 million milestone payment.</li> <li>· Isis initiated a Phase 1 study for ISIS-GSK3<sub>Rx</sub> earning \$10 million in milestone payments.</li> </ul> <p><i>Biogen Idec</i></p> <ul style="list-style-type: none"> <li>· Isis initiated the Phase 2 open-label, multiple-dose, dose-escalation pilot study of ISIS-SMN<sub>Rx</sub> in infants who have been diagnosed with Type I SMA and exceeded enrollment.</li> <li>· Isis completed enrollment for the multi-dose study in children with SMA and open-label studies for ISIS-SMN<sub>Rx</sub>.</li> <li>· ISIS-SMN<sub>Rx</sub> did not achieve breakthrough therapy.</li> <li>· Isis identified ISIS-DMPK<sub>Rx</sub> and received a \$10 million milestone payment in connection with the selection and advancement of ISIS-DMPK<sub>Rx</sub>.</li> <li>· Isis formed a broad strategic alliance with Biogen Idec to discover and develop antisense drugs to treat neurological disorders, which included a \$100 million upfront payment to Isis and the potential for Isis to receive substantial milestone payments, license fees and royalty payments for all treatments developed through the collaboration.</li> </ul> <p><i>AstraZeneca</i></p> <ul style="list-style-type: none"> <li>· Isis made substantial progress towards enrolling the lymphoma study for ISIS-STAT3<sub>Rx</sub>.</li> <li>· AstraZeneca selected ISIS-AR<sub>Rx</sub> as a development candidate and paid Isis a \$10 million milestone payment.</li> <li>· AstraZeneca initiated a Phase 1b/2a clinical study of ISIS-STAT3<sub>Rx</sub> in patients with advanced metastatic hepatocellular carcinoma.</li> </ul>



	Objective & Pre-Approved Measures	Evaluation
<b>Unplanned Accomplishments</b>		
5	Complete successful equity financing	Isis successfully completed a public offering of common stock raising \$173.3 million in net proceeds.
6	Demonstrate ISIS-APOCIII <sub>Rx</sub> efficacy in patients with familial chylomicronemia syndrome, or FCS.	Isis reported Phase 2 data on ISIS-APOCIII <sub>Rx</sub> demonstrating that ISIS-APOCIII <sub>Rx</sub> reduced triglycerides in patients with FCS. Treatment with ISIS-APOCIII <sub>Rx</sub> resulted in significant reductions of ApoC-III, triglycerides, and ApoC-III-associated very low-density lipoprotein particles.

Once the Committee establishes the Company Performance Factor, the Committee next reviews individual performance and sets each executive officer's Performance MBO. The following table illustrates the Performance MBOs approved for 2013 performance:

Name	Base Salary	Target MBO %	Company Performance Factor	Individual Performance Factor	Resulting Performance MBO	Results Considered When Setting Individual Performance Factor <sup>(1)</sup>
Stanley T. Crooke <sup>(2)</sup>	\$735,169	60%	135%	135%	\$803,907	1-6
Elizabeth L. Hougen	\$365,496	35%	135%	125%	\$215,871	1,2,4 & 5
B. Lynne Parshall <sup>(2)</sup>	\$641,574	45%	135%	135%	\$526,171	1-6
C. Frank Bennett	\$397,077	35%	135%	125%	\$234,524	2, 3, & 4
Richard S. Geary	\$398,444	35%	135%	120%	\$225,918	1,2,3,4 & 6

- (1) The numbers correspond to the enumerated objectives in the table entitled "Evaluation of 2013 Corporate Objectives" on pages 54 through 56. The Compensation Committee reviews the individual's contribution towards the corporate objective when setting the Individual Performance Factor.
- (2) Since our CEO and COO are ultimately responsible for the Company's performance, their Individual Performance Factors are usually the same as the Company Performance Factor.

The Company Performance Factor reflects an increase of 35 percentage points from the 2012 Company Performance Factor of 100%. The Committee agreed that this increase was a fair reflection of a very strong year, with nearly all corporate objectives exceeded and a percentage increase to its stock price that exceeded all other companies in the Executive Peer Group, except one. The only disappointment was our failure to achieve marketing approval for Kynamro in Europe. As noted earlier, the corporate objectives are set and approved by our Board at the beginning of each year. We ensure these objectives are aggressive and we define excellent performance as a year in which we have met most of the objectives.

#### *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 believe awarding a combination of stock options and RSUs provides a number of benefits. Stock options provide a way to align employee interests with those of upper management and the stockholders because as our stock price increases, so too does the employee's compensation. In 2011 our stockholders approved our 2011 Equity Incentive Plan which allowed us to provide RSU awards to our employees and Directors. In 2012, we started granting RSUs as part of the annual merit equity awards. RSUs are a strong retention vehicle for employees as the RSUs vest in annual installments over four years and have value upon vesting, but at the same time, require fewer shares than option awards.

Some of our largest institutional stockholders agree our stock options are performance-based and the best vehicle for our long-term compensation. Our independent compensation consultant did not recommend we change our equity vehicles. Over the past several years we discussed our use of time-vested stock options and RSU awards with our institutional stockholders. The results of this process were that one of our largest institutional stockholders agreed that time-vested options are the best long-term incentive compensation vehicle for a biopharmaceutical company at our stage, and others agreed that our time-vested stock options are performance-based compensation. Our independent compensation consultant also believes time-vested stock options are performance-based compensation and an appropriate equity vehicle for Isis. Also we would be disadvantaged if we did not offer time-vested equity awards since most of the companies we compete with for talent (including most companies in the Executive Peer Group) do not use event-based vesting for equity compensation.

Our Stock Awards reward performance and incentivize long-term stock appreciation and increased stockholder returns.

We grant existing employees new options and RSUs annually to provide a continuing financial incentive in Isis' long-term success. We set the size of the equity awards based on individual and Company performance during the previous year.

Vesting schedules reward long-term performance and incentivize long-term stock appreciation and increased stockholder returns. For each stock option and RSU granted, the Compensation Committee sets a vesting schedule over four years, with no vesting during the first year. Therefore, the stock options and RSUs granted to our executive officers directly align the interests of our executive officers with the interests of our stockholders and Isis' long-term success. The actual economic value of stock option awards depends directly on the performance of our stock price over the period during which the awards vest and the period in which the options may be exercised. In other words, the stock options are not worth anything if our stock price does not increase above the exercise price. Our employees will only realize economic value when our stock price, and consequently stockholder value, increases. Similarly, in the same way our stockholder returns increase and decrease based on our stock's performance, the value to our employees of the RSUs increases and decreases based on our stock's performance.

We do not tie vesting to the achievement of specific events, such as annual metrics, because we do not want to encourage our employees to deviate from our Company objectives, which we believe optimizes sustained stockholder value; nor do we want our employees to take unnecessary risks just to meet a short-term metric.

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. The RSU vesting schedule is typically over a 4-year period at the rate of 25% per year. In addition, as further described below, our executive officers must hold shares received upon vesting of their RSUs until they meet certain ownership thresholds or no longer serve the Company. These practices align our employee compensation with our stockholders' interests because if stockholder value declines over time, so too will the value of the equity compensation provided to all employees. We have historically had low employee turnover, particularly in our management team, and the members of our management have traditionally held their options for a long period of time before exercise. Our low turnover is indicative of our employees' commitment to Isis and its technology, and reflects our officers' belief in the long-term value of our stock.

*Our stock compensation budget minimizes dilution.* 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. This stock compensation budget, and therefore our equity compensation burn rate, is well below the Executive Peer Group average of 4.3%. We believe this stock budget is an important tool to balance our compensation objectives with stockholder interests. For 2013, 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 1.3% of our outstanding common stock on an issued and outstanding basis for that year. This budget, as well as each employee's position level and performance in the previous year, ultimately determines the size of the individual annual stock grant.

*Our executive officers and members of our Board must hold the shares issued under their RSUs until they have met an ownership guideline and all employees must hold shares purchased under our ESPP for six months.*

In February 2013, our Compensation Committee and our Board approved stock ownership and holding guidelines for our executive officers and members of the Board. These guidelines require our executive officers and non-employee Board members to hold the shares they receive under their RSU awards until they achieve the guidelines or no longer serve the Company. Shares sold or surrendered to pay for withholding taxes associated with the RSU awards are exempt from these holding requirements.

The table below indicates the stock ownership guidelines for our executive officers and Board members:

<b>Executive Officer/Director</b>	<b>Stock Ownership Guideline (as a multiple of base salary/annual cash retainer)</b>
CEO <sup>(1)</sup>	3 times Base Salary
COO	2 times Base Salary
All other executive officers	1 times Base Salary
Non-employee Directors	3 times Annual Cash Retainer

(1) Dr. Crooke currently meets these ownership guidelines.

In addition, our ESPP has a six month minimum holding period for shares purchased under the ESPP.

Dr. Crooke currently holds approximately 725,000 shares of our common stock and has held these shares throughout his 25-year tenure. As of March 31, 2014, Dr. Crooke's holding represented approximately 66 times his Base Salary.

*We have a recoupment/"clawback" policy.* If we are required to prepare an accounting restatement due to the material noncompliance of Isis, as a result of misconduct, with any financial reporting requirement under the securities laws, Isis' Chief Executive Officer and Chief Financial Officer will reimburse Isis for:

- any bonus or other incentive-based or equity-based compensation received by that person from Isis during the 12-month period following the first public issuance or filing with the SEC (whichever first occurs) of the financial document embodying such financial reporting requirement; and
- any profits realized from such executive's sale of Isis' securities during that 12-month period.

The SEC may exempt any person from the application of this executive recoupment policy, as it deems necessary and appropriate.

In addition, if and when the SEC adopts implementing regulations under Section 954, "Recovery of Erroneously Awarded Compensation" under The Dodd-Frank Wall Street Reform and Consumer Protection Act, our Nominating, Governance and Review Committee will promptly adopt appropriate updates to this policy to comport with such implementing regulations.

*We explicitly prohibit employees from "shorting" and hedging against our stock.* To help avoid situations in which 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).

10b5-1 plan required for executive officers, all vice presidents and many other employees. We have a Rule 10b5-1 trading program. Our Rule 10b5-1 trading program allows our executive officers, all vice presidents and many other employees, to establish plans that permit prearranged future sales of his or her stock when there is no material non-public information available. 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.

#### *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 67 and 68 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.

#### *2013 Say-on-Pay Vote*

We value the feedback our stockholders provide regarding executive compensation. As such, we are committed to providing our stockholders the opportunity for a "Say-on-Pay" vote annually.

In 2013 we asked our 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. At our 2013 Annual Meeting of Stockholders, we received an advisory vote in favor of our executive compensation by over 97% of the shares voted at the meeting.

## Compensation of Executive Officers

The following table shows for the fiscal years ended December 31, 2013, 2012 and 2011 compensation awarded to or paid to, or earned by, our Chief Executive Officer, Chief Financial Officer and our three other most highly compensated executive officers at December 31, 2013, 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 <sup>(1)</sup> (\$)	Stock Awards <sup>(2)(3)</sup> (\$)	Option Awards <sup>(3)</sup> (\$)	All Other Compensation <sup>(4)</sup> (\$)	Total (\$)
Stanley T. Croke Chairman, President, Chief Executive Officer	2013	\$735,169	\$803,907	\$325,971	\$877,737	\$15,752	\$2,758,536
	2012	\$735,169	\$367,585	\$90,516	\$344,921	\$17,815	\$1,556,006
	2011	\$735,169	\$535,938	--	\$611,305	\$14,920	\$1,897,332
Elizabeth L. Hougen <sup>(5)</sup> Senior Vice President, Finance and Chief Financial Officer	2013	\$365,496	\$215,871	<sup>(6)</sup> \$54,419	<sup>(6)</sup> \$113,461	\$20,618	\$769,865
	2012	\$337,036	\$131,444	\$16,462	\$62,741	\$21,148	\$568,831
B. Lynne Parshall Director, Chief Operating Officer	2013	\$641,574	\$526,171	\$152,482	\$410,463	\$20,636	\$1,751,326
	2012	\$641,574	\$256,630	\$52,136	\$198,675	\$22,600	\$1,171,615
	2011	\$641,574	\$409,244	--	\$364,913	\$19,088	\$1,434,819
C. Frank Bennett Senior Vice President, Antisense Research	2013	\$397,077	\$234,524	\$83,145	\$224,081	\$20,038	\$958,865
	2012	\$397,077	\$148,904	\$21,113	\$80,478	\$21,074	\$668,646
	2011	\$397,077	\$201,020	--	\$136,434	\$17,398	\$751,929
Richard S. Geary Senior Vice President, Development	2013	\$398,444	\$225,918	\$82,117	\$221,049	\$14,695	\$942,223
	2012	\$398,444	\$143,440	\$23,583	\$89,879	\$17,048	\$672,394
	2011	\$398,444	\$225,918	--	\$167,446	\$14,125	\$805,933

(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 2014 we paid bonuses for 2013 performance.

(2) The Company began granting restricted stock units in January 2012.

(3) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with FASB Topic ASC 718 (“ASC 718”) for stock and option awards granted to our named executive officers. ASC 718 expense for the option awards is based on the fair value of the awards on the date of grant using an option-pricing model. The fair value of RSUs is based on the market price of our common stock on the date of grant. For more information, please see Note 5 of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2013 regarding assumptions underlying valuation of equity awards.

(4) Includes AD&D, Basic Life, Medical, Dental, Vision, and 401(k) matching contributions which are available to all employees.

(5) Ms. Hougen was not a named executive officer in 2011 or 2012 and did not become an executive officer until January 2013. We are not disclosing compensation for 2011 as permitted by SEC regulations.

(6) Ms. Hougen received additional stock options and stock awards due to her promotion to Chief Financial Officer in January 2013.

## Grants of Plan-Based Awards

The following table shows for the fiscal year ended December 31, 2013, certain information regarding grants of plan-based awards to our named executive officers:

### Grants of Plan-Based Awards in Fiscal 2013

Name	Grant Date	All Other Stock Awards: Number of Shares of Stock or Units (#)	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 <sup>(1)</sup> (\$)
Stanley T. Crooke	1/30/13		133,180	\$14.69	\$877,737
	1/30/13	22,190			\$325,971
Elizabeth L. Hougen	(2)1/2/13		7,500	\$10.82	\$36,679
	1/2/13		15,700	\$10.82	\$76,782
	(2)1/2/13	1,250			\$17,600
	1/2/13	2,615			\$36,819
B. Lynne Parshall	1/30/13		62,280	\$14.69	\$410,463
	1/30/13	10,380			\$152,482
C. Frank Bennett	1/30/13		34,000	\$14.69	\$224,081
	1/30/13	5,660			\$83,145
Richard S. Geary	1/30/13		33,540	\$14.69	\$221,049
	1/30/13	5,590			\$82,117

(1) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with FASB Topic ASC 718 (“ASC 718”) for stock and option awards granted to our named executive Officers. ASC 718 expense for the option awards is based on the fair value of the awards on the date of grant using an option-pricing model. The fair value of RSUs is based on the market price of our common stock on the date of grant. For more information, please see Note 5 of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2013 regarding assumptions underlying valuation of equity awards.

(2) Granted as a result of Ms. Hougen’s promotion to Chief Financial Officer in January 2013.

### 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 30, 2013, except that Ms. Hougen’s were granted on January 2, 2013. All of these stock options were granted out of our 1989 Stock Option 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.

The Compensation Committee granted RSUs to the executive officers on January 30, 2013, except that Ms. Hougen’s were granted on January 2, 2013. All of these RSUs were granted out of our 2011 Equity Incentive Plan. The RSUs vest at the rate of 25% per year over four years with a vesting commencement date of January 15, 2013.

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

The following table shows for the fiscal year ended December 31, 2013, certain information regarding outstanding equity awards at fiscal year-end for our named executive officers.

Other than the equity awards described in the table below, there were no equity incentive plan awards outstanding for our named executive officers at December 31, 2013.

**Outstanding Equity Awards At December 31, 2013**

Name	Grant Date	Option Awards				Stock Awards	
		Number of Securities Underlying Unexercised Options (#) Exercisable <sup>(1)</sup>	Number of Securities Underlying Unexercised Options (#) Unexercisable	Option Exercise Price (\$)	Option Expiration Date	Number of Shares or Units of Stock that Have Not Vested <sup>(2)</sup>	Market Value of Shares or Units of Stock that Have Not Vested <sup>(3)</sup> (\$)
Stanley T. Croke	01/02/2009	150,000	0	\$14.47	1/1/16	--	--
	01/04/2010	116,680	2,483	\$11.27	1/3/17	--	--
	01/03/2011	89,028	33,068	\$10.29	1/2/18	--	--
	01/03/2012	51,368	55,835	\$7.25	1/2/19	--	--
	01/30/2013	0	133,180	\$14.69	1/29/20	--	--
	01/15/2012	--	--	--	--	8,932	\$355,851
	01/30/2013	--	--	--	--	22,190	\$884,050
Elizabeth L. Hougen	01/02/2009	12,657	0	\$14.47	1/1/16	--	--
	01/04/2010	19,583	417	\$11.27	1/3/17	--	--
	01/03/2011	16,041	5,959	\$10.29	1/2/18	--	--
	01/03/2012	9,343	10,157	\$7.25	1/2/19	--	--
	01/02/2013	0	15,700	\$10.82	1/1/20	--	--
	01/02/2013	0	7,500	\$10.82	1/1/20	--	--
	01/15/2012	--	--	--	--	1,624	\$64,700
	01/15/2013	--	--	--	--	1,250	\$49,800
	01/15/2013	--	--	--	--	2,615	\$104,182
B. Lynne Parshall	01/04/2010	2,648	1,324	\$11.27	1/3/17	--	--
	01/03/2011	53,144	19,740	\$10.29	1/2/18	--	--
	01/03/2012	29,588	32,161	\$7.25	1/2/19	--	--
	01/30/2013	0	62,280	\$14.69	1/29/20	--	--
	01/15/2012	--	--	--	--	5,145	\$204,977
	01/30/2013	--	--	--	--	10,380	\$413,539
C. Frank Bennett	01/02/2008	16,200	0	\$15.38	1/1/15	--	--
	01/02/2009	32,909	0	\$14.47	1/1/16	--	--
	01/04/2010	27,225	580	\$11.27	1/3/17	--	--
	01/03/2011	19,870	7,380	\$10.29	1/2/18	--	--
	01/03/2012	11,985	13,028	\$7.25	1/2/19	--	--
	01/30/2013	0	34,000	\$14.69	1/29/20	--	--
	01/15/2012	--	--	--	--	2,083	\$82,987
	01/30/2013	--	--	--	--	5,660	\$225,494
Richard S. Geary	01/04/2010	6,800	680	\$11.27	1/3/17	--	--
	01/03/2011	6,968	9,058	\$10.29	1/2/18	--	--
	01/03/2012	13,386	14,549	\$7.25	1/2/19	--	--
	01/30/2013	0	33,540	\$14.69	1/29/20	--	--
	01/15/2012	--	--	--	--	2,327	\$92,708
	01/30/2013	--	--	--	--	5,590	\$222,706

(1) 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.

(2) The RSUs were granted out of our 2011 Equity Incentive Plan. The RSUs vest at the rate of 25% per year over four years.

(3) Market value of stock awards was determined by multiplying the number of unvested shares by \$39.84, which was the closing market price of our common stock on NASDAQ on December 31, 2013, the last trading day of fiscal 2013.

## Option Exercises and Stock Vested

The following table shows for the fiscal year ended December 31, 2013, certain information regarding option exercises and stock awards vesting during the last fiscal year with respect to our named executive officers:

Name	Option Awards		Stock Awards	
	Number of Shares Acquired on Exercise (#) <sup>(1)</sup>	Value Realized on Exercise (\$)	Number of Shares Acquired on Vesting (#)	Value Realized on Vesting (\$)
Stanley T. Crooke	10,000	\$189,020	2,978	\$41,930
	1,885	\$37,512		
	24,180	\$353,874		
	10,000	\$151,450		
	30,000	\$439,890		
	5,008	\$73,347		
	11,500	\$217,120		
	10,000	\$190,800		
	26,615	\$513,536		
	8,740	\$216,560		
	10,000	\$214,900		
	10,000	\$154,920		
	8,115	\$126,919		
	10,000	\$202,600		
	10,000	\$224,450		
	10,435	\$224,457		
	20,000	\$274,600		
	12,000	\$268,570		
	10,000	\$205,900		
	30,000	\$498,690		
	6,000	\$133,122		
	12,000	\$263,568		
	20,000	\$480,080		
	19,565	\$411,941		
	30,000	\$440,040		
	24,992	\$367,632		
	10,000	\$148,050		
	10,000	\$148,050		
	20,000	\$405,820		
	2,200	\$35,244		
30,000	\$717,000			
10,000	\$229,280			
10,000	\$226,850			
30,000	\$382,380			
6,000	\$104,700			



Name	Option Awards		Stock Awards	
	Number of Shares Acquired on Exercise (#)(1)	Value Realized on Exercise (\$)	Number of Shares Acquired on Vesting (#)	Value Realized on Vesting (\$)
Elizabeth L. Hougen	9,843	\$69,098	542	\$7,631
	2,813	\$16,934		
	4,792	\$33,592		
	9,584	\$67,184		
	3,000	\$18,090		
	10,417	\$72,919		
	5,040	\$50,637		
	2,000	\$12,100		
B. Lynne Parshall(2)	30,000	\$330,000	1,715	\$24,147
	20,000	\$394,880		
	38,400	\$594,337		
	20,000	\$594,520		
	10,000	\$205,180		
	1,520	\$24,018		
	48,229	\$1,312,359		
	30,000	\$296,100		
	3,333	\$36,796		
	3,333	\$36,680		
	7,454	\$84,789		
	30,000	\$451,050		
	30,000	\$642,840		
	3,334	\$36,291		
	1,771	\$53,858		
	30,000	\$382,380		
37,811	\$1,120,642			
30,000	\$557,100			
30,000	\$488,040			
C. Frank Bennett(3)	23,800	\$367,734	695	\$9,786
	4,550	\$111,566		
	6,145	\$68,461		
	1,810	\$44,417		
	3,640	\$89,398		
	30,000	\$341,553		
	10,000	\$196,400		
10,000	\$148,450			

Name	Option Awards		Stock Awards	
	Number of Shares Acquired on Exercise #(1)	Value Realized on Exercise (\$)	Number of Shares Acquired on Vesting (#)	Value Realized on Vesting (\$)
Richard S. Geary	2,042	\$19,767	776	\$10,926
	10,358	\$204,602		
	10,435	\$139,777		
	5,000	\$49,700		
	1,000	\$8,380		
	5,007	\$93,911		
	16,960	\$263,643		
	1,049	\$21,767		
	2,220	\$41,614		
	7,060	\$139,788		
	1,565	\$21,675		
	13,730	\$135,103		
	17,933	\$337,499		
	7,000	\$58,800		
	6,270	\$61,321		
	5,000	\$54,675		
	9,000	\$187,020		
10,000	\$94,100			
4,000	\$51,760			

(1) Each individual executed each option exercise and resulting sales pursuant to the individual's Rule 10b5-1 trading plan.

(2) Includes options exercised by Ms. Parshall's daughters.

(3) Dr. Bennett had 10,322 stock options expire unexercised last year due to being blocked from trading under Isis' insider trading policy.

## 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 2013, we contributed 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 2013, the maximum matching contribution was \$3,825. In 2014, we will contribute to each participant a matching contribution of 37.5% of the first 6% of the participant's compensation that has been contributed to the plan. 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. Croke 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. Croke 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, the Compensation Committee has approved that in the event of a change of control, the vesting and exercisability of Dr. Croke and Ms. Parshall's then outstanding and unvested stock options and RSUs 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.

## 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, 2013. 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, 2013. The estimates in this table are forward-looking statements. Please see the special note regarding forward-looking statements on page 77 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

For the fiscal year ending December 31, 2013, we paid a fee of \$45,000 to each of our non-employee Directors except Mr. Castleman who became a Director on June 25, 2013 and received \$22,500. Starting in 2014, we are paying our non-employee Directors a base fee of \$50,000 with additional role-based compensation as noted below:

Role	2013 Cash Compensation	2014 Cash Compensation
Board Member (Base)	\$45,000	\$50,000
Committee Chairs (Additional)		
Audit	\$0	\$24,000
Compensation	\$0	\$15,000
Nominating & Gov.	\$0	\$10,000
Agenda	\$0	\$10,000
Committee Member (Additional)		
Audit	\$0	\$10,000
Compensation	\$0	\$7,500
Nominating & Gov.	\$0	\$5,000
Agenda	\$0	\$5,000
Scientific/Medical	\$0	\$10,000

If the Board creates new committees, we anticipate that the non-employee members of such new committee will receive additional compensation for their role on those committees. We do not pay Board members additional compensation for attending Board meetings, but we do reimburse them for the expenses they incur to attend the meetings.

In 2013, each non-employee Director also received automatic stock award grants under our Directors' Plan. On July 1, 2013, under the Directors' Plan, each of our non-employee Directors serving at that time received an option to purchase 11,250 shares of our common stock, at an exercise price of \$28.47 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, and an RSU for 1,875 shares. The options and RSUs vest over a four-year period in equal annual installments.

The following table shows for the fiscal year ended December 31, 2013 certain information with respect to the compensation of all our non-employee Directors:

**Director Compensation for Fiscal 2013<sup>(1)</sup>**

<b>Name</b>	<b>Fees Earned or Paid in Cash (\$)</b>	<b>Stock Awards (\$)</b>	<b>Option Awards \$(<sup>2</sup>)</b>	<b>All Other Compensation (\$)</b>	<b>Total (\$)</b>
Spencer R. Berthelsen	\$45,000	\$53,381	\$177,179	--	\$275,560
Breaux B. Castleman <sup>(3)</sup>	\$22,500	\$153,356	\$513,207	--	\$689,063
Joseph Klein	\$45,000	\$53,381	\$177,179	--	\$275,560
Frederick T. Muto	\$45,000	\$53,381	\$177,179	--	\$275,560
Joseph H. Wender	\$45,000	\$53,381	\$177,179	--	\$275,560

- (1) Dr. Loscalzo joined our Board in 2014 and did not receive compensation from us during fiscal 2013.
- (2) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with FASB Topic ASC 718 (“ASC 718”) for stock and option awards granted to the Directors. ASC 718 expense for the option awards is based on the fair value of the awards on the date of grant using an option-pricing model. The fair value of RSUs is based on the market price of our common stock on the date of grant. For more information, please see Note 5 of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2013 regarding assumptions underlying valuation of equity awards.
- (3) Mr. Castleman became a Director on June 25, 2013. The stock awards and option awards reported above include an additional RSU for 3,750 shares and an option to purchase 22,500 shares of our common stock Mr. Castleman received when he joined our Board.

**Outstanding Equity Awards at Fiscal Year-End – Directors**

The following table shows for the fiscal year ended December 31, 2013, certain information regarding outstanding awards at fiscal year-end of all our non-employee Directors:

**Outstanding Equity Awards At December 31, 2013**

Name	Option Awards				Stock Awards	
	Number of Securities Underlying Unexercised Options (#) Exercisable <sup>(1)</sup>	Number of Securities Underlying Unexercised Options (#) Unexercisable	Option Exercise Price (\$)	Option Expiration Date	Number of Shares or Units of Stock that Have Not Vested <sup>(2)</sup> (3)	Market Value of Shares or Units of Stock that Have Not Vested <sup>(4)</sup> (\$)
Spencer R. Berthelsen	10,000	0	\$5.72	6/30/14	2,812	\$112,030
	10,000	0	\$3.95	6/30/15		
	12,500	0	\$5.93	7/2/16		
	12,500	0	\$9.77	7/1/17		
	15,000	0	\$13.88	6/30/18		
	15,000	0	\$16.32	6/30/19		
	11,250	3,750	\$9.22	6/30/20		
	7,500	7,500	\$9.30	6/30/21		
	2,813	8,437	\$12.94	7/1/22		
0	11,250	\$28.47	6/30/23			
Breaux B. Castleman	0	22,500	\$26.66	6/24/23	5,625	\$224,100
	0	11,250	\$28.47	6/30/23		
Joseph Klein	7,500	0	\$16.32	6/30/19	2,812	\$112,030
	0	3,750	\$9.22	6/30/20		
	0	7,500	\$9.30	6/30/21		
	2,813	8,437	\$12.94	7/1/22		
	0	11,250	\$28.47	6/30/23		
Frederick T. Muto	10,000	0	\$5.72	6/30/14	2,812	\$112,030
	10,000	0	\$3.95	6/30/15		
	12,500	0	\$5.93	7/2/16		
	12,500	0	\$9.77	7/1/17		
	15,000	0	\$13.88	6/30/18		
	15,000	0	\$16.32	6/30/19		
	11,250	3,750	\$9.22	6/30/20		
	7,500	7,500	\$9.30	6/30/21		
	2,813	8,437	\$12.94	7/1/22		
0	11,250	\$28.47	6/30/23			
Joseph H. Wender	10,000	0	\$5.72	6/30/14	2,812	\$112,030
	10,000	0	\$3.95	6/30/15		
	12,500	0	\$5.93	7/2/16		
	12,500	0	\$9.77	7/1/17		
	15,000	0	\$13.88	6/30/18		
	11,250	3,750	\$9.22	6/30/20		
	7,500	7,500	\$9.30	6/30/21		
	2,813	8,437	\$12.94	7/1/22		
	0	11,250	\$28.47	6/30/23		

(1) The options were granted out of our Directors' Plan and have a term of ten years and vest at the rate of 25% per year over four years.

(2) The RSUs were granted out of our Directors' Plan and vest at the rate of 25% per year over four years.

(3) All of our non-employee Directors are subject to our Stock Holding and Ownership Guidelines for RSU Shares, which requires each non-employee Director to accumulate and maintain shares of Common Stock issued pursuant to RSUs until he has accumulated shares of Common Stock equal to three times such non-employee Director's annual cash retainer, or until his termination of service.

(4) Market value of stock awards was determined by multiplying the number of unvested shares by \$39.84, which was the closing market price of our common stock on NASDAQ on December 31, 2013, the last trading day of fiscal 2013.

### Option Exercises and Stock Vested

The following table shows for the fiscal year ended December 31, 2013, certain information regarding option exercises and stock awards vested during the last fiscal year with respect to all of our non-employee Directors:

#### Option Exercises and Stock Vested in Fiscal 2013

Name	Option Awards		Stock Awards	
	Number of Shares Acquired on Exercise (#)	Value Realized on Exercise (\$)	Number of Shares Acquired on Vesting (#)	Value Realized on Vesting (\$)
Spencer R. Berthelsen <sup>(1)</sup>	10,000	\$89,600	313	\$8,911
Breaux B. Castleman	--	--	--	--
Joseph Klein, III	<sup>(2)</sup> 86,250	\$940,545	313	\$8,911
Frederick T. Muto	10,000	\$167,900	313	\$8,911
Joseph H. Wender	<sup>(3)</sup> 25,000	\$497,926	313	\$8,911

(1) Dr. Berthelsen exercised options that would have expired on June 30, 2013 and held his shares.

(2) Mr. Klein's children exercised 67,500 shares.

(3) Mr. Wender exercised options that would have expired on June 30, 2013 and held 9,822 shares.

## 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 2013, 2012, and 2011, she received the following compensation:

Name and Principal Position	Year	Salary (\$)	Bonus <sup>(1)</sup> (\$)	Stock Awards <sup>(2)(3)</sup> (\$)	Option Awards <sup>(3)(5)</sup> (\$)	All Other Compensation <sup>(4)</sup> (\$)	Total (\$)
Rosanne Crooke Vice President, Cardiovascular Diseases Drug Discovery Research	2013	\$203,685	\$89,367	\$23,457	\$48,906	\$3,777	\$369,192
	2012	\$197,369	\$59,211	\$9,622	\$36,692	\$4,517	\$307,411
	2011	\$189,778	\$80,063	--	\$75,102	\$3,710	\$348,653

- (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 2014 we paid bonuses for 2013 performance.
- (2) The Company began granting restricted stock unit awards in January of 2012.
- (3) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with FASB Topic ASC 718 ("ASC 718") for stock and option awards granted to Dr. Crooke. ASC 718 expense for the option awards is based on the fair value of the awards on the date of grant using an option-pricing model. The fair value of RSUs is based on the market price of our common stock on the date of grant. For more information, please see Note 5 of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2013 regarding assumptions underlying valuation of equity awards.
- (4) Includes AD&D, Basic Life, Medical, Dental, Vision, and 401(k) matching contributions which are available to all employees.
- (5) 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:
  - 15,000 shares at \$10.29 per share received on January 3, 2011;
  - 11,404 shares at \$7.25 per share received on January 3, 2012; and
  - 10,000 shares at \$10.82 per share received on January 2, 2013.

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 \$241,132 in fees in 2013 for legal services, which amount is substantially less than five percent of Cooley's gross revenues for its 2013 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.



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 2014 Annual Meeting of Stockholders.

*The Compensation Committee*

Spencer R. Berthelsen, *Chairman*

Joseph H. Wender

\* 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.

## 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, 2013 with management, including a discussion of the quality, not just the acceptability, of the accounting principles, the reasonableness of significant judgments, and the clarity of disclosures in the financial statements.

The Audit Committee reviewed with our independent auditors, who are responsible for expressing an opinion on the conformity of our audited financial statements with generally accepted accounting principles, their judgments as to the quality, not just the acceptability, of our accounting principles and any other matters as are required to be discussed with the Audit Committee under generally accepted auditing standards. In addition, the Audit Committee has discussed with the independent auditors, the auditors' independence from management and Isis, including the matters in the written disclosures required by the Independence Standards Board. The Audit Committee received from Ernst & Young LLP written disclosure and the letter regarding its independence as required by 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. 16.

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, 2013 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 2014.

### *The Audit Committee*

Joseph H. Wender, *Chairman*

Breaux B. Castleman

Joseph Klein, III

\* 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.

## HOUSEHOLDING OF PROXY MATERIALS

The SEC has adopted rules that permit companies and intermediaries (e.g. brokers) to satisfy the delivery requirements for Notice Regarding the Availability of Proxy Materials with respect to two or more stockholders sharing the same address by delivering a single Notice Regarding the Availability of Proxy Materials 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 Regarding the 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 been notified by 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 Regarding 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 Regarding Availability of Proxy Materials. Stockholders who currently receive multiple copies of the Proxy Statement or Notice Regarding Availability of Proxy Materials at their address and would like to request “householding” of their communications should contact their broker.

### Other Matters

The Board of Directors knows of no other matters that will be presented for consideration at the Annual Meeting. If any other issues are properly brought before the meeting, we will ask our proxy holders to vote on the matters using their best judgment.

**For further information about Isis Pharmaceuticals, Inc., please request a copy of our Annual Report. The report includes our Form 10-K for the year ended December 31, 2013 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](http://www.isispharm.com))<sup>6</sup> to view our 2013 Annual Report. The Annual Report is not incorporated into this Proxy Statement and is not considered soliciting material.**

By Order of the Board of Directors,

B. Lynne Parshall  
Secretary

April 29, 2014

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<sup>6</sup> 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.

## 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 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, 2013, and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from the Company.

In this Proxy Statement, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries.

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

**APPENDIX A**  
**CERTIFICATE OF AMENDMENT TO THE RESTATED CERTIFICATE OF INCORPORATION**

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

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

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

**THIRD:** The Board of Directors of the Corporation, acting in accordance with the provisions of Sections 141 and 242 of the General Corporation Law of the State of Delaware, adopted resolutions at a meeting held on February 11, 2014 to amend Article V of the Restated Certificate of Incorporation of the Corporation to read in its entirety as follows:

The Corporation is authorized to issue two classes of shares designated respectively "Common Stock" and "Preferred Stock." The total number of shares of all classes of stock which the Corporation has authority to issue is 315,000,000 shares, consisting of 300,000,000 shares of Common Stock, each having a par value of \$.001, and 15,000,000 shares of Preferred Stock, each having a par value of \$.001. The Preferred Stock may be issued in one or more series. The Board of Directors is authorized to fix the number of shares of any such series of Preferred Stock and to determine the designation of any such series (a "Preferred Stock Designation"), subject to (a) such stockholder approvals as may be provided for herein and (b) the number of shares of Preferred Stock authorized at that time by this Article V. Subject to such stockholder approvals as may be provided for herein, the Board of Directors is further authorized to determine or alter the rights, preferences, privileges and restrictions granted to or imposed upon any wholly unissued series of Preferred Stock, and to increase or decrease (but not below the number of shares of such series then outstanding) the number of shares of any series of Preferred Stock. In case the number of shares of any series shall be so decreased, the shares constituting such decrease shall resume the status that they had prior to the adoption of the resolution or amendment originally fixing the number of shares of such series.

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

**IN WITNESS WHEREOF**, Isis Pharmaceuticals, Inc. has caused this Certificate of Amendment to be signed by its duly authorized officers this \_\_\_\_ day of \_\_\_\_\_, 2014.

By: \_\_\_\_\_  
B. Lynne Parshall  
Chief Operating Officer

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)

AMENDED: JUNE 7, 2012 (Amendment and Restatement approved by Board on  
March 27, 2012 and by the Stockholders on June 7, 2012)

AMENDMENT SUBJECT TO STOCKHOLDER APPROVAL: Amendment and Restatement approved by Board on February 11, 2014

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 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 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:

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

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

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

(cc) **“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.

(dd) **“RSU/Option Factor”** means the ratio, represented as a fraction, of the number of RSU Awards vs. Options in a given set of Awards, as 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. The RSU/Option Factor can be as low as zero and can be as high as (but cannot exceed) one. The RSU/Option Factor as of the date the Board approved the amendment and restatement of this Plan was 1/6.

(ee) **“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.

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

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

(hh) **“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.

(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 Company's stockholders approve 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 to the nearest whole share):

- (i) An Option to purchase 32,000 shares of Common Stock; and
- (ii) An RSU Award to receive a number of shares of Common Stock equal to 32,000 multiplied by the then applicable RSU/Option Factor.

(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, 2014, 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 16,000 of Common Stock; and
- (ii) An RSU Award to receive a number of shares of Common Stock equal to 16,000 multiplied by the then applicable RSU/Option Factor.

For example, if the RSU/Option Factor is 1/6, then the Annual Grant would be an Option to purchase 16,000 shares of Common Stock, and an RSU Award to receive 2,667 shares of Common stock (i.e., 16,000 x 1/6). 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 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 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.

## **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) Prohibition on Reduction of Exercise Prices, Cancellation and Re-Grant of Stock Awards.** Neither the Board nor any Committee (or subcommittee) shall have the authority to: (i) reduce the exercise price of any outstanding Options under the Plan, or (ii) cancel any outstanding Options that have an exercise price or strike price greater than the current Fair Market Value of the Common Stock in exchange for cash or other Stock Awards under the Plan, unless the stockholders of the Company have approved such an action within 12 months prior to such an event. 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.

**ISIS PHARMACEUTICALS, INC.**  
**2855 GAZELLE COURT**  
**CARLSBAD, CA 92010**  
**ATTN: LINDA L. POWELL**

**VOTE BY INTERNET - [www.proxyvote.com](http://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 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 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:

M75287-P46451 KEEP THIS PORTION FOR YOUR RECORDS  
 DETACH AND RETURN THIS PORTION ONLY

**THIS PROXY CARD IS VALID ONLY WHEN SIGNED AND DATED.**

<b>ISIS PHARMACEUTICALS, INC.</b>			
The Board of Directors recommends you vote FOR the following nominees to be elected for a term expiring in 2017.			
1. Election of Directors Nominees:	<b>For Withhold Abstain</b>	5. Approve an amendment and restatement of the Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan.	<b>For Against Abstain</b>
01) Spencer R. Berthelsen	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	6. Approve, by non-binding vote, executive compensation.	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
02) B. Lynne Parshall	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	7. Ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for the 2014 fiscal year.	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
03) Joseph H. Wender	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<b>NOTE:</b> Such other business as may properly come before the meeting or any adjournment thereof.	
<b>The Board of Directors recommends you vote FOR Proposals 2, 3, 4, 5, 6 and 7.</b>		<b>For Against Abstain</b>	
2. Ratify, as an advisory vote, the appointment of Breau B. Castleman to fill a vacancy on our Board of Directors for a one-year term.	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
3. Ratify, as an advisory vote, the appointment of Joseph Loscalzo to fill a vacancy on our Board of Directors for a two-year term.	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
4. Approve an amendment to the Company's Restated Certificate of Incorporation to increase the authorized number of shares of Common Stock from 200,000,000 to 300,000,000.	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
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.			
<div style="border: 1px solid black; width: 100%; height: 20px; margin-bottom: 5px;"></div> Signature [PLEASE SIGN WITHIN BOX]	<div style="border: 1px solid black; width: 100%; height: 20px; margin-bottom: 5px;"></div> Date	<div style="border: 1px solid black; width: 100%; height: 20px; margin-bottom: 5px;"></div> Signature (Joint Owners)	<div style="border: 1px solid black; width: 100%; height: 20px; margin-bottom: 5px;"></div> Date

**Important Notice Regarding the Availability of Proxy Materials for the Annual Meeting:**  
The Notice and Proxy Statement and Form 10-K are available at [www.proxyvote.com](http://www.proxyvote.com).

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**ISIS PHARMACEUTICALS, INC.**  
**Annual Meeting of Stockholders on June 10, 2014 at 2:00 PM**  
**This proxy is solicited by 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 10, 2014 or any adjournment thereof with all powers which the undersigned would possess if present at the Meeting.

**This proxy, 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 will be voted for the election of the nominees under Proposal 1, FOR Proposals 2, 3, 4, 5, 6 and 7 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**

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