

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

**SCHEDULE 14A INFORMATION**

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

Filed by the Registrant  x

Filed by a Party other than the Registrant  o

Check the appropriate box:

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

Isis Pharmaceuticals, Inc.

(Name of Registrant as Specified In Its Charter)

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

Payment of Filing Fee (Check the appropriate box):

- x No fee required.
- o Fee computed on table below per Exchange Act Rules 14a-6(i)(1) and 0-11.
  - (1) Title of each class of securities to which transaction applies:  
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- o Fee paid previously with preliminary materials.
- o Check box if any part of the fee is offset as provided by Exchange Act Rule 0-11(a)(2) and identify the filing for which the offsetting fee was paid previously. Identify the previous filing by registration statement number, or the Form or Schedule and the date of its filing.
  - (1) Amount Previously Paid:  
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  - (4) Date Filed:  
\_\_\_\_\_

April 28, 2011

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

**NOTICE OF**  
**2011 ANNUAL MEETING OF STOCKHOLDERS**  
**AND PROXY STATEMENT**

Dear Stockholders,

I am pleased to invite you to Isis Pharmaceuticals' 2011 Annual Meeting of Stockholders. We will host the meeting at our offices in Carlsbad, California on Thursday, June 16, 2011 at 2:00 p.m. Pacific Time. In addition to covering the formal items on the agenda, we will review the major developments of the past year and our plans for 2011, and answer your questions.

This booklet includes the agenda for this year's Annual Meeting and the Proxy Statement. The Proxy Statement explains the matters we will discuss in the meeting and provides additional information about Isis.

Your vote is very important. Whether or not you plan to attend the meeting, please be sure to vote your shares as soon as possible to ensure your representation at the meeting. We are distributing our Notice of Annual Meeting and Proxy Materials using the Notice and Access procedures established by the United States Securities and Exchange Commission. As a result, you will receive in the mail a notice regarding the availability of proxy materials. This notice is important because it contains a control number and instructions that will allow you to access our proxy materials and vote electronically through the Internet or request printed proxy materials so you may vote by telephone or mail.

If you are a stockholder of record (that is, if your stock is registered with us in your own name), you may also vote by telephone, or electronically through the Internet, by following the instructions included with your proxy card. If your shares are registered in the name of a broker or other nominee, your nominee may be participating in a program provided through Broadridge Financial Solutions, Inc. that also allows you to vote by phone or through the Internet. If so, the voting form your nominee sends you will provide telephone and Internet instructions.

If you plan to attend the meeting and prefer to vote in person, you may still do so even if you have already returned your proxy. If you cannot attend, please note that we will make a webcast of the presentation available on the day of the meeting and for a limited time following the meeting at [www.isispharm.com](http://www.isispharm.com).(1) In this document, the words "Isis," "we," "our" and "us" refer only to Isis Pharmaceuticals, Inc. and its subsidiaries and not any other person or entity.

**PLEASE NOTE, HOWEVER, THAT IF A BROKER, BANK OR OTHER NOMINEE HOLDS YOUR SHARES OF RECORD AND YOU WISH TO VOTE AT THE MEETING, YOU MUST OBTAIN A PROXY ISSUED IN YOUR NAME FROM THE BROKER, BANK OR OTHER NOMINEE.**

We look forward to seeing you at the meeting.

Sincerely,

B. Lynne Parshall  
Secretary

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

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

**NOTICE OF 2011 ANNUAL MEETING OF STOCKHOLDERS**

Date: Thursday, June 16, 2011

Time: 2:00 p.m., Pacific Time

Place: Isis Pharmaceuticals, Inc.  
1896 Rutherford Road  
Carlsbad, CA 92008

Dear Stockholders,

At our 2011 Annual Meeting, we will ask you to:

- Proposal 1: elect Spencer R. Berthelsen, B. Lynne Parshall and Joseph H. Wender to serve as a Director for a three-year term;
- Proposal 2: approve the Isis Pharmaceuticals, Inc. 2011 Equity Incentive Plan;
- Proposal 3: make an advisory vote on executive compensation;
- Proposal 4: make an advisory vote on the frequency of future advisory votes on executive compensation;
- Proposal 5: ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2011 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 20, 2011 you may vote at the Annual Meeting.

By order of the Board of Directors,

B. Lynne Parshall

Carlsbad, California  
April 28, 2011

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

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

**PROXY STATEMENT**

**QUESTIONS AND ANSWERS ABOUT THESE PROXY MATERIALS AND VOTING**

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

Isis' Board of Directors is soliciting your proxy to vote at the 2011 Annual Meeting of Stockholders, including at any adjournments or postponements of the meeting. We are distributing our Notice of Annual Meeting and Proxy Materials (the "Notice") using the Notice and Access procedures established by the United States Securities and Exchange Commission (the "SEC"). As a result, you received in the mail the Notice regarding the availability of proxy materials. This Notice is important because it contains a control number and instructions that will allow you to access our proxy materials and vote electronically through the Internet or request printed proxy materials so you may vote by telephone or mail. Your vote is very important. Whether or not you plan to attend the meeting, please be sure to vote your shares as soon as possible to ensure your representation at the meeting.

We intend to mail the Notice on or about May 6, 2011 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 16, 2011.

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

We will hold the meeting on Thursday, June 16, 2011, at 2:00 p.m. Pacific Time at our offices located at 1896 Rutherford Road, Carlsbad, California. You may find directions to the Annual Meeting at [\(2\)](http://www.isispharm.com) We discuss below information on how to vote in person at the Annual Meeting.

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

If you plan to attend the meeting and prefer to vote in person, you may still do so even if you have already returned your proxy.

**Who can vote at the Annual Meeting?**

Only stockholders of record at the close of business on April 20, 2011 may vote at the Annual Meeting. On this record date, there were 99,594,202 shares of common stock outstanding and entitled to vote.

*Stockholder of Record: Shares Registered in Your Name*

If on April 20, 2011 your shares were registered directly in your name with our transfer agent, American Stock Transfer & Trust Company, then you are a stockholder of record. As a stockholder of record, you may vote in person at the meeting or vote by proxy. Whether or not you plan to attend the meeting, we urge you to fill out and return the proxy card or vote by proxy over the telephone or on the Internet as instructed under "How do I vote" below to ensure your vote is counted.

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

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

If on April 20, 2011 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 phone or through the Internet. If so, the voting form your nominee sends you will provide telephone and Internet instructions. You are also invited to attend the Annual Meeting.

**PLEASE NOTE, HOWEVER, THAT IF A BROKER, BANK OR OTHER NOMINEE HOLDS YOUR SHARES OF RECORD AND YOU WISH TO VOTE AT THE MEETING, YOU MUST OBTAIN A PROXY ISSUED IN YOUR NAME FROM THE BROKER, BANK OR OTHER NOMINEE.**

### **What am I voting on?**

There are five matters scheduled for a vote:

- Proposal 1: elect Spencer R. Berthelsen, B. Lynne Parshall and Joseph H. Wender to serve as a Director for a three-year term;
- Proposal 2: approve the Isis Pharmaceuticals, Inc. 2011 Equity Incentive Plan;
- Proposal 3: make an advisory vote on executive compensation;
- Proposal 4: make an advisory vote on the frequency of future advisory votes on executive compensation; and
- Proposal 5: ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2011 fiscal year.

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

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

### **How do I vote?**

You may vote in one of the following ways:

- vote through the Internet by following the instructions included with your Notice of availability of proxy materials or proxy card;
- if you have received proxy materials electronically or by mail, you may vote by phone by following the instructions included with your proxy card;
- complete, sign, date and return your proxy card in the postage paid envelope provided; or
- attend the 2011 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 generated on the computer screen and you will be prompted to submit or revise your votes as desired.

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

#### *For Shares Registered in the Name of a Broker or Bank:*

If your broker or bank holds your shares in "street name," you will need to obtain a proxy form from the institution that holds your shares and follow the instructions included on that form regarding how to instruct your broker to vote your shares. If you do not give instructions to your broker, your broker can vote your shares with respect to "discretionary" items, but not with respect to "non-discretionary" items. Discretionary items are proposals considered routine under the rules of the New York Stock Exchange on which a broker may vote shares held in street name in the absence of your voting instructions. The proposal to ratify Ernst & Young LLP as independent auditors is a discretionary item. Proposals 1-4 regarding the election of Directors, approval of our new equity incentive plan, the advisory vote regarding executive compensation and the advisory vote on the frequency of future advisory votes on 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 phone or through the Internet by having the voting form in hand and calling the number or going to the website indicated on the form and following the instructions.

### **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 all three nominees for Director named in the proxy statement;
- “For” the approval of the Isis Pharmaceuticals, Inc. 2011 Equity Incentive Plan;
- “For” the advisory approval of executive compensation;
- “For” every year as the preferred frequency of advisory votes to approve executive compensation; and
- “For” the ratification of the Audit Committee’s selection of Ernst & Young LLP as independent auditors for our 2011 fiscal year.

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

**Who is paying for this proxy solicitation?**

Our Board of Directors is soliciting your proxy to vote at the Annual Meeting. We will bear the entire cost of soliciting proxies, including preparing, assembling, making available on the Internet and printing and mailing this Proxy Statement, the proxy card and any additional information furnished to stockholders. We will furnish copies of solicitation materials to banks, brokerage houses, fiduciaries and custodians holding in their name shares of our common stock beneficially owned by others to forward to such beneficial owners. We may reimburse persons representing beneficial owners of common stock for their costs of forwarding solicitation materials to such beneficial owners. Our Directors, officers or other employees may supplement original solicitation of proxies by telephone, electronic mail or personal solicitation. We will not pay our Directors and employees any additional compensation for soliciting proxies, but we expect to pay Georgeson Stockholder Communications Inc. its customary fee, which we estimate to be about \$12,000, for rendering solicitation services. However, please be aware that you must bear any costs associated with your Internet access, such as usage charges from Internet access providers or telephone companies.

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

If you receive more than one Notice of availability of proxy materials or proxy cards, your shares are registered in more than one name or are registered in different accounts. Please complete, sign and date and return *each* separate proxy card or vote by phone 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 1896 Rutherford Road, Carlsbad, California 92008 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 2012 Annual Meeting of Stockholders, you must send the proposal to us by no later than January 7, 2012. Stockholders wishing to submit proposals or Director nominations that are not to be included in such Proxy Statement and form of proxy must do so no later than the close of business on February 17, 2012. Stockholders should also review our bylaws, which contain additional requirements with respect to advance notice of stockholder proposals and Director nominations.

**What is the quorum requirement?**

A quorum of stockholders is necessary to hold a valid meeting. A quorum will be present at the meeting if at least a majority of the outstanding shares are represented in person or by proxy. We will count your shares towards the quorum only if you submit a valid proxy vote or vote at the meeting. We will count abstentions and broker non-votes towards the quorum requirement.

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

**How are votes counted?**

Each share of our common stock that you own entitles you to one vote. Your Notice of availability of proxy materials and proxy card indicates the number of shares of our common stock that you owned at the close of business on April 20, 2011. The inspector of election will count votes for the meeting, and will separately count “For” and “Against” votes, abstentions and broker non-votes. With respect to the election of Directors, stockholders do not affirmatively vote “Against” Directors. Instead, if you do not want to elect a particular Director, you may simply withhold your “For” vote. The inspector of election will count abstentions towards the vote total for each proposal, and for Proposals 2, 3 and 5 abstentions will have the same effect as “Against” votes. With respect to Proposal 4 regarding how often you wish us to include an advisory vote on executive compensation, the inspector of election will count the number of votes regarding every year, every other year, and every third year, and abstentions will have no effect. Broker non-votes have no effect and the inspector of election will not count them towards the vote total for any proposal.

### 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 1-4 regarding the election of Directors, approval of our new equity incentive plan, the advisory vote regarding executive compensation and the advisory vote on the frequency of future advisory votes on 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. If you do not give your broker instructions for a non-discretionary item, the inspector of elections will treat your shares as broker non-votes.

### How many votes are needed to approve each proposal?

- For the election of directors, the three nominees receiving the most “For” votes from the holders of shares present in person or represented by proxy and entitled to vote on the election of directors will be elected. Only votes “For” or “Withheld” will affect the outcome;
- To be approved, Proposal 2 regarding the Isis Pharmaceuticals, Inc. 2011 Equity Incentive Plan must receive “For” votes from the holders of a majority of shares present and entitled to vote either in person or represented by proxy. If you mark your proxy to “Abstain” from voting, it will have the same effect as an “Against” vote. Broker non-votes will have no effect;
- We will consider Proposal 3 regarding advisory approval of the compensation of our executive officers, to be approved if it receives “For” votes from the holders of a majority of shares either present in person or represented by proxy and entitled to vote. If you “Abstain” from voting, it will have the same effect as an “Against” vote. Broker non-votes will have no effect;
- For Proposal 4, the advisory vote on the frequency of stockholder advisory votes on executive compensation, we will consider the frequency receiving the most “For” votes from the holders of shares present in person or represented by proxy and entitled to vote as the frequency preferred by the stockholders. Abstentions and Broker non-votes will have no effect; and
- To be approved, Proposal 5, ratification of the selection of Ernst & Young LLP as our independent auditors for our 2011 fiscal year, must receive “For” votes from the holders of a majority of shares present in person or by proxy and entitled to vote. If you “Abstain” from voting, it will have the same effect as an “Against” vote.

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

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

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

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

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

We encourage you to conserve natural resources and to reduce printing and mailing costs by signing up for electronic delivery of our stockholder communications after you place your current vote at [www.proxyvote.com](http://www.proxyvote.com).

## PROPOSAL 1

### ELECTION OF DIRECTORS

#### Information about our Board of Directors

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

In addition, the Board may elect a new Director to fill any vacant spot, including a vacancy caused by an increase in the size of the Board. However, the Board believes it is important for our stockholders to ratify any member of the Board who the Board appoints. As a result, whenever the Board appoints a new member, the Board will submit such new member's directorship for approval at the next regularly scheduled Annual Meeting of Stockholders. If the stockholders elect the Board member, he or she will serve the remaining term of the class of Directors to which he or she was elected.

The Board represents the interests of our stockholders by overseeing the Chief Executive Officer and other members of senior management in our operation. The Board's goal is to optimize long-term value by providing guidance and strategic oversight to us on our stockholders' behalf.

### **Information about the 2011 Elections**

The Board has nominated three Directors for election at the 2011 Annual Meeting. Each of the nominees currently serves as one of our Directors. Spencer R. Berthelsen, B. Lynne Parshall and Joseph H. Wender each has 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 2014 Annual Meeting or, in each case, until his or her successor is elected and has qualified, or until his or her death, resignation or removal.

Our stockholders elect Directors by a plurality of the votes of the shares represented in person or by proxy at the meeting and entitled to vote in the election of Directors. As a result, the three nominees receiving the most "For" votes (among votes properly cast in person or by proxy) will be elected. Abstentions and broker non-votes have no effect on the vote.

The Nominating, Governance and Review Committee made its report to the Board on March 23, 2011. 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 as Directors to be elected at the Annual Meeting. We provide below a short biography of each of the nominees and of each Director whose term of office will continue after the Annual Meeting. Each person nominated for election has agreed to serve if elected, and we have no reason to believe that any of the nominees cannot serve. However, if any nominee cannot serve, we may vote your proxy for another nominee proposed by the Board, or the Board may reduce the number of authorized Directors.

### **Biographies of Nominees for Election for a Three-year Term Expiring at the 2014 Annual Meeting**

**Spencer R. Berthelsen**, M.D., age 59, has served as a Director of Isis since May 2002. Since 1980, he has practiced Internal Medicine with the Kelsey Seybold Clinic, a 350 physician medical group based in the Texas Medical Center in Houston. Dr. Berthelsen has served in various senior leadership positions at Kelsey Seybold, including Chairman of the Department of Internal Medicine, Medical Director and Managing Director. He has been Chairman of their Board of Directors since October 2001. He is a Clinical Professor of Medicine at Baylor College of Medicine. Dr. Berthelsen has served on the Board of the Texas Academy of Internal Medicine in the past and the Caremark National Pharmacy and Therapeutics Committee from 1999 through 2005.

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The Board believes Dr. Berthelsen is uniquely suited to serve on the Board because of his current position managing a large multispecialty group practice and 30 years of experience as a practicing physician.

**B. Lynne Parshall**, age 56, has served as a Director of Isis since September 2000. She has been our Chief Operating Officer since December 2007 and previously served as our Executive Vice President since December 1995. She has served as our Chief Financial Officer since June 1994, and our Secretary since November 1991. From February 1993 to December 1995, she was a Senior Vice President of Isis, and from November 1991 to February 1993, she was a Vice President of Isis. Prior to joining Isis, Ms. Parshall practiced law at Cooley LLP, outside counsel to Isis, where she was a partner from 1986 to 1991. Ms. Parshall is a member of the American, California and San Diego bar associations. Within the last five years, Ms. Parshall formerly served as a Director of CardioDynamics International Corporation and Corautus Genetics Inc., both biopharmaceutical companies.

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

**Joseph H. Wender**, age 66, has served as a Director of Isis since January 1994. Mr. Wender began with Goldman, Sachs & Co. in 1971 and became a General Partner of that firm in 1982, where he headed the Financial Institutions Group for over a decade. Mr. Wender worked at GSC Group from 2005 through 2007 where he was a Senior Managing Director. 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. Within the last five years, Mr. Wender formerly served on the Board of First Coastal Bancshares, a bank holding company, and Neurome, a biopharmaceutical company.

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

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

### **Biographies of Directors Whose Terms Expire at the 2012 Annual Meeting**

**Richard D. DiMarchi**, Ph.D., age 58, has served as a Director of Isis since December 2004. Dr. DiMarchi has been a Professor and the Jack and Linda Gill Distinguished Chair in Biomolecular Science at Indiana University, Bloomington, Indiana since August 2003. He previously served as Chairman of the Chemistry Department, and is a co-founder of Marcadia Biotech and Ambrx, Inc. Ambrx is a privately held biotechnology company and Marcadia was purchased on December 30, 2010 by Roche. Prior to joining Indiana University, Dr. DiMarchi worked for 22 years at Eli Lilly and Company in several senior management positions, including Group Vice President, Biotechnology and Product Development, from 1996 to 2003, and Vice President, Endocrine Research and Clinical Investigation, from 1992 to 1996.

The Board believes Dr. DiMarchi is uniquely suited to serve on the Board primarily because with his current position as a Professor and Chair in Biomolecular Science at Indiana University, as well as his over 22 years of drug development experience at Eli Lilly and Company, he brings specialized experience, and talent to help us evaluate our drug discovery and development opportunities.

**Frederick T. Muto**, age 57, 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 a founding partner of Cooley LLP's San Diego office and serves on Cooley's management and compensation committees.

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

### **Biographies of Directors Whose Terms Expire at the 2013 Annual Meeting**

**Stanley T. Crooke**, M.D., Ph.D., age 66, 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. Within the last five years, Dr. Crooke formerly served as a Director of Antisense Therapeutics Ltd., a biopharmaceutical company.

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

**Joseph Klein, III**, age 50, 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 currently serves on the board of directors of one other publicly-traded biotechnology company, Savient Pharmaceuticals, Inc. since May 2006. Mr. Klein serves on the board of directors of The Prospector Funds, Inc., an SEC Registered Investment Company that manages two no-load mutual funds. Mr. Klein also serves on the boards of private and non-profit entities. Within the last five years, Mr. Klein formerly served on the board of directors of seven publicly held biotechnology companies: BioMarin Pharmaceutical Inc., Clinical Data, Inc., Genaisance Pharmaceuticals, Inc., Guilford Pharmaceuticals, Inc., NPS Pharmaceuticals, Inc., OSI Pharmaceuticals, Inc. and PDL BioPharma, Inc.

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

**John C. Reed**, M.D., Ph.D., age 52, has served as a Director of Isis since February 2002. Dr. Reed served as the President and Chief Executive Officer since January 2002, and in 2010 he became CEO, Professor, and Donald Bren Chief Executive Chair, of Sanford-Burnham Medical Research Institute, an independent, nonprofit, public benefit organization dedicated to biomedical research. Dr. Reed has been with Sanford-Burnham Medical Research Institute for the past nineteen years, serving as the Deputy Director of the Cancer Center beginning in 1994, as Scientific Director of the Institute beginning in 1995, and as Cancer Center Director in 2002. He also currently serves as an adjunct professor in the medical schools at University of California San Diego School of Medicine and University of Central Florida, and in the graduate Schools of Arts and Sciences at the University of Florida and San Diego State University's Biology department. Dr. Reed was recognized as the world's most highly cited scientist in the field of cell biology for the decade 1995-2005. He is the author of approximately 800 scientific and medical journal publications. Within the last five years, Dr. Reed formerly served as a director of Stratagene, Inc. and Repros Therapeutics Inc., both biopharmaceutical companies, Pharmion Corporation, a publicly-traded specialty pharmaceutical company focused on oncology, and was appointed to the Independent Citizen's Oversight Committee of the California Institute for Regenerative Medicine.

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

### **Independence of the Board of Directors**

As required under The Nasdaq Stock Market ("Nasdaq") listing standards, a majority of the members of a listed Company's Board of Directors must qualify as "independent," as affirmatively determined by the Nominating, Governance and Review Committee of the Board of Directors. The Nominating, Governance and Review Committee consults with our legal counsel to ensure that the Board's determinations are consistent with all relevant securities and other laws and regulations regarding the definition of "independent," including those set forth in the Nasdaq listing standards and applicable SEC rules and regulations, as in effect from time to time.

Consistent with these considerations, after review of all relevant transactions or relationships between each Director, or any of his or her family members, and Isis, its senior management and its independent auditors, the Board affirmatively has determined that all of our Directors are independent Directors within the meaning of the applicable Nasdaq listing standards and SEC rules and regulations, except for Dr. Crooke and Ms. Parshall, our Chief Executive Officer and Chief Operating Officer, respectively. In making this determination, the Board found that none of these Directors or nominees for Director has a material 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, of which he is not a member.

### **Information Regarding the Board of Directors and its Committees**

The Board has three committees: an Audit Committee, a Compensation Committee, and a Nominating, Governance and Review Committee. Below is a description of each committee of our Board. Each of the committees has authority to engage legal counsel or other experts or consultants as it deems appropriate to carry out its responsibilities. The Board has determined that each member of each committee:

- meets the applicable rules and regulations regarding “independence,” including, but not limited to, Rule 5605(a)(2) of the Nasdaq listing standards and applicable SEC rules and regulations;
- is not an officer or employee of Isis; and
- is free of any relationship that would interfere with his individual exercise of independent judgment with regard to Isis.

Our Chief Executive Officer is the Chairman of the Board. The Board believes that Isis’ CEO is best situated to serve as Chairman because he has served as CEO since Isis was formed over 21 years ago and he is the Director most familiar with our business and industry. Because of that experience, he is the Director most capable of effectively identifying strategic priorities and leading the discussion and execution of strategy. Independent Directors and management have different perspectives and roles in strategy development. Our independent Directors bring experience, oversight and expertise from outside the Company and industry, while the CEO brings Company-specific experience and expertise. The Board believes that the combined role of Chairman and CEO promotes strategy development and execution, and facilitates information flow between management and the Board, which are essential to effective governance.

One of the key responsibilities of the Board is to develop strategic direction and hold management accountable for executing the established strategy. As part of each Board meeting, our independent Directors meet in executive session without the presence of our employee Directors. We do not formally have a single “lead independent director.” Instead the Chairpersons of the Audit Committee, the Compensation Committee, and the Nominating, Governance and Review Committee on a rotating basis preside over the executive sessions. This rotating approach

provides added balance to the process, thereby ensuring healthy discussion since the same individual does not continuously lead each executive session. In addition, Mr. Wender (chairman of the Audit Committee), Dr. DiMarchi and Mr. Muto (both independent Board members) are part of the committee that sets the agenda for each Board meeting. The Board believes the combined role of Chairman and CEO, together with the executive sessions and agenda setting described above, is in the best interest of stockholders because it provides the appropriate balance between developing strategy and independently overseeing management.

#### *Risk Oversight*

Our Board administers its risk oversight function directly and through both its Audit Committee, and its Nominating, Governance and Review Committee. The Audit Committee oversees management of financial risks and related party transactions. The Nominating, Governance and Review Committee manages risks associated with the independence of the Board and potential conflicts of interests at the Board level, and periodically reviews our policies and procedures, and makes recommendations when appropriate. We provide a complete description of each committee and its respective roles and responsibilities on pages 11 through 15. While each committee is responsible for evaluating certain risks and overseeing the management of such risks, these committees regularly inform the entire Board of Directors about such risks through committee reports.

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

#### **Meetings and Attendance; Committee Members**

The Board met seven times in 2010, four regularly scheduled meetings and three special meetings. During 2010, all Directors attended 100% of the meetings of the Board. In addition, all Directors attended 100% of the meetings of the Board committees on which they served, except Dr. Berthelsen who attended 80% of the Audit Committee meetings. 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 2010 for each of the Board committees and identifies our current Board and Committee members.

| <b>Name</b>                               | <b>Audit</b> | <b>Compensation</b> | <b>Nominating, Governance and Review</b> | <b>Attended 2010 Annual Meeting</b> |
|---|--------------|---------------------|--|-------------------------------------|
| Dr. Spencer R. Berthelsen                 | X            | X*                  | X*                                       | X                                   |
| Dr. Stanley T. Crooke                     | —            | —                   | —  | X                                   |
| Dr. Richard D. DiMarchi                   | —            | X                   | —  | X                                   |
| Mr. Joseph Klein                          | X            | —                   | —  | X                                   |
| Mr. Frederick T. Muto(1)                  | —            | —                   | —  | X                                   |
| Ms. B. Lynne Parshall                     | —            | —                   | —  | X                                   |
| Dr. John C. Reed                          | —            | X                   | X  | X                                   |
| Mr. Joseph H. Wender                      | X*           | —                   | —  |                                     |
| <b>Total meetings in fiscal year 2010</b> | <b>5</b>     | <b>4(2)</b>         | <b>2</b>                                 |                                     |

\* Committee Chairperson

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

(2) Also acted by written consent 13 times. Our Compensation Committee acts by unanimous written consent each month to confirm stock options granted in connection with new hires and promotions.

## Audit Committee

The Audit Committee of the Board of Directors oversees our corporate accounting and financial reporting process. For this purpose, the Audit Committee performs several functions.

The Audit Committee:

- reviews the annual and quarterly financial statements and oversees the annual and quarterly financial reporting processes, including a session with the auditors where Isis' employees and management are not present;
- selects and hires our independent auditors;
- oversees the independence of our independent auditors;
- evaluates our independent auditors' performance; and
- has the authority to hire its own outside consultants and advisors if necessary.

In addition to the responsibilities listed above, the Audit Committee has the following functions:

- reviewing our annual budget with management and, if acceptable, recommending the budget to the Board for approval;
- setting and approving our investment policy;
- receiving and considering our independent auditors' comments as to internal controls, adequacy of staff and management performance and procedures in connection with internal controls;
- reviewing and, if appropriate, approving related party transactions;
- establishing and enforcing procedures for the receipt, retention and treatment of complaints regarding accounting or auditing improprieties; and
- pre-approving all audit and non-audit services provided by our independent auditors that are not prohibited by law.

Our Audit Committee charter requires that each member must be independent. We consider the members to be independent as long as they:

- do not accept any consulting, advisory or other compensatory fee from us, except in connection with their service as a Director;
- are not an affiliate of Isis or one of its subsidiaries; and
- meet all of the other Nasdaq independence requirements.

In addition, all Audit Committee members must be financially literate and at least one member must be a "financial expert," as defined by SEC regulations. Our Board has determined that the Audit Committee's financial expert is Mr. Wender based on, among other things, his over 36 years of experience as an investment banker with Goldman, Sachs & Co. We provide the Audit Committee with the funding it needs to perform its duties.

In 2010, the Audit Committee met five times and did not act by unanimous written consent. You can find our Audit Committee charter on our corporate website at [www.isispharm.com](http://www.isispharm.com).<sup>(3)</sup> Each member meets the membership criteria set forth in the Audit Committee charter and as stated above.

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

## Compensation Committee

The primary function of the Compensation Committee of the Board of Directors is to review, modify (as needed) and approve our overall compensation strategy and policies and approve the compensation and other terms of employment of our executive officers, including our Chief Executive Officer. We include a full list of the Compensation Committee's responsibilities as part of the Compensation Discussion and Analysis ("CD&A") set forth on pages 36 through 43 of this Proxy Statement. The charter of the Compensation Committee grants the Compensation Committee full access to all of our books, records, facilities and personnel, as well as authority to obtain, at our expense, advice and assistance from internal and external legal, accounting or other advisors and consultants and other external resources that the Compensation Committee considers necessary or appropriate in the performance of its duties. In particular, the Compensation Committee has the sole authority to retain independent compensation consultants to assist in its evaluation of executive and Director compensation, including the authority to approve the consultant's reasonable fees and other retention terms.

We also have a Non-Management Stock Option Committee that, as delegated by the Compensation Committee, may award stock options (and if Proposal 2 is approved, other types of equity awards) to employees who are below director level in accordance with guidelines adopted by the Compensation Committee. The Non-Management Stock Option Committee has one member, Dr. Crooke.

The Compensation Committee met four times in 2010, two regularly scheduled meetings and two special meetings and acted by unanimous written consent 13 times. You can find our Compensation Committee charter on our corporate website at [www.isispharm.com](http://www.isispharm.com).(4)

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, 2010, our Compensation Committee was composed of Drs. Berthelsen, DiMarchi and Reed. None of the members of the Compensation Committee has ever been an employee or officer of Isis. None of our executive officers serves as a member of the Board of Directors or Compensation Committee of any other entity that has one or more executive officers serving as a member of our Board of Directors or Compensation Committee.

### **Nominating, Governance and Review Committee**

#### *Role and Responsibilities*

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

- interviewing, evaluating, nominating and recommending individuals for membership on our Board of Directors. As part of this process, the Nominating, Governance and Review Committee will consider nominees recommended by our stockholders;
- on an annual basis, reviewing the performance of the Board and its committees, including evaluating the Board's ability to function as a group and the integrity, independence and competency of the individual Board members;
- periodically reviewing our policies and procedures and recommending appropriate changes, if any;
- annually reviewing and assessing the adequacy of our corporate governance guidelines and recommending any proposed changes to the Board for approval; and
- performing such other functions as may be necessary or convenient for the efficient discharge of the foregoing.

The Nominating, Governance and Review Committee met twice during 2010. You can find our Nominating, Governance and Review Committee charter on our corporate website at [www.isispharm.com](http://www.isispharm.com).(4)

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

#### *Director Nominations - Quality Standards*

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

The minimum membership requirements are as follows:

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

In addition to these minimum standards, the Nominating, Governance and Review Committee will consider such factors as:

- possessing relevant expertise to offer advice and guidance to management;
- having sufficient time to devote to Isis' affairs;
- demonstrating excellence in his or her field;
- having sound business judgment; and
- having commitment to rigorously represent the long-term interests of our stockholders.

In considering Director nominations, the Nominating Committee evaluates and considers the total mix of competencies represented on the Board as a whole, as well as the competencies each member, or nominee brings to the Board. In general, the constitution of the Board is diversified across three large categories: (1) investment banking, financial accounting and corporate governance experience; (2) medical and scientific expertise; and (3) employee vs. 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 operation, which can help the Board make important management and compensation decisions. Nonemployee directors can compare the opportunities and challenges presented to Isis against the facts and circumstances these Directors are experiencing outside Isis. As a rule, we have a significantly higher number of non-employee directors vs. employee directors. Finally, we do not discriminate against nominees on the basis of race, religion, national origin, sexual orientation, disability or any other basis prohibited by applicable law.

#### *Director Nominations - Process*

The Nominating, Governance and Review Committee will consider Director candidates our stockholders recommend. The Committee does not intend to alter the manner in which it evaluates candidates, including the minimum criteria set forth above, based on whether or not a stockholder recommended the candidate.

The Committee reviews new candidates for Director in the context of the Board's composition, our operating requirements and our stockholders' long-term interests. In conducting this assessment, the Committee considers diversity, maturity, skills, the minimum membership requirements discussed above, and such other factors as it deems appropriate given the current needs of the Board and Isis, to maintain a balance of knowledge, experience and capability. In the case of incumbent Directors whose terms of office are set to expire, the Nominating, Governance and Review Committee reviews such Directors' overall service to Isis during their term, including the number of meetings attended, level of participation, quality of performance, and any other relationships and transactions that might impair such Directors' independence. The Committee then uses its network of contacts to compile a list of potential candidates, but may also engage, if it deems appropriate, a paid professional search firm. The Committee conducts any appropriate and necessary inquiries into the backgrounds and qualifications of possible candidates after considering the function and needs of the Board.

The Committee meets to discuss and consider the candidates' qualifications and determines whether each candidate is independent, which determination is based upon applicable Nasdaq listing standards, applicable SEC rules and regulations and the advice of counsel, if necessary. Finally, the Committee then selects a nominee for recommendation to the Board by majority vote. To date, the Nominating, Governance and Review Committee has not paid a fee to any third party to assist in the process of identifying or evaluating Director candidates.

#### *Stockholder Recommendations for Directors*

Stockholders who wish to recommend individuals for consideration by the Nominating, Governance and Review Committee to become nominees for election to the Board included in our Proxy Statement may do so by delivering a written recommendation to the Secretary of Isis at the following address: 1896 Rutherford Road, Carlsbad, CA 92008, by January 7, 2012. Submissions must include:

- the name, age, business address and residence address of the nominee;
- the principal occupation or employment of the nominee;
- the stock ownership in Isis of the nominee;
- the stock ownership in Isis of the stockholder making the nomination, including any trading in derivative securities that may disguise ownership occurring within the last 12 months;
- the information relating to the nominee that is required to be disclosed in solicitations of proxies under applicable securities laws;
- the nominee's written consent to being named in the proxy statement as a nominee and to serving as a director if elected;
- other information as we may reasonably require to determine the eligibility of the proposed nominee to serve as an independent director or that could be material to a reasonable stockholder's understanding of the independence of the proposed nominee; and
- any voting commitments the nominee has to third parties.

In addition, the nominee will need to complete a written questionnaire regarding the background and qualifications of the nominee, and the background of any other person or entity on whose behalf the nomination is being made. The nominee must also agree to comply with all of our applicable publicly disclosed corporate governance, conflict of interest, confidentiality and stock ownership and trading policies and guidelines. The description of the requirements for Director nominations set forth above is qualified in its entirety by reference to the full and complete Amended and Restated Bylaws, a copy of which is available by contacting our Corporate Secretary; or as an exhibit to our Current Report on Form 8-K filed with the SEC on June 4, 2009. To date, the Board has not received or rejected a timely Director nominee for election at the upcoming meeting from a stockholder or stockholders holding more than 5% of our voting stock.

## Stockholder Communications with the Board of Directors

We make every effort to ensure that our Board or individual Directors as applicable, hear the views of stockholders, and provide appropriate responses to stockholders in a timely manner. Stockholders who wish to communicate with the Board, or individual Directors, may do so by sending written communications addressed to the Secretary of Isis at 1896 Rutherford Road, Carlsbad, CA 92008. If you wish to communicate with the independent Directors about your concerns or issues, you may address correspondence to a particular Director or to the independent Directors generally. If you do not name a particular Director, depending on the subject matter, we will forward the letter to the Chair of the Audit, Compensation, or Nominating, Governance and Review Committee. One or more of our employees designated by the Board will review these communications and will determine whether to present the materials to the Board. The purpose of this screening is to allow the Board to avoid having to consider irrelevant or inappropriate communications, such as advertisements, commercial solicitations and hostile communications. All communications directed to the Audit Committee in accordance with our Code of Ethics policy that relates to questionable accounting or auditing matters involving Isis will be promptly and directly forwarded to the Audit Committee. Other than the processes described above, our Board has not adopted a formal written process for stockholder communications with the Board. We believe our Board's responsiveness to stockholder communications has been excellent.

## Code of Ethics and Business Conduct

We have adopted a Code of Ethics that applies to all officers, Directors and employees. We have posted our Code of Ethics on our website. If we make any substantive amendments to the Code of Ethics or grant any waiver from a provision of the Code of Ethics to any executive officer or Director, we will promptly disclose the nature of the amendment or waiver on our website at [www.isispharm.com](http://www.isispharm.com).(5)

## Corporate Governance Guidelines

In 2003, the Board of Directors documented the governance practices we follow by adopting corporate governance guidelines to ensure that the Board will have the necessary authority and practices in place to review and evaluate our business operations as needed and to make decisions that are independent of our management. The guidelines are also intended to align our Directors' and management's interests with those of our stockholders. The corporate governance guidelines set forth the practices the Board intends to follow with respect to board composition and selection, board meetings and involvement of senior management, Chief Executive Officer performance evaluation and succession planning, and Board committees and compensation. The Board adopted the corporate governance guidelines to, among other things, reflect changes to the Nasdaq listing standards and SEC rules adopted to implement provisions of the Sarbanes-Oxley Act of 2002. You may view our corporate governance guidelines, as well as the charters for each committee of the Board, at [www.isispharm.com](http://www.isispharm.com).(5)

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

## PROPOSAL 2

### APPROVAL OF THE ISIS PHARMACEUTICALS, INC. 2011 EQUITY INCENTIVE PLAN

In March 2011, the Compensation Committee of the Board, and the Board, adopted the Isis Pharmaceuticals, Inc. 2011 Equity Incentive Plan (the "2011 Plan"), subject to stockholder approval.

Subject to stockholder approval of this Proposal 2, there are an aggregate of 2,000,000 shares of common stock reserved for issuance under the 2011 Plan. The main reason we adopted the 2011 Plan is so that we can begin granting a combination of stock options and restricted stock units (RSUs) as part of our overall compensation strategy. We believe providing our employees a combination of stock options and RSUs will have the following benefits:

- retain the highest quality employees while motivating all employees to achieve key drivers of stock value;
- issue fewer shares, thereby reducing dilution;
- better align employee and stockholder interests; and
- encourage long term holding by executive employees because stock settlement for RSUs does not require a same-day-sale.

If approved, the 2011 Plan will allow us to continue to grant stock options and other awards at levels determined appropriate by our Board. Our management, Board and Compensation Committee believe that stock awards are a key aspect of our ability to attract and retain qualified personnel in the face of intense competition for experienced scientists and other personnel among many pharmaceutical and health care companies. The 2011 Plan will also allow us to utilize a broad array of equity incentives and performance cash incentives to secure and retain the services of our employees, consultants and directors, and to provide long term incentives that align the interests of our employees, consultants and directors with the interests of our stockholders.

### Required Vote and Board of Directors Recommendation

Approval of Proposal 2 requires the affirmative vote of a majority of the shares present or represented by proxy and entitled to vote at the Annual Meeting. Abstentions will be counted toward the tabulation of votes cast on the proposal and will have the same effect as "Against" votes. Broker non-votes will have no effect on the outcome of the vote.

Our Board believes that approval of Proposal 2 is in our best interests, and the best interests of our stockholders for the reasons stated above.

## DESCRIPTION OF THE ISIS PHARMACEUTICALS, INC. 2011 EQUITY INCENTIVE PLAN

Below is a high-level summary of the terms of the 2011 Plan. This summary is qualified in its entirety by reference to the complete text of the 2011 Plan. We encourage our stockholders to read the actual text of the 2011 Plan in its entirety, a copy of which we filed with this Proxy Statement.

The 2011 Plan:

- is administered by our Compensation Committee, which is composed entirely of independent Directors;
- has a term ending on June 15, 2021;

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- prohibits the repricing of any option or stock appreciation rights (SARs) outstanding under the 2011 Plan, or “cashing-out” underwater awards unless approved by our stockholders;
- is limited to the granting of stock options, SARs, restricted stock awards, RSUs, performance stock awards, and performance cash awards;
- requires that each newly granted option and stock appreciation right not become fully vested until a date at least two years after the date of grant, except in the case of death, disability, retirement, and change of control;
- requires that nearly all newly granted restricted stock award and RSUs granted to employees that vest on the basis of continuous service not become fully vested until a date at least three years after the date of grant, except in the case of death, disability, retirement and change of control;
- requires that nearly all newly granted restricted stock award and RSUs granted to employees that vest on the basis of performance goals not become fully vested until a date at least one year after the date of grant, except in the case of death, disability, retirement and change of control;
- limits our ability to accelerate vesting only in case of death, disability, retirement and change of control; and
- requires all options and SARs outstanding under the 2011 Plan to have an exercise or strike price of not less than 100% of the fair market value of our common stock on the date of grant.

### **Purpose**

Our current stock option plan, the 1989 Stock Option Plan, does not allow us to grant any stock awards, other than stock options. The main purpose of adopting the 2011 Plan is to allow us to give our employees (including officers), Directors and consultants an opportunity to benefit from increases in value of our common stock through the granting of a combination of stock options and RSUs. We believe providing our employees a combination of stock options and RSUs will have the following benefits:

- retain the highest quality employees while motivating all employees to achieve key drivers of stock value;
- issue fewer shares, thereby reducing dilution;
- better align employee and stockholder interests; and
- encourage long term holding by executive employees because stock settlement for RSUs does not require a same-day-sale.

If this Proposal 2 is approved, we initially intend to grant our employees a combination of stock options and RSUs, where we will allocate 75% of the value to stock options and allocate 25% of the value to RSUs; and we will assume that each share subject to an RSU is worth three shares subject to a stock option. For example, for the 2010 merit stock option awards, the Compensation Committee of the Board set an option budget of 1.5 million shares. If this Proposal 2 is approved, under our intended structure a 1.5 million share budget would mean that we could grant options to purchase up to 1,125,000 shares (i.e. 75% of 1.5 million) and RSUs equal to 125,000 shares (i.e. 25% of 1.5 million *divided by* 3), which would result in us issuing stock awards for a total of up to 1.25 million shares. Over time we may change the overall mix of equity awards we grant to our employees, Directors and consultants.

### **Background**

The terms of the 2011 Plan provide for the grant of stock options, SARs, restricted stock awards, RSUs, performance stock awards and performance cash awards that may be settled in cash, stock, or other property.

### **Shares Available for Awards**

If this Proposal 2 is approved, there will be a total of 2,000,000 shares of our common stock reserved for issuance under the 2011 Plan. We believe the initial 2,000,000 shares will be sufficient to meet our expected requirements for RSUs for at least the next three years.

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If, under the 2011 Plan, a stock option or RSU is cancelled or terminated, then any unexercised shares subject to such cancelled or terminated stock options or unissued shares subject to such cancelled or terminated RSU will become available for issuance under the 2011 Plan. In addition, if we issue

common stock pursuant to a stock award and the common stock is later forfeited, then the forfeited shares will again become available for issuance under the 2011 Plan. Any shares we reacquire pursuant to our withholding obligations in connection with a restricted stock award, RSU, performance stock award or other stock award will again become available for issuance under the 2011 Plan. Any shares we reacquire pursuant to our withholding obligations in connection with a stock option or stock appreciation right or as consideration for the exercise of a stock option or stock appreciation right will become available for issuance under the 2011 Plan.

### **Eligibility**

All of our employees, numbering approximately 323 as of the record date, and our directors and consultants are eligible to participate in the 2011 Plan and may receive all types of awards available under the 2011 Plan.

### **Administration**

Our Board administers the 2011 Plan. The Board may delegate authority to administer the 2011 Plan to a committee, but may retain the authority to concurrently administer the 2011 Plan with the committee and may, at any time, revert in itself some or all of the powers previously delegated to the Committee. Our Board has delegated administration of the 2011 Plan to the Compensation Committee of the Board (the "Committee"). Subject to the terms of the 2011 Plan, the Committee may determine the recipients, numbers and types of stock awards to be granted, and terms and conditions of the stock awards, including the period of their exercisability and vesting. Subject to the limitations set forth below, the Committee also determines the fair market value applicable to a stock award and the exercise price of stock options and SARs granted under the 2011 Plan.

In the discretion of the Board, the Committee may consist solely of two or more "non-employee directors" within the meaning of Rule 16b-3 of the Securities Exchange Act of 1934 (the "Exchange Act") or solely of two or more "outside directors" within the meaning of Section 162(m) of the Internal Revenue Code of 1986, as amended (the "Code"). If this Proposal 2 is approved, we will also have a Non-Management Stock Award Committee that, as delegated by the Compensation Committee, may award stock awards to employees who are below director level in accordance with guidelines adopted by the Compensation Committee. The Non-Management Stock Award Committee has one member, Dr. Crooke. As used herein, except as explicitly stated otherwise, with respect to the 2011 Plan, the "Board" refers to any committee the Board appoints or, if applicable, any subcommittee, as well as to the Board itself.

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

Under the 2011 Plan, the Board cannot reprice any outstanding options or SARs by reducing the exercise price of the stock award or cancel any outstanding options or SARs 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.

### **Minimum Vesting; Restrictions on Accelerated Vesting.**

Under the 2011 Plan, no option or SAR granted to an employee or member of the Board will become 100% vested in a period of less than two years after the grant of such Option *except that* the vesting of an Option or SAR may accelerate (or may be accelerated by the Board or Committee) in the of death, disability, retirement, corporate sale or change of control.

Under the 2011 Plan, no restricted stock award or RSU award granted to an employee or discretionary restricted stock award or RSU award granted to a member of the Board will vest more rapidly than:

- ratably over a three-year period for awards that vest based on continuous service; and
- one year for awards that vest upon the achievement of performance goals;

*except that* the vesting of an Option or SAR may accelerate (or may be accelerated by the Board or Committee) in the case of death, disability, retirement, corporate sale or change of control; and Isis may grant up to 200,000 shares worth of restricted stock awards and RSUs that vest earlier than the minimum periods described above.

### **No Evergreen**

The 2011 Plan does not include any automatic share reserve increase provision (i.e., an evergreen provision).

### **Stock Options**

The Board may grant stock options under the 2011 Plan pursuant to stock option agreements. The Plan permits the grant of stock options that qualify as nonstatutory stock options, or NSOs. Individual stock option agreements may be more restrictive as to any or all of the permissible terms described in this section.

#### *Exercise Price; Payment*

The exercise price of stock options may not be less than 100% of the fair market value of the common stock subject to the stock option on the date of grant. As of April 15, 2011, the closing price of our common stock as reported on Nasdaq was \$8.86 per share.

#### *Vesting*

Stock options granted under the 2011 Plan may become exercisable in cumulative increments, or "vest," as determined by our Board at the rate specified in the stock option agreement, subject to the minimum vesting requirements described above. Shares covered by different stock options granted under the 2011 Plan may be subject to different vesting schedules as our Board may determine.

### *Term*

In general, the term of stock options granted under the 2011 Plan may not exceed ten years. Unless the terms of an optionholder's stock option agreement or other agreement with the Company provide for earlier or later termination:

- if an optionholder's service relationship with us, or any affiliate of ours, ceases due to disability, the optionholder may exercise any vested stock options for up to 12 months after the date the service relationship ends;
- if an optionholder's service relationship with us, or any affiliate of ours, ceases due to death, the optionholder, or his or her beneficiary, may exercise any vested stock options for up to 18 months after the date the service relationship ends; and
- if an optionholder's service relationship with us, or any affiliate of ours, ceases for any reason, other than as described above, the optionholder may exercise any vested stock options for up to three months after the date the service relationship ends.

Under the 2011 Plan, the stock option term may be extended in the event that exercise of the stock option following termination of service is prohibited by applicable securities laws or if the sale of stock received upon exercise of a stock option would violate the Company's insider trading policy. In no event may a stock option be exercised after its expiration date.

### *Consideration*

Our Board will determine acceptable forms of consideration for the purchase of our common stock pursuant to the exercise of a stock option under the 2011 Plan, which may include cash, check, bank draft or money order made payable to us, shares of our common stock payment pursuant to a program developed under Regulation T as promulgated by the Federal Reserve Board, or a net exercise feature.

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### *Transferability*

Generally, an optionholder may not transfer a stock option other than by will or the laws of descent and distribution or a domestic relations order. However, to the extent permitted under the terms of the applicable stock option agreement, an optionholder may designate a beneficiary who may exercise the stock option following the optionholder's death.

### ***Restricted Stock Unit Awards***

RSUs may be granted under the 2011 Plan pursuant to restricted stock unit award agreements. Payment of any purchase price may be made in any legal form acceptable to the Board. We will settle a payment due to a recipient of a restricted stock unit award by delivery of shares of our common stock, by cash, by a combination of cash and stock, or in any other form of consideration determined by our Board and set forth in the restricted stock unit award agreement. We may credit dividend equivalents in respect of shares of our common stock covered by a restricted stock unit award. RSUs may be subject to vesting in accordance with a vesting schedule to be determined by our Board, subject to the minimum vesting requirements described earlier. Except as otherwise provided in the applicable RSU award agreement, RSUs that have not vested will be forfeited upon the participant's termination of continuous service for any reason.

### ***Restricted Stock Awards***

The Board may grant restricted stock awards under the 2011 Plan pursuant to restricted stock award agreements. The Board may grant a restricted stock award in consideration for cash, check, bank draft or money order payable to us, the recipient's services performed for us or an affiliate of ours, or any other form of legal consideration acceptable to the Board. Shares of our common stock acquired under a restricted stock award may be subject to forfeiture to us in accordance with a vesting schedule to be determined by our Board. Holders of awards may only transfer their rights to acquire shares of our common stock under a restricted stock award upon such terms and conditions as are set forth in the restricted stock award agreement. Except as otherwise provided in the applicable restricted stock award agreement, restricted stock awards that have not vested will be forfeited upon the participant's termination of continuous service for any reason.

### ***Stock Appreciation Rights***

The Board may grant SARs under the 2011 Plan pursuant to SAR agreements. Each stock appreciation right is denominated in common stock share equivalents. The Board will determine the strike price of each stock appreciation right but the strike price cannot be less than 100% of the fair market value of the stock subject to the stock appreciation right at the time of grant. Our Board may also impose restrictions or conditions upon the vesting of SARs that it deems appropriate, subject to the minimum vesting requirements described earlier. We may settle SARs in our common stock, in cash, in a combination of cash and stock, or in any other form of legal consideration approved by our Board and set forth in the stock appreciation right agreement. SARs will be subject to the same conditions upon termination and restrictions on transfer as stock options under the 2011 Plan.

### ***Performance Awards***

The 2011 Plan provides for the grant of two types of performance awards: performance stock awards and performance cash awards. The Board may grant, vest or settle performance awards based upon the attainment of specified performance goals during a specified period of time. The Committee will determine the length of any performance period, the performance goals to be achieved during the performance period, and the measure of whether and to what degree such performance goals have been attained. The maximum amount covered by a performance award that may be granted to any individual in a calendar year (whether the grant, vesting or exercise is contingent upon the attainment during a performance period of the performance goals) may not exceed 750,000 shares of our common stock in the case of performance stock awards, or \$2,000,000 in the case of performance cash awards.

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In granting a performance award, the Committee will set a period of time, called a performance period over which the attainment of one or more performance goals will be measured for the purpose of determining whether the award recipient has a vested right in or to such award. Within the time period prescribed by Section 162(m) of the Code, at a time when the achievement of the performance goals remains substantially uncertain and before the earlier of the 90th day of a performance period or the date on which twenty-five percent of the performance period has elapsed, the Committee will establish the performance goals, based upon one or more criteria, called performance criteria enumerated in the 2011 Plan and described below. As soon as administratively practicable following the end of the performance period, the Committee will certify (in writing) whether the performance goals have been satisfied.

The Board will determine performance goals under the 2011 Plan, based on any one or more of the following performance criteria:

- earnings (including earnings per share and net earnings);
- earnings before interest, taxes and depreciation;
- earnings before interest, taxes, depreciation and amortization;
- total stockholder return;
- return on equity or average stockholders' equity;
- return on assets, investment, or capital employed;
- stock price;
- margin (including gross margin);
- income (before or after taxes);
- operating income;
- operating income after taxes;
- pre-tax profit;
- operating cash flow;
- sales or revenue targets;
- increases in revenue or product revenue;
- expenses and cost reduction goals;
- improvement in or attainment of working capital levels;
- economic value added (or an equivalent metric);
- market share;
- cash flow;
- cash flow per share;
- share price performance;
- debt reduction;
- implementation or completion of projects or processes (including, but not limited to, development and regulatory milestones);
- customer satisfaction;
- stockholders' equity;
- capital expenditures;
- debt levels;
- operating profit or net operating profit;
- workforce diversity;
- growth of net income or operating income; billings; and
- to the extent that an Award is not intended to comply with Section 162(m) of the Code, other measures of performance selected by the Board.

The Board is authorized to determine whether, when calculating the attainment of performance goals for a performance period, as follows:

- to exclude restructuring and/or other nonrecurring charges;
- to exclude exchange rate effects, as applicable, for non-U.S. dollar denominated Performance Goals;
- to exclude the effects of changes to generally accepted accounting principles;
- to exclude the effects of any statutory adjustments to corporate tax rates;
- to exclude the effects of any "extraordinary items" as determined under generally accepted accounting principles; and
- to exclude accounting expenses relating to share-based compensation.

Compensation attributable to performance-based awards under the 2011 Plan will qualify as performance-based compensation, provided that:

- the award is granted by a compensation committee comprised solely of "outside directors;"
- the award is granted (or exercisable) only upon the achievement of an objective performance goal established in writing by the compensation committee while the outcome is substantially uncertain and before the earlier of the 90<sup>th</sup> day of the performance period and the date on which twenty-five percent of the performance period has elapsed; and
- the compensation committee certifies in writing prior to the granting, payment or exercisability of the award that the performance goal has been satisfied.

### ***Changes to Capital Structure***

In the event of certain capitalization adjustments, the Board will appropriately adjust:

- the class(es) and maximum number of securities subject to the 2011 Plan;

- the class(es) and maximum number of securities that may be awarded to any person pursuant to Section 162(m) limits; and
- the class(es) and number of securities and price per share of stock subject to outstanding stock awards.

### ***Corporate Transactions***

In the event of certain significant corporate transactions, the Board has the discretion to take one or more of the following actions with respect to outstanding stock awards under the 2011 Plan:

- arrange for assumption, continuation, or substitution of a stock award by a surviving or acquiring entity (or its parent company);
- arrange for the assignment of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award to the surviving or acquiring corporation (or its parent company);
- accelerate the vesting and exercisability of a stock award followed by the termination of the stock award;
- arrange for the lapse of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award;
- cancel or arrange for the cancellation of a stock award, to the extent not vested or not exercised prior to the effective date of the corporate transaction, in exchange for cash consideration, if any, as the Board, in its sole discretion, may consider appropriate; and
- arrange for the surrender of a stock award in exchange for a payment equal to the excess of (a) the value of the property the holder of the stock award would have received upon the exercise of the stock award, over (b) any exercise price payable by such holder in connection with such exercise.

The Board need not take the same action for each stock award.

For purposes of the 2011 Plan, a corporate transaction will be deemed to occur in the event of the consummation of:

- a sale of all or substantially all of our consolidated assets;
- a sale of at least 90% of our outstanding securities;
- a merger or consolidation in which we are not the surviving corporation; or
- a merger or consolidation in which we are the surviving corporation but shares of our outstanding common stock are converted into other property by virtue of the transaction.

The acceleration of vesting of an award in the event of a corporate transaction under the 2011 Plan may be viewed as an anti-takeover provision, which may have the effect of discouraging a proposal to acquire or otherwise obtain control of the Company.

### ***Change in Control***

A stock award may be subject to additional acceleration of vesting and exercisability upon or after specified change in control transactions (as defined in the 2011 Plan), as provided in the stock award agreement or in any other written agreement between us or any affiliate and the participant, but in the absence of such provision, no acceleration will occur.

The acceleration of vesting of an award in the event of a change in control event under the 2011 Plan may be viewed as an anti-takeover provision, which may have the effect of discouraging a proposal to acquire or otherwise obtain control of the Company.

### ***Plan Amendments***

Our Board will have the authority to amend or terminate the 2011 Plan. However, no amendment or termination of the plan will adversely affect any rights under awards already granted to a participant unless agreed to by the affected participant. We will obtain stockholder approval of any amendment to the 2011 Plan as required by applicable law and listing requirements.

### ***Plan Termination***

Unless sooner terminated by our Board, the 2011 Plan will automatically terminate on the day before the tenth anniversary of the date the 2011 Plan is approved by our stockholders.

## **U.S. FEDERAL INCOME TAX CONSEQUENCES**

The information set forth below is a summary only and does not purport to be complete. The information is based upon current federal income tax rules and therefore is subject to change when those rules change. Because the tax consequences to any recipient may depend on his or her particular situation, each recipient should consult the recipient's tax adviser regarding the federal, state, local, and other tax consequences of the grant or exercise of an award or the disposition of stock acquired as a result of an award. The 2011 Plan is not qualified under the provisions of Section 401(a) of the Code and is not subject to any of the provisions of the Employee Retirement Income Security Act of 1974. Our ability to realize the benefit of any tax deductions described below depends on our generation of taxable income, as well as the requirement of reasonableness, the provisions of Section 162(m) of the Code and the satisfaction of our tax reporting obligations.

## ***Nonstatutory Stock Options***

Generally, there is no taxation upon the grant of an NSO if the stock option is granted with an exercise price equal to the fair market value of the underlying stock on the grant date. On exercise, an optionholder will recognize ordinary income equal to the excess, if any, of the fair market value on the date of exercise of the stock over the exercise price. If the optionholder is employed by us or one of our affiliates, that income will be subject to withholding taxes. The optionholder's tax basis in those shares will be equal to their fair market value on the date of exercise of the stock option, and the optionholder's capital gain holding period for those shares will begin on that date.

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 optionholder.

## ***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 only be delivered 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.

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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.

## ***Restricted Stock Awards***

Generally, the recipient of a restricted stock award will recognize ordinary income at the time the stock is received equal to the excess, if any, of the fair market value of the stock received over any amount paid by the recipient in exchange for the stock. If, however, the stock is not vested when it is received (for example, if the employee is required to work for a period of time in order to have the right to sell the stock), the recipient generally will not recognize income until the stock becomes vested, at which time the recipient will recognize ordinary income equal to the excess, if any, of the fair market value of the stock on the date it becomes vested over any amount paid by the recipient in exchange for the stock. A recipient may, however, file an election with the Internal Revenue Service, within 30 days following his or her receipt of the stock award, to recognize ordinary income, as of the date the recipient receives the award, equal to the excess, if any, of the fair market value of the stock on the date the award is granted over any amount paid by the recipient for the stock.

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

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.

## ***Stock Appreciation Rights***

We may grant under the 2011 Plan SARs separate from any other award or in tandem with other awards under the 2011 Plan.

Where the SARs are granted with a strike price equal to the fair market value of the underlying stock on the grant date, the recipient will recognize ordinary income equal to the fair market value of the stock or cash received upon such exercise.

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 appreciation right.

## ***Section 162 Limitations***

Compensation of persons who are "covered employees" of the Company is subject to the tax deduction limits of Section 162(m) of the Code. Awards that qualify as "performance-based compensation" are exempt from Section 162(m), thereby permitting us to claim the full federal tax deduction otherwise allowed for such compensation. The 2011 Plan is intended to enable the Committee to make awards, including cash performance awards, that will be exempt from the deduction limits of Section 162(m). Under Section 162(m), compensation attributable to stock options and SARs will qualify as performance-based compensation if (i) such awards are approved by a compensation committee composed solely of "outside directors," (ii) the plan contains a per-

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employee limitation on the number of shares for which such awards may be granted during a specified period, (iii) the per-employee limitation is approved by the stockholders, and (iv) the exercise or strike price of the award is no less than the fair market value of the stock on the date of grant. Compensation attributable to restricted stock awards, RSUs and performance awards and other stock-based awards will qualify as performance-based compensation, provided that (a) the award is approved by a compensation committee composed solely of "outside directors," (b) the award is granted, becomes vested or is settled, as applicable, only upon the achievement of an objective performance goal established in writing by the compensation committee while the outcome is substantially uncertain and before the earlier of the 90<sup>th</sup> day of the performance period and the date on which twenty-five percent of the performance period has lapsed, (c) a committee of outside directors certifies in writing prior to the granting (or vesting or settlement) of the award that the performance goal has

been satisfied, and (d) prior to the granting (or vesting or settlement) of the award, the stockholders have approved the material terms of the award (including the class of employees eligible for such award, the business criteria on which the performance goal is based, and the maximum amount, or formula used to calculate the maximum amount, payable upon attainment of the performance goal).

## EQUITY COMPENSATION PLAN INFORMATION, INCLUDING ISIS' OTHER PLANS

The 2011 Plan is in addition to the Isis Pharmaceuticals, Inc. 1989 Stock Option Plan, as amended and restated (the "89 Plan"). We also maintain our Amended and Restated 2002 Non-Employee Director Stock Option Plan (the "Director Plan") that may be used only for grants of stock options to our non-employee directors and our Amended and Restated 2000 Employee Stock Purchase Plan (the "ESPP") which permits full-time employees to purchase common stock through payroll deductions.

### Equity Compensation Plan Information

The following table sets forth information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of December 31, 2010.

| 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)     | 7,053,248  | \$ 10.59   | 5,200,855(c)   |
| Equity compensation plans not approved by stockholders(b) | 2,757,255  | \$ 13.95   | —  |
| Total   | 9,810,503  | \$ 11.54   | 5,200,855  |

(a) Consists of three Isis plans: the 89 Plan, the Director Plan and the 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, 139,306 remained available for purchase under the ESPP as of December 31, 2010. 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

The 2000 Broad-Based Equity Incentive Plan, or the 2000 Plan, expired on January 5, 2010, so we may no longer grant new options under the 2000 Plan.

We adopted the 2000 Plan to provide our employees, officers, directors and consultants an opportunity to benefit from increases in the value of our common stock through the granting of 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.

As of December 31, 2010, options to purchase an aggregate of 2,757,255 shares had been granted and were outstanding under the 2000 Plan, options to purchase an aggregate of 3,164,043 shares had been exercised under the 2000 Plan, and no shares remained available for grant thereunder.

Options outstanding 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 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.

### New Plan Benefits

The following table presents a hypothetical example of potential RSUs we may grant under the 2011 Plan to (i) each executive officer named in the Summary Compensation Table under “Executive Compensation—Compensation of Executive Officers”, (ii) all executive officers as a group, (iii) all non-employee Directors as a group, and (iv) all non-executive officer employees as a group; based upon the merit based options these individuals received during the fiscal year ended December 31, 2010. This information is for illustration only and may not be indicative of grants we may make in the future under the 2011 Plan. Please see the special note regarding forward-looking statements on page 54 of this Proxy Statement.

#### NEW PLAN BENEFITS

##### 2011 EQUITY INCENTIVE PLAN\*

| Name and Position   | Number of Shares Underlying RSUs |
|---|----------------------------------|
| Stanley T. Crooke Chairman, Chief Executive Officer and President             | 29,790                           |
| B. Lynne Parshall Director, Chief Operating Officer & Chief Financial Officer | 15,888                           |
| C. Frank Bennett Senior Vice President, Antisense Research                    | 6,951                            |
| Richard S. Geary Senior Vice President, Development                           | 8,160                            |
| All Executive Officers as a Group   | 60,790                           |
| All Non-Employee Directors as a Group   | 0                                |
| All Non-Executive Officer Employees as a Group                                | 279,732                          |

\* Under this hypothetical example, in addition to the RSUs described above, each executive officer would likely receive a stock option under the 89 Plan to purchase shares of our common stock equal to 75% of the options the officer received during the fiscal year ended December 31, 2010.

### PROPOSAL 3

#### ADVISORY VOTE ON EXECUTIVE COMPENSATION

The recently enacted Dodd-Frank Wall Street Reform and Consumer Protection Act of 2010, called the “Dodd-Frank Act”, enables the Company’s stockholders to vote to approve, on an advisory (nonbinding) basis, the compensation of our Chief Executive Officer, Chief Financial Officer and our two other executive officers at December 31, 2010, called our “named executive officers” as disclosed in this Proxy Statement in accordance with the SEC’s rules.

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

**“RESOLVED, that Isis’ stockholders approve, on an advisory basis, the compensation of the named executive officers, as disclosed in this Proxy Statement for the 2011 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 page 36 through 43. Below is a high-level summary of some of our compensation practices. This summary is qualified by the detailed disclosure contained in the EXECUTIVE COMPENSATION section of this Proxy Statement.

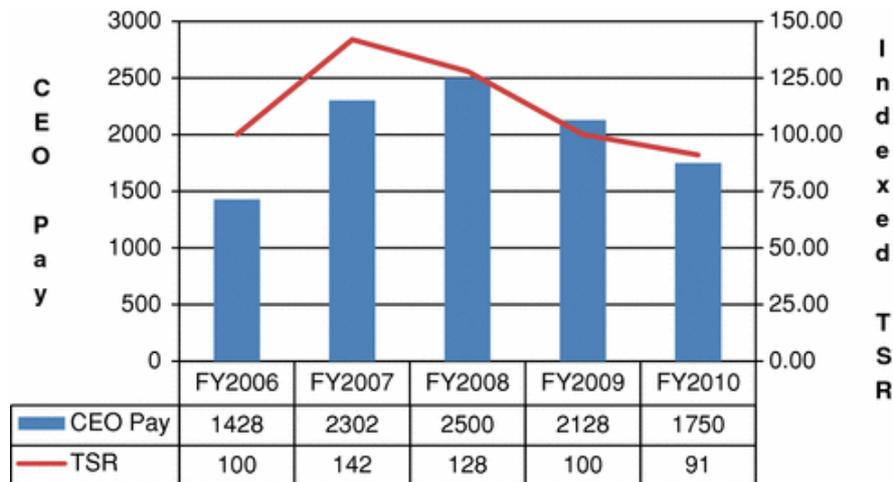
- we use a combination of compensation vehicles that provide a balanced mix of fixed and variable cash incentives, and long-term equity incentives;
- our cash bonuses are not guaranteed (i.e. are 100% at risk) and include a multiplier based on Isis’ performance;
- our Compensation Committee sets a strict budget for equity awards and salary increases given to all employees under the annual merit review;
- our change of control agreements require a “double trigger” before we make a cash payment to an eligible executive officer;
- our policies do not provide for “gross-up” payments;
- our policies do not provide for perquisites for any employees, including our executive officers;
- we incorporate a number of features into our compensation philosophy and objectives to mitigate the risk that our compensation policies and practices could encourage unnecessary or imprudent business risk taking;
- the 89 Plan and the proposed 2011 Plan prohibit the repricing of any options outstanding under such plans, unless approved by our

stockholders;

- the 89 Plan and the proposed 2011 Plan require minimum vesting periods, except in the case of death, disability, or retirement, or a change of control; and
- our ESPP Plan requires employees to hold shares they purchase under the ESPP for a minimum of six months.

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The following graphs show the relationship of our Chief Executive Officer's compensation (in thousands) compared to the total return (TSR) on \$100 invested on December 31, 2006 in our common stock through December 31, 2010. Although we do not use our stock price as the sole measure of the Company's performance, as illustrated our CEO's compensation is in alignment with our stock performance over the period shown, where Dr. Crooke's compensation generally increased when performance was strong, and decreased when performance declined.(6)



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. Abstentions will have the same effect as votes "Against" this Proposal 3. Brokers do not have discretion to vote uninstructed shares with respect to this Proposal 3. 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 3.

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

#### **THE BOARD OF DIRECTORS RECOMMENDS THAT STOCKHOLDERS VOTE "FOR" PROPOSAL 3**

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

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#### **PROPOSAL 4**

##### **ADVISORY VOTE ON THE FREQUENCY OF THE VOTE ON EXECUTIVE COMPENSATION**

Isis is presenting this proposal, commonly known as a "say-on-frequency vote," which gives you as a stockholder the opportunity to inform us regarding how often you wish us to include a "say-on-pay" proposal, similar to Proposal 3, in our Proxy Statement. Please note that as a stockholder you have the choice to vote for one of the following choices, as indicated on the proxy card: to hold the advisory vote on executive compensation every year, every other year, every third year, or to abstain from voting.

##### **Board Recommendation**

The Board of Directors values constructive dialogue on executive compensation and other important governance topics with our stockholders. The Board believes an advisory vote every year will provide an effective way to obtain information on stockholder sentiment about our executive compensation program.

##### **Required Vote of Stockholders**

We will consider the frequency with the highest number of votes from the holders of shares present in person or represented by proxy and entitled to vote at the Annual Meeting as the frequency preferred by the stockholders. While this say on frequency vote is advisory in nature and therefore will not bind us to

adopt any particular frequency, our Board of Directors intends to carefully consider the stockholder vote resulting from the proposal in determining how frequently we will hold “say-on-pay” votes.

**THE BOARD OF DIRECTORS RECOMMENDS THAT STOCKHOLDERS VOTE FOR “EVERY YEAR”**

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**PROPOSAL 5**

**RATIFICATION OF SELECTION OF INDEPENDENT AUDITORS**

The Audit Committee of the Board of Directors has selected Ernst & Young LLP as our independent registered public accounting firm for our 2011 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 2011 Annual Meeting to answer any questions and make a statement should they desire to do so.

Although our bylaws do not require stockholders to approve our independent registered public accounting firm, the Audit Committee of the Board would like our stockholders’ opinion as a matter of good corporate practice. If the stockholders vote against Ernst & Young LLP, the Audit Committee of the Board will reconsider whether to keep the firm. However, even if the stockholders ratify the selection, the Audit Committee of the Board may choose to appoint a different independent accounting firm at any time during the year if it believes that a change would be in the best interests of our stockholders and Isis.

The affirmative vote of the holders of a majority of the shares present in person or represented by proxy and entitled to vote at the 2011 Annual Meeting will be required to ratify the selection of Ernst & Young LLP.

As of December 31, 2010, none of our finance or accounting employees had been employed by Ernst & Young LLP during the past six years.

**Independent Auditors’ Fees**

The Audit Committee has adopted a policy and procedures for the pre-approval of audit and permissible non-audit services rendered by our independent registered public accounting firm, Ernst & Young LLP. The policy generally pre-approves specific services in the defined categories of audit services, audit-related services, and tax services up to pre-determined amounts. The Audit Committee may pre-approve services as part of its approval of the scope of the engagement of the independent auditor or on an individual explicit case-by-case basis before the Audit Committee engages the independent registered public accounting firm to provide each service. As an additional measure to ensure auditor independence, beginning in 2004, the Audit Committee engaged Deloitte Tax LLP as our primary tax advisor. The Audit Committee pre-approved the fees described below.

**Audit Fees**

For the fiscal years ended December 31, 2010 and 2009, 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 \$491,000 and \$513,000, respectively. In addition, Ernst & Young LLP billed us \$66,000 and \$28,000 in 2010 and 2009, respectively. The additional fees in 2010 were primarily consultations related to the accounting for the lease agreement associated with the construction of our new 176,000 square foot research facility compared to the additional fees in 2009 which were primarily related to consultations for implementing new accounting standards. Furthermore, Ernst & Young LLP audited the financial statements of our jointly owned subsidiary Regulus Therapeutics, Inc. (“Regulus”) and billed Regulus \$80,000 and \$86,000 for the 2010 and 2009 audit, respectively.

**Audit Related Fees**

For the years ended December 31, 2010 and 2009, there were no audit related fees billed by Ernst & Young LLP that were reasonably related to the performance of the audit or review of our financial statements that are not included under “Audit Fees” above.

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**Tax Fees**

For the years ended December 31, 2010 and 2009, there were no tax fees billed by Ernst & Young LLP for tax related matters that were not part of the integrated audit fees. In 2010 and 2009, we utilized Deloitte Tax LLP for the majority of our tax services.

**Financial Information Systems Design and Implementation Fees**

During the fiscal years ended December 31, 2010 and 2009, there were no fees billed by Ernst & Young LLP for information technology consulting.

**All Other Fees**

During the fiscal years ended December 31, 2010 and 2009, 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, 2010, none of the total hours expended on our financial audit by Ernst & Young LLP were provided by persons other than Ernst & Young LLP’s employees.

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

## SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

This table outlines the ownership of our common stock as of April 15, 2011 by:

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

| Beneficial Owner   | Beneficial Ownership (1) |                      |
|--|--------------------------|----------------------|
|  | Number of Shares         | Percent of Total (2) |
| FMR LLC (3)<br>82 Devonshire Street<br>Boston, MA 02109  | 13,362,240               | 13.4                 |
| Columbia Wanger Asset Management, LLC (4)<br>227 West Monroe Street, Suite 3000<br>Chicago, IL 60606 | 6,166,000                | 6.2                  |
| BlackRock, Inc. (5)<br>40 East 52 <sup>nd</sup> Street<br>New York, NY 10022                         | 5,649,805                | 5.7                  |
| Genzyme Corporation (6)<br>500 Kendall Street<br>Cambridge, MA 02142                                 | 5,000,000                | 5.0                  |
| Spencer R. Berthelsen (7)  | 122,495                  | *                    |
| Stanley T. Crooke (8)  | 1,781,647                | 1.8                  |
| Richard D. DiMarchi (9)  | 63,125                   | *                    |
| Joseph Klein, III (10)   | 61,225                   | *                    |
| Frederick T. Muto (11)   | 78,625                   | *                    |
| B. Lynne Parshall (12)   | 420,553                  | *                    |
| John C. Reed (13)  | 93,125                   | *                    |
| Joseph H. Wender (14)  | 118,125                  | *                    |
| C. Frank Bennett (15)  | 193,068                  | *                    |
| Richard S. Geary (16)  | 113,806                  | *                    |
| All Directors and executive officers as a group (ten persons) (17)                                   | 3,045,794                | 3.0                  |

\*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 99,594,202 shares of common stock outstanding on April 15, 2011, 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 13,362,240 shares as a result of acting as investment adviser to various investment companies. The ownership of one investment company, Fidelity Growth Company Fund, amounted to 9,917,681 shares. Edward C. Johnson 3d and FMR LLC, through its control of Fidelity, and the funds each has sole power to dispose of the 13,362,240 shares owned by the Funds.

Neither FMR LLC nor Edward C. Johnson 3d, Chairman of FMR LLC, has the sole power to vote or direct the voting of the shares owned directly by the Fidelity funds, which power resides with the funds' Boards of Trustees. Fidelity carries out the voting of the shares under written guidelines established by the funds' Boards of Trustees.

- (4) The shares reported herein include shares held by Columbia Acorn Trust (CAT), a Massachusetts business trust that is advised by Columbia Wanger Asset Management, LLC. CAT held 5.1% of the shares of our common stock on December 31, 2010.
- (5) Various persons at BlackRock, Inc. have the right to receive or the power to direct the receipt of dividends from, or the proceeds from the sale of shares of our common stock. No one person's interest in the shares of our common stock was more than five percent of the total outstanding common shares on December 31, 2010.
- (6) On January 7, 2008 we entered into a Stock Purchase Agreement with Genzyme Corporation pursuant to which we issued and sold to Genzyme 5,000,000 shares of common stock for an aggregate purchase price of \$150,000,000, representing a per share purchase price of \$30.
- (7) Includes 70 shares owned by Dr. Berthelsen's daughter for which he disclaims beneficial ownership. Includes 93,125 shares of common stock issuable upon exercise of options held by Dr. Berthelsen that are exercisable on or before June 14, 2011.
- (8) Includes 858,926 shares of common stock issuable upon exercise of options held by Dr. Crooke that are exercisable on or before June 14, 2011. Also includes 47,330 shares of common stock issuable upon exercise of options held by Rosanne Crooke, Dr. Crooke's wife, that are exercisable on or before June 14, 2011. Dr. Crooke disclaims beneficial ownership of the shares of common stock owned and issuable upon exercise of options held by his wife.
- (9) Includes 63,125 shares of common stock issuable upon exercise of options held by Dr. DiMarchi that are exercisable on or before June 14, 2011.
- (10) Includes 53,125 shares of common stock issuable upon exercise of options held by Mr. Klein that are exercisable on or before June 14, 2011 and 100 shares of common stock indirectly beneficially owned by Mr. Klein's son.
- (11) Includes 1,500 shares of common stock indirectly beneficially owned through the Cooley LLP Salary Deferral and Profit Sharing Plan and 77,125 shares of common stock issuable upon exercise of options held by Mr. Muto that are exercisable on or before June 14, 2011.
- (12) Includes 388,568 shares of common stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before June 14, 2011, and an aggregate of 30,000 shares of common stock issuable upon exercise of options which Ms. Parshall transferred to her two daughters that are exercisable on or before June 14, 2011.

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- (13) Includes 93,125 shares of common stock issuable upon exercise of options held by Dr. Reed that are exercisable on or before June 14, 2011.
- (14) Includes 77,125 shares of common stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before June 14, 2011.
- (15) Includes 192,014 shares of common stock issuable upon exercise of options held by Dr. Bennett that are exercisable on or before June 14, 2011.
- (16) Includes 109,793 shares of common stock issuable upon exercise of options held by Dr. Geary that are exercisable on or before June 14, 2011.
- (17) Includes an aggregate of 2,083,381 shares issuable upon exercise of options held by all current Directors and executive officers as a group that are exercisable on or before June 14, 2011.

#### **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, 2010, all Section 16(a) filing requirements applicable to our officers, Directors and greater than ten percent beneficial owners were complied with.

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## **EXECUTIVE COMPENSATION**

### **Compensation Discussion and Analysis**

#### *Compensation Overview and the Role of the Compensation Committee*

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

The Compensation Committee's responsibilities include:

- overall compensation strategy;
- reviewing and approving corporate performance goals and objectives relevant to the compensation of our executive officers;
- evaluating and recommending to the Board the compensation plans and programs advisable for Isis, as well as modifying or terminating existing plans and programs;
- establishing policies with respect to equity compensation arrangements;
- reviewing and approving compensation arrangements for our executive officers, including our Chief Executive Officer;
- reviewing and approving compensation arrangements for our Directors;
- administering our benefit plans, including stock based awards and employee stock purchase plans;
- evaluating risks associated with the compensation policies and assessing whether risks arising from our compensation policies and practices are reasonably likely to have a material adverse effect on us;
- performing other functions as may be necessary or convenient in the efficient discharge of the foregoing; and
- reporting to the Board of Directors from time to time, or whenever it shall be called upon to do so.

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

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

#### *Compensation Philosophy & Objectives*

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

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

We incorporate a number of features into our compensation philosophy and objectives to mitigate the risk that our compensation policies and practices could encourage unnecessary or imprudent business risk taking. We use a combination of compensation vehicles that provide a balanced mix of fixed and variable cash incentives, and long-term equity incentives. Our cash bonuses are not guaranteed (i.e. are 100% at risk) and include a multiplier based on Isis' performance. Therefore, if Isis does not perform well, the cash bonus can be, and has been, zero. When setting our Company objectives, which then become our CEO's individual objectives, we structure the objectives so that they are results driven rather than task driven. For example, we typically include a number of objectives based on positive clinical trial data, such as in 2010 we had a Company objective of achieving positive Phase 3 studies for mipomersen to support the initial regulatory filings for marketing approval in the United States, Europe and other jurisdictions. This type of objective only rewards our executives if the data are positive, because we must encourage the prudent spending of stockholder money on development decisions. In other words, we do not want to structure our objectives to reward "bad bets." We also align our Company objectives and individual objectives with the long term strategy of Isis, and use little or no metric-based objectives such as earnings per share. This way, we avoid the temptation to deviate from Isis' long-term strategy just to meet a short-term metric. In addition, all of our stock options vest over a period of four years, with no vesting during the first year, and we set the option exercise price at the fair market value of our stock on the date of grant. This practice ensures that our equity compensation does not reward short term imprudent risk taking at the expense of long term stockholder value, because if stockholder value declines over time, so too will the value of the equity compensation. We cover the specific elements of our compensation policy and practices in more detail below.

#### *Elements of Executive Compensation*

Employees in our organization do not share either accountability or responsibility equally for strategic and/or tactical decisions. It is well ingrained in our culture that not everyone should share the same level of risk/reward for the consequences of these decisions. As a result, we have structured the various components of our compensation systems to reflect accountability both for the successes or failures (both long-term and short-term) of Isis and of individuals. Our senior management team is paid for results and their use of judgment in executing the strategies they have established; therefore, the more senior the person, the greater percentage of "at risk" cash compensation. The more junior employees are compensated for accomplishing their work well and therefore have a lower "at risk" portion to their cash compensation.

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

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

- the Compensation Committee's performance assessment of the CEO and executive officers;
- competitive compensation practices;
- individual performance and contributions to Isis' objectives;
- increased efficiencies and process improvements;
- effective collaboration and teamwork;
- individual expertise, skills and knowledge;
- the need to retain and motivate; and
- the magnitude of the impact a judgment by the individual can have on Isis' success or failure.

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

*Base Salary*

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

We determine base compensation levels throughout Isis primarily by market forces. First, we look externally at what comparable companies in the geographical or recruiting area are paying for comparable jobs. We use AON's Radford Global Life Sciences Survey to obtain this information targeting the 50<sup>th</sup> - 75<sup>th</sup> percentile. Examples of other participating public companies in the San Diego area are: Arena Pharmaceuticals, Ligand Pharmaceuticals, and Neurocrine Biosciences. We then look at the salary required to attract a particular candidate. The third step is to determine whether the scope of job responsibilities and internal equity warrant a given base salary.

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

Each year our employees are eligible to receive an appropriate merit salary increase. The Compensation Committee sets a Company-wide merit increase budget percentage based on external factors such as the average merit increase being used by comparable companies, as well as Isis' performance. The Company-wide merit increase budget percentage serves as the basis for each individual salary increase. The actual merit increase award for each employee, including our executive officers, will vary, higher or lower, from the Company-wide budget percentage depending upon the respective individual's contributions to Isis. Regardless of individual employee variances the Company-wide approved merit budget is not exceeded.

The Compensation Committee evaluates each executive officer's performance to set their annual merit increase. As part of this process, the Compensation Committee reviews the written reports prepared by the CEO evaluating the performance of each individual executive officer. The Compensation Committee carefully considers these reports since our CEO is in the best position to evaluate our executive officers' day-to-day and overall performance. The Compensation Committee then meets in executive session and evaluates the CEO's performance, primarily based upon the CEO's achievement of set objectives for the year. At the end of this process, the Compensation Committee determines the CEO's merit increase and approves or recommends changes to the merit increases for the remaining executive officers. The CEO has no role in determining his own compensation.

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

$$\text{Current Base Salary (x) Merit Increase} = \text{Increase to Base Salary}$$

For example, Dr. Crooke's 2011 salary of \$735,169 was calculated as follows:

|                         |     |                       |   |                                |
|-------------------------|-----|-----------------------|---|--------------------------------|
| <u>2010 Base Salary</u> | (x) | <u>Merit Increase</u> | = | <u>Increase to Base Salary</u> |
| \$710,995               | (x) | 3.4%                  | = | \$24,174                       |

The 2010 merit budget approved by the Compensation Committee for the entire Company was 3.5% of salaries. Actual merit increases ranged from 0% — 5.5% with a weighted average of 3.5%. The weighted average merit increase for all of our other executive officers for 2011 salaries was 3.84% with a range of 3.4% — 5.0%. The 2010 merit budget was a 0.5% decrease from the 2009 merit budget of 4.0%. This decrease was driven by the general decrease we observed in the market balanced against Isis' strong performance in 2010. The Compensation Committee believes the level of increase is in line with comparable companies and was deserved based on

performance. The Compensation Committee approved this budget based on Isis' accomplishments in 2010, as noted in the section entitled "Evaluation of 2010; Business Highlights" below, and competitive information on the planned merit increases provided by other local biotech companies. Our Executive Director of Human Resources obtained planned merit increases by surveying local companies through the Biotech Employee Development Coalition and by reviewing data provided by AON's Radford Global Life Sciences.

As part of the approval process, to ensure that the proposed merit increases are reasonable, the Compensation Committee analyzes the impact of the proposed merit increase on the CEO's salary. In 2011, Dr. Crooke's proposed new base salary of \$735,169 placed him above the 75<sup>th</sup> percentile of Radford (\$600,000) and below the 90<sup>th</sup> percentile of Radford (\$828,500); based on this information further analysis was performed. The Compensation Committee reviewed a report of peer group companies obtained by utilizing the most recent data available from Equilar's Executive Insight research database, a resource for benchmarking executive compensation and analyzing CEO and executive pay trends. Using the search criteria of: 1) CEO tenure of 14+ years 2) Biotech/Biopharmaceuticals industry; and 3) market capitalization between \$1 billion and \$3 billion, we identified eight peer group CEOs.(7) This information illustrated that Dr. Crooke's base pay was below the CEO average base salary of \$740,184 for these eight companies and, as such, the Compensation Committee believed Dr. Crooke's 3.4% increase was appropriate based on his accomplishments for the year as well as the market data. The merit increases for all other executives, and their impact, were compared to Radford data only. The results as a whole showed that we pay our executives, on average, above the 75<sup>th</sup> percentile. The Compensation Committee determined that this was reasonable based on the longevity of many of our executive officers, as well as their performance in 2010. The average tenure of our executive officers, excluding our CEO, is 18.7 years. The average tenure of our executive officers, including our CEO, is 19.5 years. Dr. Crooke has been the CEO for 21 years.

#### Cash Bonus — At Risk

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

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

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

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

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

The Compensation Committee sets the Company Success Factor based on Isis' achievement of set objectives for the year. At the end of each year, the Compensation Committee meets to evaluate Isis' overall performance. The Committee measures Isis' performance based upon the achievement of goals that were set at the beginning of the year and agreed upon by our Board and upper management. The Compensation Committee may also consider unexpected accomplishments, as well as failures, that occurred through the year. The committee then reviews the MBO Company Success Factor history/events from the prior 15 years to form a comparison for our current year's successes and/or failures.

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

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

Once the Compensation Committee has determined the elements of the formula above, the formula is applied to each executive officer. For example, Dr. Crooke's cash bonus based on his, as well as Isis' performance in 2010, was calculated as follows and equaled \$343,411:

|                    |     |                     |     |                               |     |                                  |
|--------------------|-----|---------------------|-----|-------------------------------|-----|----------------------------------|
| <u>Base Salary</u> | (x) | <u>Target MBO %</u> | (x) | <u>Company Success Factor</u> | (x) | <u>Individual Success Factor</u> |
| \$710,995          | (x) | 40%                 | (x) | 105%                          | (x) | 115%                             |

The average Individual Success Factor for our other executive officers was 120%.

The Compensation Committee set the Company Success Factor for the 2010 MBO at 105% due to our strong achievements for the year, including successfully completing three Phase 3 studies of mipomersen where each study met all primary, secondary and tertiary endpoints. The section entitled "Evaluation of 2010; Business Highlights" below provides a full review of our accomplishments. This MBO target reflects a decrease of 10 percentage points from the 2009 Company Success Factor of 115%. Although Isis had a very successful year, including accomplishing most of the corporate objectives, the Compensation Committee noted that Isis' stock price did not perform well, representing a disconnect between Isis' stock price and Isis' accomplishments for the year. The Committee discussed this disconnect at length and affirmed the desire to see our stock price align with our progress for the sake of our shareholders. However, given this disconnect, the Committee felt it was appropriate to set the Company Success Factor at an amount below the factor the Committee would have otherwise set based on the accomplishments for the year.

An executive officer's salary plus bonus represents the officer's total cash compensation. Our philosophy has been to have the CEO's total cash compensation be between 20-30 times the lowest level compensation. Dr. Crooke's total cash compensation is an average of 20.05 times that of the average cash compensation for our lowest level employees and 1.63 times greater than the average of our other executive officers. Shareholder advocates organizations, such as ISS, consider up to 3:1 an appropriate ratio when measuring CEO compensation against all Executive Officers and Vice Presidents.

### *Stock Options*

We use our stock option program to give all employees, including Isis' executive officers, an economic interest in the long-term appreciation of our common stock. We grant existing employees new options on an annual basis to provide a continuing financial incentive and equity in Isis' growth.

Each year the Compensation Committee approves a budget that sets the number of stock options we can grant our employees for annual merit awards. We do not grant options that exceed this budget without the Compensation Committee's approval. Over the past five years, the average option budget set by the Compensation Committee has been approximately 1.7% of our outstanding common stock on an issued and outstanding basis. We believe the merit option budget is an important tool to balance our equity compensation objectives with stockholder interests. For 2010, the Compensation Committee set the option budget at 1.5 million shares, which represented 1.5% of our outstanding common stock on an issued and outstanding basis for that year. This overall maximum, plus each employee's position and performance in the previous year, ultimately determines the size of the individual annual option grant.

Starting in 2012 we plan to award stock based compensation through a combination of stock options and RSUs if our stockholders approve the 2011 Equity Incentive Plan proposed under Proposal 2. We believe awarding a combination of stock options and RSUs will provide a number of benefits as RSUs are a strong retention vehicle for employees as they do not go "underwater" but at the same time require fewer shares than option awards to deliver competitive value.

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For each stock option, the Compensation Committee sets a vesting schedule that is typically over a 4-year period at the rate of 25% at the end of the first year and then at the rate of 2.08% per month for 36 months thereafter during the optionee's employment or services as a consultant or director. We have historically had low employee turnover, particularly in our management team and the members of our management have historically held their options for a long period of time before exercise. For example, our executive officers received merit stock options in January of 2001, but each officer held these options until at least the last 15 days of the 10-year term of such options, even though our stock price had traded significantly higher earlier in the life of these options. The low turnover is indicative of our employees' commitment to Isis and its technology. As such, we believe our officers see the long term value of our stock and therefore we do not require our employees to own a minimum number of shares of our stock, or hold shares of our stock they acquire for minimum periods of time with the exception of our ESPP which has a six month minimum hold period for shares purchased under the ESPP.

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

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

### *Perquisites*

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

### *Retirement & Other Benefits*

Isis maintains a highly competitive position with regard to the benefits offered to all regular employees, including our executive officers. These benefits include medical, dental and vision insurance, 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; the more money an Isis employee makes, the more he or she contributes to the costs of his/her family's health care.

### *Retention and Change of Control Agreements*

Isis' retention agreements for our Chief Executive Officer and Chief Operating Officer and the related severance compensation provisions are designed 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 48-49 of this Proxy Statement, we provide a component of severance compensation for our Chief Executive Officer and Chief Operating Officer 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.

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

*Evaluation of 2010; Business Highlights*

2010 was a good year for Isis. Isis successfully met its objective for mipomersen, most notably successfully completing three Phase 3 studies where each study met all primary, secondary and tertiary endpoints. In addition, we exceeded our financial guidance, and ended 2010 with \$472.4 million of cash, cash equivalents and short-term investments significantly in excess of the \$450 million projected. However, as noted above, the Compensation Committee considered that Isis’ stock price did not perform well, resulting in a lower Company Success Factor for the MBO.

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

**2010 Business Highlights**

**Drug Development Highlights**

- Mipomersen continued to advance in clinical development and move closer to the market for patients with very high cholesterol, at high cardiovascular risk and who cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies. Isis and Genzyme successfully completed four Phase 3 studies that the companies plan to include in the initial United States and European filings for marketing approval for mipomersen. These filings will seek approval for the treatment of patients with homozygous familial hypercholesterolemia in the United States and Europe. The European filing may also include patients with severe heterozygous familial hypercholesterolemia. Genzyme is also preparing for filings in markets beyond the United States and Europe. In all four studies, all primary, secondary and tertiary endpoints were met.
- Isis and its partners continued to advance the drugs in Isis’ pipeline and reported clinical results in a broad range of diseases, including positive clinical Phase 1 data on five drugs. Isis added three new drugs to its pipeline.
- Isis and its partners initiated Phase 1 clinical studies on three drugs, initiated seven Phase 2 studies on four drugs, and initiated two Phase 3 studies on OGX-011.

**Corporate Highlights**

- Isis formed a new strategic alliance worth up to nearly \$1.5 billion with GSK to develop antisense drugs to treat rare and infectious diseases. Isis received a \$35 million upfront payment and a \$5 million milestone payment related to the identification of ISIS-GSK1Rx, the first drug selected as part of our collaboration with GSK.
- Isis and Bristol-Myers Squibb extended their collaboration by two years to discover a more potent PCSK9 drug to move forward in development.
- Isis earned in excess of \$15 million in milestone payments and sublicensing fees in 2010 as Isis’ partners advanced drugs in development.

- Regulus formed a new alliance with sanofi-aventis worth potentially over \$750 million to develop and commercialize microRNA therapeutics, including Regulus’ leading fibrosis program targeting miR-21. Isis received \$1.9 million, which represents 7.5 percent of the \$25 million upfront payment Regulus received from sanofi-aventis.
- sanofi-aventis invested \$10 million in Regulus, valuing Regulus at more than \$130 million.
- Regulus and GSK established a new collaboration to develop and commercialize microRNA therapeutics targeting microRNA 122, or miR-122, for hepatitis C viral infection.

**Compensation of Executive Officers**

The following table shows for the fiscal years ended December 31, 2010, 2009 and 2008 compensation awarded to or paid to, or earned by, our Chief Executive Officer, Chief Financial Officer and our two other executive officers at December 31, 2010, called our “named executive officers.”

In 2010, 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**

| <u>Name and Principal Position</u> | <u>Year</u> | <u>Salary (\$)</u> | <u>Bonus(1) (\$)</u> | <u>Option Awards(2) (\$)</u> | <u>All Other Compensation(3) (\$)</u> | <u>Total (\$)</u> |
|------------------------------------|-------------|--------------------|----------------------|------------------------------|---------------------------------------|-------------------|
| Stanley T. Crooke,<br>Chairman,    | 2010        | \$ 710,995         | \$ 343,411           | \$ 681,324                   | \$ 14,111                             | \$ 1,749,841      |
|                                    | 2009        | \$ 683,649         | \$ 361,650           | \$ 1,069,879                 | \$ 13,258                             | \$ 2,128,436      |

|                                    |      |    |         |    |         |    |            |    |        |    |           |
|------------------------------------|------|----|---------|----|---------|----|------------|----|--------|----|-----------|
| President, Chief Executive Officer | 2008 | \$ | 648,009 | \$ | 438,054 | \$ | 1,401,888  | \$ | 12,248 | \$ | 2,500,199 |
| B. Lynne Parshall                  | 2010 | \$ | 620,478 | \$ | 262,230 | \$ | 363,374    | \$ | 17,813 | \$ | 1,263,895 |
| Director, Chief Operating Officer, | 2009 | \$ | 596,613 | \$ | 276,157 | \$ | 557,971    | \$ | 16,567 | \$ | 1,447,308 |
| Chief Financial Officer            | 2008 | \$ | 529,095 | \$ | 334,499 | \$ | 914,444(4) | \$ | 15,208 | \$ | 1,793,246 |
| C. Frank Bennett                   | 2010 | \$ | 384,020 | \$ | 133,063 | \$ | 158,977    | \$ | 17,178 | \$ | 693,238   |
| Senior Vice President, Antisense   | 2009 | \$ | 369,250 | \$ | 146,500 | \$ | 234,725    | \$ | 16,226 | \$ | 766,701   |
| Research                           | 2008 | \$ | 345,873 | \$ | 170,625 | \$ | 339,995    | \$ | 15,136 | \$ | 871,629   |
| Richard S. Geary                   | 2010 | \$ | 379,470 | \$ | 161,370 | \$ | 186,622(4) | \$ | 14,087 | \$ | 741,549   |
| Senior Vice President,             | 2009 | \$ | 364,000 | \$ | 169,533 | \$ | 206,559    | \$ | 12,328 | \$ | 752,420   |
| Development                        | 2008 | \$ | 299,873 | \$ | 150,150 | \$ | 345,140    | \$ | 11,559 | \$ | 806,722   |

- (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 2011 we paid bonuses for 2010 performance.
- (2) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with FASB Topic ASC 718 ("ASC 718") for stock options granted to the Named Executive Officers. ASC 718 expense for the stock options is based on the fair value of the options on the date of grant using the Black-Scholes option-valuation model. For more information, please see Note 6 of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2010 regarding assumptions underlying valuation of equity awards.
- (3) Includes AD&D, Basic Life, Medical, Dental, Vision, and 401(k) matching contributions which are available to all employees.
- (4) Additional options granted as a result of Ms. Parshall's promotion to Chief Operating Officer and Dr. Geary's promotion to Senior Vice President.

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## Grants of Plan-Based Awards

The following table shows for the fiscal year ended December 31, 2010, certain information regarding grants of plan-based awards to the Named Executive Officers:

### Grants of Plan-Based Awards in Fiscal 2010

| Name              | Grant Date | All Other Option Awards:<br>Number of Securities<br>Underlying Options<br>(#) | Exercise or Base Price of<br>Option Awards<br>(\$/Sh) | Grant Date Fair<br>Value of Stock and<br>Option Awards(1)<br>(\$) |
|-------------------|------------|---|---|---|
| Stanley T. Crooke | 1/4/10     | 119,163   | \$ 11.27  | \$ 681,324  |
| B. Lynne Parshall | 1/4/10     | 63,554  | \$ 11.27  | \$ 363,374  |
| C. Frank Bennett  | 1/4/10     | 27,805  | \$ 11.27  | \$ 158,977  |
| Richard S. Geary  | 1/4/10     | 32,640  | \$ 11.27  | \$ 186,622  |

- (1) Amounts represent the aggregate expense that will be recognized for financial statement reporting purposes in accordance with ASC 718 for stock options granted to the Named Executive Officers. ASC 718 expense for the stock options is based on the fair value of the options on the date of grant using the Black-Scholes option-valuation model. For more information, please see Note 6 of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2010 regarding assumptions underlying valuation of equity awards.

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

The Compensation Committee granted merit non-statutory stock options to the executive officers on January 4, 2010, the same date on which the committee granted stock options to our other employees.

All of these stock options were granted out of our 89 Plan. The options have a term of seven years and vest at the rate of 25% for the first year and then at the rate of 2.08% per month for 36 months thereafter during the optionee's employment.

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

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

The following table shows for the fiscal year ended December 31, 2010, certain information regarding outstanding option awards at fiscal year-end for the Named Executive Officers.

Other than the options described in the table below, there were no equity incentive plan awards outstanding for the Named Executive Officers at December 31, 2010. In addition, there were no stock awards outstanding for the individuals named below at December 31, 2010.

### Outstanding Option Awards At December 31, 2010

| Name                | Number of Securities Underlying Unexercised Options (#) Exercisable | Number of Securities Underlying Unexercised Options (#) Unexercisable | Full (1) Vest Date | Option Exercise Price (\$) | Option Expiration Date |
|---------------------|---|---|--------------------|----------------------------|------------------------|
| Stanley T. Crooke   | 75,720  | 0   | 1/3/09             | \$ 5.80                    | 1/2/12                 |
|                     | 50,000  | 0   | 1/2/07             | \$ 6.84                    | 1/1/13                 |
|                     | 128,924   | 0   | 1/3/10             | \$ 5.25                    | 1/2/13                 |
|                     | 50,000  | 0   | 9/21/10            | \$ 7.26                    | 9/20/13                |
|                     | 175,016   | 3,724   | 1/2/11             | \$ 11.12                   | 1/1/14                 |
|                     | 80,000  | 0   | 1/2/08             | \$ 6.81                    | 1/1/14                 |
|                     | 138,903   | 51,592  | 1/2/12             | \$ 15.38                   | 1/1/15                 |
|                     | 71,875  | 78,125  | 1/2/13             | \$ 14.47                   | 1/1/16                 |
|                     | 0   | 119,163   | 1/4/14             | \$ 11.27                   | 1/3/17                 |
| B. Lynne Parshall   | 30,263(2)   | 0   | 1/3/09             | \$ 5.80                    | 1/2/12                 |
|                     | 25,000  | 0   | 1/2/07             | \$ 6.84                    | 1/1/13                 |
|                     | 49,506(2)   | 0   | 1/3/10             | \$ 5.25                    | 1/2/13                 |
|                     | 30,000  | 0   | 9/21/10            | \$ 7.26                    | 9/20/13                |
|                     | 75,840  | 1,614   | 1/2/11             | \$ 11.12                   | 1/1/14                 |
|                     | 38,400  | 0   | 1/2/08             | \$ 6.81                    | 1/1/14                 |
|                     | 66,733  | 24,787  | 1/2/12             | \$ 15.38                   | 1/1/15                 |
|                     | 16,875  | 13,125  | 9/16/12            | \$ 16.45                   | 9/15/15                |
| 37,485              | 40,744  | 1/2/13  | \$ 14.47           | 1/1/16                     |                        |
|                     | 0   | 63,554  | 1/4/14             | \$ 11.27                   | 1/3/17                 |
| C. Frank Bennett    | 19,000  | 0   | 1/2/06             | \$ 21.05                   | 1/1/12                 |
|                     | 7,055   | 0   | 1/3/09             | \$ 5.80                    | 1/2/12                 |
|                     | 11,500  | 0   | 1/2/07             | \$ 6.84                    | 1/1/13                 |
|                     | 20,322  | 0   | 1/3/10             | \$ 5.25                    | 1/2/13                 |
|                     | 35,392  | 753   | 1/2/11             | \$ 11.12                   | 1/1/14                 |
|                     | 28,800  | 0   | 1/2/08             | \$ 6.81                    | 1/1/14                 |
|                     | 33,687  | 12,513  | 1/2/12             | \$ 15.38                   | 1/1/15                 |
|                     | 15,769  | 17,140  | 1/2/13             | \$ 14.47                   | 1/1/16                 |
| 0                   | 27,805  | 1/4/14  | \$ 11.27           | 1/3/17                     |                        |
| Richard S. Geary(3) | 8,000   | 0   | 1/2/06             | \$ 21.05                   | 1/1/12                 |
|                     | 5,044   | 0   | 1/3/09             | \$ 5.80                    | 1/2/12                 |
|                     | 11,686  | 0   | 1/3/10             | \$ 5.25                    | 1/2/13                 |
|                     | 1,049   | 0   | 1/2/08             | \$ 6.81                    | 1/1/14                 |
|                     | 18,645  | 397   | 1/2/11             | \$ 11.12                   | 1/1/14                 |
|                     | 7,291   | 2,709   | 1/1/12             | \$ 15.75                   | 12/31/14               |
|                     | 17,500  | 6,500   | 1/2/12             | \$ 15.38                   | 1/1/15                 |
|                     | 5,833   | 4,167   | 8/16/12            | \$ 19.08                   | 8/15/15                |
| 13,876              | 15,084  | 1/2/13  | \$ 14.47           | 1/1/16                     |                        |
| 0                   | 32,640  | 1/4/14  | \$ 11.27           | 1/3/17                     |                        |

(1) These options vest at the rate of 25% for the first year and then at the rate of 2.08% per month for 36 months thereafter during the optionee's employment.

(2) Includes an aggregate of 30,000 shares of common stock issuable upon exercise of options which Ms. Parshall transferred to her two daughters.

(3) Dr. Geary had 5,000 stock options expire during 2010.

### Option Exercises

The following table shows for the fiscal year ended December 31, 2010, certain information regarding option exercises and stock vested during the last fiscal year with respect to the Named Executive Officers:

#### Option Exercises in Fiscal 2010(1)

| Name              | Option Awards                                     |                                 |
|-------------------|---|---------------------------------|
|                   | Number of Shares Acquired on Exercise (2) (3) (#) | Value Realized on Exercise (\$) |
| Stanley T. Crooke | 10,000  | \$ 6,900.00                     |

|                     |          |    |           |
|---------------------|----------|----|-----------|
|                     | 20,000   | \$ | 15,900.00 |
|                     | 4,000    | \$ | 3,600.00  |
|                     | 16,000   | \$ | 14,320.00 |
|                     | 6,400    | \$ | 4,416.00  |
|                     | 10,800   | \$ | 8,586.00  |
| B. Lynne Parshall   | 800      | \$ | 720.00    |
|                     | 1,300(4) | \$ | 1,170.00  |
|                     | 8,700(4) | \$ | 7,786.50  |
|                     | 4,600    | \$ | 3,174.00  |
|                     | 7,700    | \$ | 6,121.50  |
|                     | 1,500    | \$ | 1,350.00  |
| C. Frank Bennett    | 6,200    | \$ | 5,549.00  |
|                     | 1,000    | \$ | 3,950.00  |
|                     | 3,000    | \$ | 11,739.90 |
|                     | 6,000    | \$ | 25,260.00 |
|                     | 1,980    | \$ | 1,366.20  |
| Richard S. Geary(5) | 3,300    | \$ | 2,623.50  |
|                     | 600      | \$ | 540.00    |
|                     | 2,600    | \$ | 2,327.00  |

- (1) We currently do not utilize stock awards as part of our compensation plan. As such, we do not include information regarding stock awards that would otherwise appear as blank columns in this table.
- (2) Each individual executed each option exercise and resulting sales pursuant to the individual's Rule 10b5-1 trading plan.
- (3) Each exercised option would have expired on 1/4/11, except 10,000 shares exercised by Dr. Bennett were subject to an option that would have expired on 1/2/12.
- (4) Includes options exercised by Ms. Parshall's daughters.
- (5) Dr. Geary had 5,000 stock options expire during 2010.

## Post-Employment Compensation

### *Pension Benefits and Nonqualified Deferred Compensation*

We do not provide pension arrangements or post-retirement health coverage for our executives or employees. Our executive officers are eligible to participate in our 401(k) contributory defined contribution plan. In any plan year, we will contribute to each participant a matching contribution equal to 25% of the first 6% of the participant's compensation that has been contributed to the plan. In 2010, the maximum matching contribution was \$3,675. We do not provide any nonqualified defined contribution or other deferred compensation plans.

### *Employment Agreements*

All of our employees, including our executive officers, are employees-at-will and as such do not have employment contracts with us, except in the case of some retention 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, on May 16, 2007, the Compensation Committee approved amending the stock option agreements of Dr. Croke and Ms. Parshall, such that in the event of a change of control, the vesting and exercisability of their then outstanding and unvested stock options will be accelerated in full, to the extent permitted by the applicable stock option plan.

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, 2010. 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, 2010. The estimates in this table are forward-looking statements. Please see the special note regarding forward-looking statements on page 54 of this Proxy Statement.

| Name              | Termination Event         |                                    |
|-------------------|---------------------------|------------------------------------|
|                   | Termination Without Cause | Termination in a Change of Control |
| Stanley T. Crooke | —                         | \$ 2,132,985                       |
| B. Lynne Parshall | \$ 930,717                | \$ 1,551,195                       |

### Director Compensation

We pay our non-employee Directors a fee of \$30,000 per year. We do not pay additional compensation for attending Board or Board committee meetings, but we do reimburse Board members for the expenses they incur to attend the meetings. For the fiscal year ending December 31, 2010, we paid total fees of \$30,000 to each of our non-employee Directors.

In 2010, each non-employee Director also received automatic stock option grants under our Director Plan. On July 1, 2010, under the Director Plan, each of our non-employee Directors serving at that time received an option to purchase 15,000 shares of our common stock, at an exercise price of \$9.22 per share, the fair market value of the common stock on the date of the grant, based on the closing sales price reported on Nasdaq. The options vest over a four-year period in equal annual installments.

The following table shows for the fiscal year ended December 31, 2010 certain information with respect to the compensation of all our non-employee Directors:

#### Director Compensation for Fiscal 2010

| Name                  | Fees Earned or Paid in Cash (\$) | Option Awards(1) (\$) | All Other Compensation (\$) | Total (\$) |
|-----------------------|----------------------------------|-----------------------|-----------------------------|------------|
| Spencer R. Berthelsen | \$ 30,000                        | \$ 85,848             | —                           | \$ 115,848 |
| Richard D. DiMarchi   | \$ 30,000                        | \$ 85,848             | —                           | \$ 115,848 |
| Joseph Klein          | \$ 30,000                        | \$ 85,848             | —                           | \$ 115,848 |
| Frederick T. Muto     | \$ 30,000                        | \$ 85,848             | —                           | \$ 115,848 |
| John C. Reed(2)       | \$ 30,000                        | \$ 85,848             | —                           | \$ 115,848 |
| Joseph H. Wender(2)   | \$ 30,000                        | \$ 85,848             | —                           | \$ 115,848 |

(1) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with FASB Topic ASC 718 ("ASC 718") for stock options granted to the Named Executive Officers. ASC 718 expense for the stock options is based on the fair value of the options on the date of grant using the Black-Scholes option-valuation model. For more information, please see Note 6 of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2010 regarding assumptions underlying valuation of equity awards.

(2) Dr. Reed and Mr. Wender had 10,000 and 4,000 stock options, respectively, expire last year due to the option price being underwater.

### Outstanding Equity Awards at Fiscal Year-End — Directors

The following table shows for the fiscal year ended December 31, 2010, certain information regarding outstanding awards at fiscal year-end of all our non-employee Directors: (none of our non-employee Directors exercised options in 2010).

| Name                  | Number of Securities Underlying Unexercised Options (#) |               |
|-----------------------|---|---------------|
|                       | Exercisable   | Unexercisable |
| Spencer R. Berthelsen | 93,125  | 36,875        |
| Richard D. DiMarchi   | 63,125  | 36,875        |
| Joseph Klein          | 53,125  | 36,875        |
| Frederick T. Muto     | 95,125  | 36,875        |
| John C. Reed          | 93,125  | 36,875        |
| Joseph H. Wender      | 77,125  | 36,875        |

### 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 2010, 2009, and 2008, she received the following compensation:

| Name                             | Year | Salary (\$) | Bonus(1) (\$) | Option Awards(2) (\$) | All Other Compensation(3) (\$) | Total (\$) |
|----------------------------------|------|-------------|---------------|-----------------------|--------------------------------|------------|
| Rosanne Crooke,                  | 2010 | \$ 160,600  | \$ 55,446     | \$ 120,977            | \$ 3,394                       | \$ 340,417 |
| Vice President, Cardiovascular   | 2009 | \$ 147,002  | \$ 42,263     | \$ 49,929             | \$ 336                         | \$ 239,530 |
| Diseases Drug Discovery Research | 2008 | \$ 140,002  | \$ 45,501     | \$ 61,416             | \$ 3,331                       | \$ 250,250 |

- (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 2011 we paid bonuses for 2010 performance.
- (2) These amounts represent the estimated fair values of stock option grants we recognized as share-based compensation expense. The estimated fair value amounts were determined using option-pricing models 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:
  - 8,300 shares at \$15.38 per share received on January 2, 2008;
  - 7,000 shares at \$14.47 per share received on January 2, 2009;
  - 6,600 shares at \$11.27 received on January 4, 2010; and
  - 18,750 shares at \$9.22 received on July 19, 2010 for her promotion to Vice President.
- (3) Includes AD&D, Basic Life, Medical, Dental, Vision, and 401(k) company contributions which are available to all employees.

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One of our Directors, Mr. Muto, who was elected to the Board in March 2001, is a partner at Cooley LLP, our outside legal counsel. We paid Cooley LLP an aggregate of \$53,000 for Isis and \$254,000 for Regulus in fees in 2010 for legal services, which amount is substantially less than five percent of Cooley's gross revenues for its 2010 fiscal year.

We have entered into indemnity agreements with each of our executive officers and Directors and certain non-executive officers which provide, among other things, that we will indemnify such officer or Director, under the circumstances and to the extent provided for therein, for expenses, damages, judgments, fines and settlements he or she may be required to pay in actions or proceedings which he or she is or may be made a party by reason of his or her position as a Director, officer or other agent of Isis, and otherwise to the fullest extent permitted under Delaware law and our bylaws. Our bylaws provide that we will indemnify our Directors and executive officers to the fullest extent not prohibited by Delaware law or any other applicable law, except that we will generally not be required to indemnify a Director or executive officer in connection with any proceeding initiated by such Director or executive officer.

#### *Policies and Procedures Regarding Related Party Transactions*

A committee of the Board composed entirely of independent Directors approves transactions with related persons, as defined under SEC regulations. The Compensation Committee of the Board approves all compensation we pay to employees that may qualify as a related person and the Audit Committee approves all other related party transactions, as specified in its charter. The committees only approve related-party transactions at committee meetings, or by unanimous written consent in lieu of a meeting, and record the approvals in the minutes of the committee.

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

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

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### **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 2011 Annual Meeting of stockholders.

*The Compensation Committee*  
Spencer R. Berthelsen, *Chairman*  
Richard D. DiMarchi  
John C. Reed

### 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 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, 2010 with management, including a discussion of the quality, not just the acceptability, of the accounting principles, the reasonableness of significant judgments, and the clarity of disclosures in the financial statements.

The Audit Committee reviewed with our independent auditors, who are responsible for expressing an opinion on the conformity of our audited financial statements with generally accepted accounting principles, their judgments as to the quality, not just the acceptability, of our accounting principles and any other matters as are required to be discussed with the Audit Committee under generally accepted auditing principles. In addition, the Audit Committee has discussed with the independent auditors, the auditors’ independence from management and Isis, including the matters in the written disclosures required by the Independence Standards Board. The Audit Committee received from Ernst & Young LLP written disclosure and the letter regarding its independence as required by applicable requirements of the Public Company Accounting Oversight Board regarding Ernst & Young LLP’s communications with the Audit Committee concerning independence. The Audit Committee also discussed with our independent auditors the matters required by the Statement on Auditing Standards No. 61, as amended.

The Audit Committee discussed with our independent auditors the overall scope and plans for their audit. The Audit Committee met with the independent auditors, with and without management present, to discuss the results of their examinations, their evaluations of our internal controls, and the overall quality of our financial reporting.

In reliance on the reviews and discussions referred to above, the Audit Committee recommended to the Board of Directors, and the Board has approved, that the audited financial statements be included in our Annual Report on Form 10-K for the fiscal year ended December 31, 2010 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 2011.

#### *The Audit Committee*

Joseph H. Wender, *Chairman*  
Spencer R. Berthelsen  
Joseph Klein, III

### HOUSEHOLDING OF PROXY MATERIALS

The SEC has adopted rules that permit companies and intermediaries (e.g. brokers) to satisfy the delivery requirements for proxy statements and annual reports with respect to two or more stockholders sharing the same address by delivering a single Proxy Statement addressed to those stockholders. This process, which is commonly referred to as “householding,” potentially means extra convenience for stockholders and cost savings for companies.

This year, a number of brokers with account holders who are our stockholders will be “householding” our proxy materials. A single notice of internet availability of proxy materials will be delivered to multiple stockholders sharing an address unless contrary instructions have been received from the affected stockholders. Once you have received notice from your broker that they will be “householding” communications to your address, “householding” will continue until you are notified otherwise or until you revoke your consent. If, at any time, you no longer wish to participate in “householding” and would prefer to receive a separate notice of internet availability of proxy materials, please notify your broker and direct your written request to Isis Pharmaceuticals, Inc., Attn: Linda Powell, Assistant Corporate Secretary, 1896 Rutherford Road, Carlsbad, California 92008; or contact Linda Powell at (760) 603-2471; and we will promptly provide you a separate notice of internet availability of proxy materials. Stockholders who currently receive multiple copies of the Proxy Statement or Notice of Internet Availability of Proxy Materials at their address and would like to request “householding” of their communications should contact their broker.

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\* 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 of 1933 or the Securities Exchange Act of 1934.

### 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, 2010 that we filed with the SEC, and is available free of charge. Please send written requests to:

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

You may also visit our website (www.isispharm.com(8)) to view our 2010 Annual Report. The Annual Report is not incorporated into this Proxy Statement and is not considered solicitating material.

By Order of the Board of Directors,

B. Lynne Parshall  
Secretary

April 28, 2011

### Special Note Regarding Forward-Looking Statements

This Proxy Statement includes forward-looking statements regarding Isis Pharmaceuticals' business, the financial position and outlook for Isis as well as Regulus, its jointly-owned subsidiary, 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, 2010, which is on file with the SEC. Copies of this and other documents are available from the Company.

(Isis Pharmaceuticals is a registered trademark of Isis Pharmaceuticals), (Inc. Regulus Therapeutics is a trademark of Regulus Therapeutics Inc).

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

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## ISIS PHARMACEUTICALS, INC.

### 2011 EQUITY INCENTIVE PLAN

ADOPTED BY THE BOARD OF DIRECTORS: MARCH 23, 2011

APPROVED BY THE STOCKHOLDERS: \_\_\_\_\_, 2011

TERMINATION DATE: \_\_\_\_\_, 2021

#### 1. GENERAL.

(a) **Eligible Award Recipients.** The persons eligible to receive Awards are Employees, Directors and Consultants.

(b) **Available Awards.** The Plan provides for the grant of the following Awards: (i) Stock Options, (ii) Stock Appreciation Rights (iii) Restricted Stock Awards, (iv) Restricted Stock Unit Awards, (v) Performance Stock Awards, and (vi) Performance Cash Awards.

(c) **Purpose.** The Company, by means of the Plan, seeks to secure and retain the services of the group of persons eligible to receive Awards as set forth in Section 1(a), to provide incentives for such persons to exert maximum efforts for the success of the Company and any Affiliate and to provide a means by which such eligible recipients may be given an opportunity to benefit from increases in value of the Common Stock through the granting of Awards.

#### 2. ADMINISTRATION.

(a) **Administration by Board.** The Board shall administer the Plan unless and until the Board delegates administration of the Plan to a Committee or Committees, as provided in Section 2(c).

(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 from time to time (A) which of the persons eligible under the Plan shall be granted Awards; (B) when and how each Award shall be granted; (C) what type or combination of types of Award shall be granted; (D) the provisions of each Award granted (which need not be identical), including the time or times when a person shall be permitted to receive cash or Common Stock pursuant to a Stock Award; (E) the number of shares of Common Stock with respect to which a Stock Award shall be granted to each such person; and (F) the Fair Market Value applicable to a Stock Award.

(ii) To construe and interpret the Plan and 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 Stock Award Agreement or in the written terms of a Performance Cash Award, in a manner and to the extent it shall deem necessary or expedient to make the Plan or Award fully effective.

(iii) To settle all controversies regarding the Plan and Awards granted under it.

(iv) Subject to the limitations set forth in Sections 5(f) and 8(j), to accelerate the time at which an Award may first be exercised or the time during which an Award or any part thereof will vest in accordance with the Plan, notwithstanding the provisions in the Award stating the time at which it may first be exercised or the time during which it will vest.

(v) To suspend or terminate the Plan at any time. Suspension or termination of the Plan shall not impair rights and obligations under any Award granted while the Plan is in effect except with the written consent of the affected Participant.

(vi) To amend the Plan in any respect the Board deems necessary or advisable. However, except as provided in Section 9(a) relating to Capitalization Adjustments, to the extent required by applicable law or listing requirements, stockholder approval shall be required for any amendment of the Plan that either (A) materially increases the number of shares of Common Stock available for issuance under the Plan, (B) materially expands the class of individuals eligible to receive Awards under the Plan, (C) materially increases the benefits accruing to Participants under the Plan or materially reduces the price at which shares of Common Stock may be issued or purchased under the Plan, (D) materially extends the term of the Plan, or (E) expands the types of Awards available for issuance under the Plan. Except as provided above, rights under any Award granted before amendment of the Plan shall not be impaired by any amendment of the Plan unless (1) the Company requests the consent of the affected Participant, and (2) such Participant consents in writing.

(vii) To submit any amendment to the Plan for stockholder approval, including, but not limited to, amendments to the Plan intended to satisfy the requirements of (A) Section 162(m) of the Code regarding the exclusion of performance-based compensation from the limit on corporate deductibility of compensation paid to Covered Employees, or (B) Rule 16b-3.

(viii) To approve forms of Award Agreements for use under the Plan and to amend the terms of any one or more Awards, including, but not limited to, (subject to the limitations on repricing and non-acceleration as provided in Section 2(f), 5(f), and 8(j)) amendments to provide terms more favorable to the Participant than previously provided in the Award Agreement, subject to any specified limits in the Plan that are not subject to Board discretion; *provided however*, that a Participant's rights under any Award shall not be impaired by any such amendment unless (A) the Company requests the consent of the affected Participant, and (B) such Participant consents in writing. Notwithstanding the foregoing, subject to the limitations of applicable law, if any, the Board may amend the terms of any one or more Awards without the affected Participant's consent if necessary to bring the Award into compliance with Section 409A of the Code.

(ix) 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 or Awards.

(x) To adopt such procedures and sub-plans as are necessary or appropriate to permit participation in the Plan by Employees, Directors or Consultants who are foreign nationals or employed outside the United States.

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**(c) Delegation to Committee.**

(i) **General.** The Board may delegate some or all of the administration of the Plan to a Committee or Committees. If administration of the Plan is delegated to a Committee, the Committee shall have, in connection with the administration of the Plan, the powers theretofore possessed by the Board that have been delegated to the Committee, including the power to delegate to a subcommittee of the Committee any of the administrative powers the Committee is authorized to exercise (and references in this Plan to the Board shall thereafter be to the Committee or subcommittee), subject, however, to such resolutions, not inconsistent with the provisions of the Plan, as may be adopted from time to time by the Board. The Committee may, at any time, abolish the subcommittee and/or revest in the Committee any powers delegated to the subcommittee. The Board may retain the authority to concurrently administer the Plan with the Committee and may, at any time, revest in the Board some or all of the powers previously delegated.

(ii) **Section 162(m) and Rule 16b-3 Compliance.** The Committee may consist solely of two or more Outside Directors, in accordance with Section 162(m) of the Code, or solely of two or more Non-Employee Directors, in accordance with Rule 16b-3.

(d) **Delegation to an Executive Officer.** The Board may delegate to one or more Executive Officers of the Company the authority to do one or both of the following: (i) designate Employees who are not Executive Officers of the Company or any of its Subsidiaries to be recipients of Options and Stock Appreciation Rights (and, to the extent permitted by applicable law, other Stock Awards) and the terms thereof, and (ii) determine the number of shares of Common Stock to be subject to such Stock Awards granted to such Employees; *provided, however*, that the Board resolutions regarding such delegation shall specify the total number of shares of Common Stock that may be subject to the Stock Awards granted by such Executive Officer and that such Executive Officer may not grant a Stock Award to himself or herself or to other Executive Officers. Notwithstanding the foregoing, the Board may not delegate authority to an Executive Officer to determine the Fair Market Value pursuant to Section 13(w) below.

(e) **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.

(f) **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 or Stock Appreciation Rights under the Plan, or (ii) cancel any outstanding Options or Stock Appreciation Rights 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.

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**3. SHARES SUBJECT TO THE PLAN.**

(a) **Share Reserve.** Subject to Section 9(a) relating to Capitalization Adjustments, the aggregate number of shares of Common Stock that may be issued pursuant to Stock Awards from and after the Effective Date shall not exceed 2,000,000 shares (the "**Share Reserve**"). For clarity, the Share Reserve

in this Section 3(a) is a limitation on the number of shares of the Common Stock that may be issued pursuant to the Plan and does not limit the granting of Stock Awards except as provided in Section 7(a). Shares may be issued in connection with a merger or acquisition as permitted by, as applicable, NASDAQ Listing Rule 5635(c) or, if applicable, NYSE Listed Company Manual Section 303A.08, AMEX Company Guide Section 711 or other applicable rule, and such issuance shall not reduce the number of shares available for issuance under the Plan. Furthermore, if a Stock Award or any portion thereof (i) expires or otherwise terminates without all of the shares covered by such Stock Award having been issued or (ii) is settled in cash (*i.e.*, the Participant receives cash rather than stock), such expiration, termination or settlement shall not reduce (or otherwise offset) the number of shares of Common Stock that may be available for issuance under the Plan.

**(b) Reversion of Shares to the Share Reserve.** If any shares of Common Stock issued pursuant to a Stock Award are forfeited back to the Company because of the failure to meet a contingency or condition required to vest such shares in the Participant, then the shares that are forfeited shall revert to and again become available for issuance under the Plan. Any shares reacquired by the Company pursuant to Section 8(f) or as consideration for the exercise of an Option shall again become available for issuance under the Plan.

**(c) Section 162(m) Limitation on Annual Grants.** Subject to the provisions of Section 9(a) relating to Capitalization Adjustments, at such time as the Company may be subject to the applicable provisions of Section 162(m) of the Code, a maximum of 2,000,000 shares of Common Stock subject to Options or Stock Appreciation Rights (in each case whose value is determined by reference to an increase over an exercise or strike price of at least 100% of the Fair Market Value on the date any such Stock Award is granted) may be granted to any Participant during any calendar year. Notwithstanding the foregoing, if any additional Options or Stock Appreciation Rights are granted to any Participant during any calendar year (in each case whose value is determined by reference to an increase over an exercise or strike price of at least 100% of the Fair Market Value on the date of the Stock Award), compensation attributable to the exercise of such additional Stock Awards shall not satisfy the requirements to be considered “qualified performance-based compensation” under Section 162(m) of the Code unless such additional Stock Award is approved by the Company’s stockholders.

**(d) Source of Shares.** The stock issuable under the Plan shall be (i) shares of authorized but unissued Common Stock or (ii) shares of reacquired Common Stock, including shares repurchased by the Company on the open market or otherwise.

#### 4. ELIGIBILITY.

**(a) Eligibility for Specific Stock Awards.** Stock Awards may be granted to Employees, Directors and Consultants; *provided, however*, Options and SARs may not be granted to Employees, Directors and Consultants who are providing Continuous Service only to any “parent” of the Company, as such term is defined in Rule 405 promulgated under the Securities Act, unless the stock underlying such Stock Awards is treated as “service recipient stock” under Section 409A of the Code because the Stock Awards are granted pursuant to a corporate transaction (such as a spin off transaction) or unless such Stock Awards comply with the distribution requirements of Section 409A of the Code.

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#### 5. PROVISIONS RELATING TO OPTIONS AND STOCK APPRECIATION RIGHTS.

Each Option or SAR shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. The provisions of separate Options or SARs need not be identical; *provided, however*, that each Option Agreement or Stock Appreciation Right Agreement shall conform to (through incorporation of provisions hereof by reference in the applicable Award Agreement or otherwise) the substance of each of the following provisions:

**(a) Term.** No Option or SAR shall be exercisable after the expiration of ten years from the date of its grant or such shorter period specified in the Award Agreement.

**(b) Exercise Price.** The exercise price (or strike price) of each Option or SAR shall be not less than 100% of the Fair Market Value of the Common Stock subject to the Option or SAR on the date the Option or SAR is granted. Notwithstanding the foregoing, an Option or SAR may be granted with an exercise price (or strike price) lower than 100% of the Fair Market Value of the Common Stock subject to the Option or SAR if such Option or SAR is granted pursuant to an assumption of or substitution for another option or stock appreciation right pursuant to a Corporate Transaction and in a manner consistent with the provisions of Sections 409A and, if applicable, 424(a) of the Code. Each SAR will be denominated in shares of Common Stock equivalents.

**(c) Purchase Price for Options.** The purchase price of Common Stock acquired pursuant to the exercise of an Option shall be paid, to the extent permitted by applicable law and as determined by the Board in its sole discretion, by any combination of the methods of payment set forth below. The Board shall have the authority to grant Options that do not permit all of the following methods of payment (or otherwise restrict the ability to use certain methods) and to grant Options that require the consent of the Company to utilize a particular method of payment. The permitted methods of payment are as follows:

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

**(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;

**(iii)** by delivery to the Company (either by actual delivery or attestation) of shares of Common Stock; or

**(iv)** by a “net exercise” arrangement pursuant to which the Company will reduce the number of shares of Common Stock issuable upon exercise by the largest whole number of shares with a Fair Market Value that does not exceed the aggregate exercise price; *provided, however*, that the Company shall accept a cash or other payment from the Participant to the extent of any remaining balance of the aggregate exercise price not satisfied by such reduction in the number of whole shares to be issued; *provided, further*, that shares of Common Stock will no longer be subject to an Option and will not be exercisable thereafter to the extent that (A) shares issuable upon exercise are reduced to pay the exercise price pursuant to the “net exercise,” (B) shares are delivered to the Participant as a result of such exercise, and (C) shares are withheld to satisfy tax withholding obligations.

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**(d) Exercise and Payment of a SAR.** To exercise any outstanding Stock Appreciation Right, the Participant must provide written notice of exercise to the Company in compliance with the provisions of the Stock Appreciation Right Agreement evidencing such Stock Appreciation Right. The appreciation distribution payable on the exercise of a Stock Appreciation Right will be not greater than an amount equal to the excess of (A) the aggregate Fair Market Value (on the date of the exercise of the Stock Appreciation Right) of a number of shares of Common Stock equal to the number of Common Stock equivalents in which the Participant is vested under such Stock Appreciation Right, and with respect to which the Participant is exercising the Stock Appreciation Right on such date, over (B) the strike price that will be determined by the Board at the time of grant of the Stock Appreciation Right. The appreciation distribution in respect to a Stock Appreciation Right may be paid in Common Stock, in cash, in any combination of the two or in any other form of consideration, as determined by the Board and contained in the Stock Appreciation Right Agreement evidencing such Stock Appreciation Right.

**(e) Transferability of Options and SARs.** The Board may, in its sole discretion, impose such limitations on the transferability of Options and SARs as the Board shall determine. In the absence of such a determination by the Board to the contrary, the following restrictions on the transferability of Options and SARs shall apply:

**(i) Restrictions on Transfer.** An Option or SAR shall not be transferable except by will or by the laws of descent and distribution and shall be exercisable during the lifetime of the Participant only by the Participant; *provided, however*, that the Board may, in its sole discretion, permit transfer of the Option or SAR in a manner that is not prohibited by applicable tax and securities laws upon the Participant's request. Except as explicitly provided herein, neither an Option nor a SAR may be transferred for consideration.

**(ii) Domestic Relations Orders.** Notwithstanding the foregoing, an Option or SAR may be transferred pursuant to a domestic relations order.

**(iii) Beneficiary Designation.** Notwithstanding the foregoing, the Participant may, by delivering written notice to the Company, in a form provided by or otherwise satisfactory to the Company and any broker designated by the Company to effect Option exercises, designate a third party who, in the event of the death of the Participant, shall thereafter be entitled to exercise the Option or SAR and receive the Common Stock or other consideration resulting from such exercise. In the absence of such a designation, the executor or administrator of the Participant's estate shall be entitled to exercise the Option or SAR and receive the Common Stock or other consideration resulting from such exercise.

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**(f) Vesting Generally.** The total number of shares of Common Stock subject to an Option or SAR may vest and therefore become exercisable in periodic installments that may or may not be equal. The Option or SAR may be subject to such other terms and conditions on the time or times when it may or may not be exercised (which may be based on the satisfaction of Performance Goals or other criteria) as the Board may deem appropriate. The vesting provisions of individual Options or SARs may vary; *provided, however*, that no Option or SAR granted to an employee or member of the Company's Board of Director will become 100% vested in a period of less than 2 years after the grant of such Option or SAR *except that* the vesting of an Option or SAR may accelerate (or may be accelerated by the Board or Committee) (i) as provided in Section 9(c); (ii) in the event of the Participant's death or Disability, (iii) upon a Corporate Transaction in which such Stock Award is not assumed or continued, (iv) upon a Change in Control, or (v) upon the Participant's retirement (as such term may be defined in the Participant's Award Agreement or in another applicable agreement). The provisions of this Section 5(f) are subject to any Option or SAR provisions governing the minimum number of shares of Common Stock as to which an Option or SAR may be exercised.

**(g) Termination of Continuous Service.** Except as otherwise provided in the applicable Award Agreement or other agreement between the Participant and the Company (validly executed by an authorized Executive Officer of the Company), if a Participant's Continuous Service terminates (other than upon the Participant's death or Disability), the Participant may exercise his or her Option or SAR (to the extent that the Participant was entitled to exercise such Award as of the date of termination of Continuous Service) but only within such period of time ending on the earlier of (i) the date three months following the termination of the Participant's Continuous Service (or such longer or shorter period specified in the applicable Award Agreement), or (ii) the expiration of the term of the Option or SAR as set forth in the Award Agreement. If, after termination of Continuous Service, the Participant does not exercise his or her Option or SAR within the time specified herein or in the Award Agreement (as applicable), the Option or SAR shall terminate.

**(h) Extension of Termination Date.** If the exercise of an Option or SAR following the termination of the Participant's Continuous Service (other than upon the Participant'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 or SAR shall terminate on the earlier of (i) the expiration of a total period of three months (that need not be consecutive) after the termination of the Participant's Continuous Service during which the exercise of the Option or SAR would not be in violation of such registration requirements, or (ii) the expiration of the term of the Option or SAR as set forth in the applicable Award Agreement. In addition, unless otherwise provided in a Participant's Award Agreement, if the immediate sale of any Common Stock received upon exercise of an Option or SAR following the termination of the Participant's Continuous Service would violate the Company's insider trading policy, then the Option or SAR 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 Participant's Continuous Service during which the sale of Common Stock received upon exercise of the Option or SAR would not be in violation of the Company's insider trading policy, or (ii) the expiration of the term of the Option or SAR as set forth in the applicable Award Agreement.

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**(i) Disability of Participant.** Except as otherwise provided in the applicable Award Agreement or other agreement between the Participant and the Company (validly executed by an authorized Executive Officer of the Company), if a Participant's Continuous Service terminates as a result of the Participant's Disability, the Participant may exercise his or her Option or SAR (to the extent that the Participant was entitled to exercise such Option or SAR as of the date of termination of Continuous Service), but only within such period of time ending on the earlier of (i) the date 12 months following such termination of Continuous Service (or such longer or shorter period specified in the Award Agreement), or (ii) the expiration of the term of the Option or SAR as set forth in the Award Agreement. If, after termination of Continuous Service, the Participant does not exercise his or her Option or SAR within the time specified herein or in the Award Agreement (as applicable), the Option or SAR (as applicable) shall terminate.

**(j) Death of Participant.** Except as otherwise provided in the applicable Award Agreement or other agreement between the Participant and the Company (validly executed by an authorized Executive Officer of the Company), if (i) a Participant's Continuous Service terminates as a result of the Participant's death, or (ii) the Participant dies within the period (if any) specified in the Award Agreement for exercisability after the termination of the Participant's Continuous Service (for a reason other than death), then the Option or SAR may be exercised (to the extent the Participant was entitled to exercise such Option or SAR as of the date of death) by the Participant's estate, by a person who acquired the right to exercise the Option or SAR by bequest or inheritance or by a person designated to exercise the Option or SAR upon the Participant's death, but only within the period ending on the earlier of (i) the date 18 months following the date of death (or such longer or shorter period specified in the Award Agreement), or (ii) the expiration of the term of such Option or SAR as set forth in the Award Agreement. If, after the Participant's death, the Option or SAR is not exercised within the time specified herein or in the Award Agreement (as applicable), the Option or SAR shall terminate.

**(k) Non-Exempt Employees.** Without limiting the provisions set forth in Section 5(f), no Option or SAR, whether or not vested, granted to an Employee who is a non-exempt employee for purposes of the Fair Labor Standards Act of 1938, as amended, shall be first exercisable for any shares of Common Stock until at least six months following the date of grant of the Option or SAR. Notwithstanding the foregoing, consistent with the provisions of the Worker Economic Opportunity Act, (i) in the event of the Participant's death or Disability, (ii) upon a Corporate Transaction in which such Option or SAR is not assumed, continued, or substituted, (iii) upon a Change in Control, or (iv) upon the Participant's retirement (as such term may be defined in the Participant's Award Agreement or in another applicable agreement or in accordance with the Company's then current employment policies and guidelines), any such vested Options and SARs may be exercised earlier than six months following the date of grant. The foregoing provision is intended to operate so that any income derived by a non-exempt employee in connection with the exercise or vesting of an Option or SAR will be exempt from his or her regular rate of pay.

## 6. PROVISIONS OF STOCK AWARDS OTHER THAN OPTIONS AND SARs.

**(a) Restricted Stock Awards.** Each Restricted Stock Award Agreement shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. To the extent consistent with the Company's Bylaws, at the Board's election, shares of Common Stock may be (i) held in book entry form subject to the Company's instructions until any restrictions relating to the Restricted Stock Award lapse; or (ii) evidenced by a certificate, which certificate shall be held in such form and manner as determined by the Board. The terms and conditions of Restricted Stock Award Agreements may change from time to time, and the terms

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and conditions of separate Restricted Stock Award Agreements need not be identical; *provided, however*, that each Restricted Stock 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:

**(i) Consideration.** A Restricted Stock Award may be awarded in consideration for (A) cash, check, bank draft or money order payable to the Company, (B) past services to the Company or an Affiliate, or (C) any other form of legal consideration (including future services) that may be acceptable to the Board, in its sole discretion, and permissible under applicable law.

**(ii) Vesting.** Shares of Common Stock awarded under the Restricted Stock Award Agreement may be subject to forfeiture to the Company in accordance with a vesting schedule to be determined by the Board.

**(iii) Termination of Participant's Continuous Service.** If a Participant's Continuous Service terminates, the Company may receive through a forfeiture condition or a repurchase right any or all of the shares of Common Stock held by the Participant that have not vested as of the date of termination of Continuous Service under the terms of the Restricted Stock Award Agreement.

**(iv) Transferability.** Rights to acquire shares of Common Stock under the Restricted Stock Award Agreement shall be transferable by the Participant only upon such terms and conditions as are set forth in the Restricted Stock Award Agreement, as the Board shall determine in its sole discretion, so long as Common Stock awarded under the Restricted Stock Award Agreement remains subject to the terms of the Restricted Stock Award Agreement.

**(v) Dividends.** A Restricted Stock Award Agreement may provide that any dividends paid on Restricted Stock will be subject to the same vesting and forfeiture restrictions as apply to the shares subject to the Restricted Stock Award to which they relate.

**(b) Restricted Stock Unit Awards.** 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:

**(i) 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 Participant upon delivery of each share of Common Stock subject to the Restricted Stock Unit Award. The consideration to be paid (if any) by the Participant 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.

**(ii) Vesting.** Subject to the limitations set forth in Section 8(j), at the time of the grant of a Restricted Stock Unit Award, the Board may impose such restrictions on or conditions to the vesting of the Restricted Stock Unit Award as it, in its sole discretion, deems appropriate.

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**(iii) 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.

**(iv) 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.

**(v) 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.

**(vi) Termination of Participant'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 Participant's termination of Continuous Service.

**(c) Performance Awards.**

**(i) Performance Stock Awards.** A Performance Stock Award is a Stock Award that may vest or may be exercised contingent upon the attainment during a Performance Period of certain Performance Goals. A Performance Stock Award may, but need not, require the completion of a specified period of Continuous Service. The length of any Performance Period, the Performance Goals to be achieved during the Performance Period, and the measure of whether and to what degree such Performance Goals have been attained shall be conclusively determined by the Committee, in its sole discretion. The maximum number of shares covered by an Award that may be granted to any Participant in a calendar year attributable to Stock Awards described in this Section 6(c)(i) (whether the grant, vesting or exercise is contingent upon the attainment during a Performance Period of the Performance Goals) shall not exceed 750,000 shares of Common Stock. The Board may provide for or, subject to such terms and conditions as the Board may specify, may permit a Participant to elect for, the payment of any Performance Stock Award to be deferred to a specified date or event. In addition, to the extent permitted by applicable law and the applicable Award Agreement, the Board may determine that cash may be used in payment of Performance Stock Awards.

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**(ii) Performance Cash Awards.** A Performance Cash Award is a cash award that may be paid contingent upon the attainment during a Performance Period of certain Performance Goals. A Performance Cash Award may also require the completion of a specified period of Continuous Service. At the time of grant of a Performance Cash Award, the length of any Performance Period, the Performance Goals to be achieved during the Performance Period, and the measure of whether and to what degree such Performance Goals have been attained shall be conclusively determined by the Committee, in its sole discretion. In any calendar year, the Committee may not grant a Performance Cash Award that has a maximum value that may be paid to any Participant in excess of \$2,000,000. The Board may provide for or, subject to such terms and conditions as the Board may specify, may permit a Participant to elect for, the payment of any Performance Cash Award to be deferred to a specified date or event. The Committee may specify the form of payment of Performance Cash Awards, which may be cash or other property, or may provide for a Participant to have the option for his or her Performance Cash Award, or such portion thereof as the Board may specify, to be paid in whole or in part in cash or other property.

**(iii) Board Discretion.** The Board retains the discretion to reduce or eliminate the compensation or economic benefit due upon attainment of Performance Goals and to define the manner of calculating the Performance Criteria it selects to use for a Performance Period.

**(iv) Section 162(m) Compliance.** Unless otherwise permitted in compliance with the requirements of Section 162(m) of the Code with respect to an Award intended to qualify as "performance-based compensation" thereunder, the Committee shall establish the Performance Goals applicable to, and the formula for calculating the amount payable under, the Award no later than the earlier of (a) the date 90 days after the commencement of the applicable Performance Period, or (b) the date on which 25% of the Performance Period has elapsed, and in either event at a time when the achievement of the applicable Performance Goals remains substantially uncertain. Prior to the payment of any compensation under an Award intended to qualify as "performance-based compensation" under Section 162(m) of the Code, the Committee shall certify the extent to which any Performance Goals and any other material terms under such Award have been satisfied (other than in cases where such relate solely to the increase in the value of the Common Stock). Notwithstanding satisfaction of any completion of any Performance Goals, to the extent specified at the time of grant of an Award to "covered employees" within the meaning of Section 162(m) of the Code, the number of shares of Common Stock, Options, cash or other benefits granted, issued, retainable and/or vested under an Award on account of satisfaction of such Performance Goals may be reduced by the Committee on the basis of such further considerations as the Committee, in its sole discretion, shall determine.

**7. 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 reasonably 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

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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 that 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 Participant 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 Participant 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.

## 8. MISCELLANEOUS.

(a) **Use of Proceeds from Sales of Common Stock.** Proceeds from the sale of shares of Common Stock pursuant to Stock Awards shall constitute general funds of the Company.

(b) **Corporate Action Constituting Grant of Stock Awards.** Corporate action constituting a grant by the Company of a Stock Award to any Participant shall be deemed completed as of the date of such corporate action, unless otherwise determined by the Board, regardless of when the instrument, certificate, or letter evidencing the Stock Award is communicated to, or actually received or accepted by, the Participant.

(c) **Stockholder Rights.** No Participant 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 (i) such Participant has satisfied all requirements for exercise of the Stock Award pursuant to its terms, if applicable, and (ii) the issuance of the Common Stock subject to such Stock Award has been entered into the books and records of the Company.

(d) **No Employment or Other Service Rights.** Nothing in the Plan, any Stock Award Agreement or any other instrument executed thereunder or in connection with any Award granted pursuant thereto shall confer upon any Participant any right to continue to serve the Company or an Affiliate in the capacity in effect at the time the Stock Award was granted 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.

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(e) **Investment Assurances.** The Company may require a Participant, as a condition of exercising or acquiring Common Stock under any Stock Award, (i) to give written assurances satisfactory to the Company as to the Participant'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 Participant is acquiring Common Stock subject to the Stock Award for the Participant'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 (A) the issuance of the shares 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 (B) as to any particular requirement, counsel for the Company determines 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 or the Company's insider trading policy, including, but not limited to, legends restricting the transfer of the Common Stock.

(f) **Withholding Obligations.** Unless prohibited by the terms of an Award Agreement, the Company may, in its sole discretion, satisfy any federal, state or local tax withholding obligation relating to an Award by any of the following means or by a combination of such means: (i) causing the Participant to tender a cash payment; (ii) withholding shares of Common Stock from the shares of Common Stock issued or otherwise issuable to the Participant in connection with the 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 lesser amount as may be necessary to avoid classification of the Stock Award as a liability for financial accounting purposes); (iii) withholding cash from an Award settled in cash; (iv) withholding payment from any amounts otherwise payable to the Participant; or (v) by such other method as may be set forth in the Award Agreement.

(g) **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 Participant has access).

(h) **Deferrals.** To the extent permitted by applicable law, the Board, in its sole discretion, may determine that the delivery of Common Stock or the payment of cash, upon the exercise, vesting or settlement of all or a portion of any Award may be deferred and may establish programs and procedures for deferral elections to be made by Participants. Deferrals by Participants will be made in accordance with Section 409A of the Code. Consistent with Section 409A of the Code, the Board may provide for distributions while a Participant is still an employee or otherwise providing services to the Company. The Board is authorized to make deferrals of Awards and determine when, and in what annual percentages, Participants may receive payments, including lump sum payments, following the Participant's termination of Continuous Service, and implement such other terms and conditions consistent with the provisions of the Plan and in accordance with applicable law.

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(i) **Compliance with Section 409A.** To the extent that the Board determines that any Award granted hereunder is subject to Section 409A of the Code, the Award Agreement evidencing such Award shall incorporate the terms and conditions necessary to avoid the consequences specified in Section 409A(a)(1) of the Code. To the extent applicable, the Plan and Award Agreements shall be interpreted in accordance with Section 409A of the Code. Notwithstanding anything to the contrary in this Plan (and unless the Award Agreement specifically provides otherwise), if the shares of Common Stock are publicly traded and a Participant holding an Award that constitutes "deferred compensation" under Section 409A of the Code is a "specified employee" for purposes of Section 409A of the Code, no distribution or payment of any amount shall be made upon a "separation from service" before a date that is six months following the date of such Participant's "separation from service" (as defined in Section 409A of the Code without regard to alternative definitions thereunder) or, if earlier, the date of the Participant's death.

(j) **Minimum Vesting.** After the Effective Date of the Plan, except for Awards granted to Non-Employee Directors as non-discretionary initial or annual grants, generally (i) no Restricted Stock Award, or Restricted Stock Unit Award that vests on the basis of the Participant's Continuous Service with the Company shall vest at a rate that is any more rapid than ratably over a three-year period and (ii) no Restricted Stock Award or Restricted Stock Unit

Award that vests based on the satisfaction of Performance Goals shall provide for a Performance Period of less than 12 months; *provided, however*, that, the vesting of a Restricted Stock Award or Restricted Stock Unit Award may accelerate (or may be accelerated by the Board or Committee) in the event of the Participant's death or Disability, upon a Corporate Transaction in which such Stock Award is not assumed or continued, upon a Change in Control, or upon the Participant's retirement (as such term may be defined in the Participant's Award Agreement or in another applicable agreement). Notwithstanding the foregoing, Stock Awards granted after the Effective Date that do not meet these vesting guidelines shall be limited to 10% of the total number of shares reserved for issuance under the Plan.

(k) **Compliance with Insider-Trading Policy.** The Company may limit or restrict a Participant's ability to exercise options or sell stock pursuant to the Company's then-applicable insider-trading policy (or similar policy adopted by the Company).

## 9. ADJUSTMENTS UPON CHANGES IN COMMON STOCK; OTHER CORPORATE EVENTS.

(a) **Capitalization Adjustments.** In the event of a Capitalization Adjustment, the Board shall appropriately and proportionately adjust: (i) the class(es) and maximum number of securities subject to the Plan pursuant to Section 3(a), (ii) the class(es) and maximum number of securities that may be awarded to any person pursuant to Sections 3(c) and 6(c)(i), and (iii) the class(es) and number of securities and price per share of stock subject to outstanding Stock Awards. The Board shall make such adjustments, and its determination shall be final, binding and conclusive.

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(b) **Dissolution or Liquidation.** Except as otherwise provided in the Stock Award Agreement, in the event of a dissolution or liquidation of the Company, all outstanding Stock Awards (other than Stock Awards consisting of vested and outstanding shares of Common Stock not subject to a forfeiture condition or the Company's right of repurchase) shall terminate immediately prior to the completion of such dissolution or liquidation, and the shares of Common Stock subject to the Company's repurchase rights or subject to a forfeiture condition may be repurchased or reacquired by the Company notwithstanding the fact that the holder of such Stock Award is providing Continuous Service, *provided, however*, that the Board may, in its sole discretion, cause some or all Stock Awards to become fully vested, exercisable and/or no longer subject to repurchase or forfeiture (to the extent such Stock Awards have not previously expired or terminated) before the dissolution or liquidation is completed but contingent on its completion.

(c) **Corporate Transaction.** The following provisions shall apply to Stock Awards in the event of a Corporate Transaction unless otherwise provided in the instrument evidencing the Stock Award or any other written agreement between the Company or any Affiliate (validly executed by an authorized Executive Officer of the Company or such Affiliate) and the Participant or unless otherwise expressly provided by the Board at the time of grant of a Stock Award. In the event of a Corporate Transaction, then, notwithstanding any other provision of the Plan, the Board shall take one or more of the following actions with respect to Stock Awards, contingent upon the closing or completion of the Corporate Transaction:

(i) arrange for the surviving corporation or acquiring corporation (or the surviving or acquiring corporation's parent company) to assume or continue the Stock Award or to substitute a similar stock award for the Stock Award (including, but not limited to, an award to acquire the same consideration paid to the stockholders of the Company pursuant to the Corporate Transaction);

(ii) arrange for the assignment of any reacquisition or repurchase rights held by the Company in respect of Common Stock issued pursuant to the Stock Award to the surviving corporation or acquiring corporation (or the surviving or acquiring corporation's parent company);

(iii) accelerate the vesting, in whole or in part, of the Stock Award (and, if applicable, the time at which the Stock Award may be exercised) 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 five days prior to the effective date of the Corporate Transaction), with such Stock Award terminating if not exercised (if applicable) at or prior to the effective time of the Corporate Transaction;

(iv) arrange for the lapse of any reacquisition or repurchase rights held by the Company with respect to the Stock Award;

(v) cancel or arrange for the cancellation of the Stock Award, to the extent not vested or not exercised prior to the effective time of the Corporate Transaction, in exchange for such cash consideration, if any, as the Board, in its sole discretion, may consider appropriate; or

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(vi) make a payment, in such form as may be determined by the Board equal to the excess, if any, of (A) the value of the property the Participant would have received upon the exercise of the Stock Award, over (B) any exercise price payable by such holder in connection with such exercise.

The Board need not take the same action or actions with respect to all Stock Awards or portions thereof or with respect to all Participants.

(d) **Change in Control.** A Stock Award may be subject to additional acceleration of vesting and exercisability upon or after a Change in Control as may be provided in the Stock Award Agreement for such Stock Award or as may be provided in any other written agreement between the Company or any Affiliate (validly executed by an authorized Executive Officer of the Company or such Affiliate) and the Participant, but in the absence of such provision, no such acceleration shall occur.

## 10. TERMINATION OR SUSPENSION OF THE PLAN.

(a) **Plan Term.** The Board may suspend or terminate the Plan at any time. Unless terminated sooner by the Board, the Plan shall automatically terminate on the day before the tenth anniversary of the date the Plan is approved by the stockholders of the Company. No 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 Award granted while the Plan is in effect except with the written consent of the affected Participant.

## 11. EFFECTIVE DATE OF PLAN.

This Plan shall become effective on the date of the annual meeting of stockholders of the Company held in 2011 provided this Plan is approved by the Company's stockholders at such meeting (the "**Effective Date**").

## 12. CHOICE OF LAW.

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

## 13. DEFINITIONS. As used in the Plan, the following definitions shall apply to the capitalized terms indicated below:

(a) "**Affiliate**" means, at the time of determination, any "parent" or "subsidiary" of the Company as such terms are defined in Rule 405 promulgated under the Securities Act. The Board shall have the authority to determine the time or times at which "parent" or "subsidiary" status is determined within the foregoing definition, and such determination shall be final, binding and conclusive on all persons.

(b) "**Award**" means a Stock Award or a Performance Cash Award.

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(c) "**Award Agreement**" means a written agreement between the Company and a Participant evidencing the terms and conditions of an Award.

(d) "**Board**" means the Board of Directors of the Company.

(e) "**Capitalization Adjustment**" means any change that is made in, or other events that occur with respect to, the Common Stock subject to the Plan or subject to any Stock Award after the Effective Date without the receipt of consideration by the Company through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, large nonrecurring cash dividend, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or any similar equity restructuring transaction, as that term is used in Statement of Financial Accounting Standards No. 123 (revised). Notwithstanding the foregoing, the conversion of any convertible securities of the Company shall not be treated as a Capitalization Adjustment.

(f) "**Change in Control**" means the consummation, 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. Notwithstanding the foregoing, a Change in Control shall not be deemed to occur (A) on account of the acquisition of securities of the Company directly from the Company, (B) on account of the acquisition of securities of the Company by an investor, any affiliate thereof or any other Exchange Act Person that acquires the Company's securities in a transaction or series of related transactions the primary purpose of which is to obtain financing for the Company through the issuance of equity securities, or (C) solely because the level of Ownership held by any Exchange Act Person (the "**Subject Person**") exceeds the designated percentage threshold 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 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 designated percentage threshold, 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, either (A) 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 (B) more than 50% of the combined outstanding voting power of the parent of the surviving Entity in such merger, consolidation or similar transaction, in each case in substantially the same proportions as their Ownership of the outstanding voting securities of the Company immediately prior to such transaction;

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(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, except for a liquidation into a parent corporation;

(iv) there is consummated a sale, lease, exclusive 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 outstanding voting securities of the Company immediately prior to such sale, lease, license or other disposition; or

(v) individuals who, on the date the 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, (A) the term Change in Control shall not include a sale of assets, merger or other transaction effected exclusively for the purpose of changing the domicile of the Company, and (B) the definition of Change in Control (or any analogous term) in an individual written agreement between the Company or any Affiliate and the Participant (validly executed by an authorized Executive Officer of

the Company or such Affiliate) shall supersede the foregoing definition with respect to Awards subject to such agreement; *provided, 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.

(g) “**Code**” means the Internal Revenue Code of 1986, as amended, including any applicable regulations and guidance thereunder.

(h) “**Committee**” means a committee of one or more Directors to whom authority has been delegated by the Board in accordance with Section 2(c).

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

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

(k) “**Consultant**” means any person, including an advisor, who is (i) engaged by the Company or an Affiliate to render consulting or advisory services and is compensated for such services, or (ii) serving as a member of the board of directors of an Affiliate and is compensated for such services. However, service solely as a Director, or payment of a fee for such service, shall not cause a Director to be considered a “Consultant” for purposes of the Plan. Notwithstanding the foregoing, a person is treated as a Consultant under this Plan only if a Form S-8 Registration Statement under the Securities Act is available to register either the offer or the sale of the Company’s securities to such person.

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(l) “**Continuous Service**” means that the Participant’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 Participant renders service to the Company or an Affiliate as an Employee, Consultant or Director or a change in the entity for which the Participant renders such service, provided that there is no interruption or termination of the Participant’s service with the Company or an Affiliate, shall not terminate a Participant’s Continuous Service; *provided, however*, if the Entity for which a Participant is rendering services ceases to qualify as an Affiliate, as determined by the Board, in its sole discretion, such Participant’s Continuous Service shall be considered to have terminated on the date such Entity ceases to qualify as an Affiliate. To the extent permitted by law, 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 (i) any leave of absence approved by the Board or Chief Executive Officer, including sick leave, military leave or any other personal leave, or (ii) transfers between the Company, an Affiliate, or their successors. Notwithstanding the foregoing, a leave of absence shall be treated as Continuous Service for purposes of vesting in a Stock Award only to such extent as may be provided in the Company’s leave of absence policy, in the written terms of any leave of absence agreement or policy applicable to the Participant, or as otherwise required by law.

(m) “**Corporate Transaction**” means the consummation, 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 sole 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.

(n) “**Covered Employee**” shall have the meaning provided in Section 162(m)(3) of the Code.

(o) “**Director**” means a member of the Board.

(p) “**Disability**” means, with respect to a Participant, the inability of such Participant to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months, as provided in Sections 22(e)(3) and 409A(a)(2)(c)(i) of the Code, and shall be determined by the Board on the basis of such medical evidence as the Board deems warranted under the circumstances.

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(q) “**Effective Date**” has the meaning set forth in Section 11 of the Plan.

(r) “**Employee**” means any person employed by the Company or an Affiliate. However, service solely as a Director, or payment of a fee for such services, shall not cause a Director to be considered an “Employee” for purposes of the Plan.

(s) “**Entity**” means a corporation, partnership, limited liability company or other entity.

(t) “**Exchange Act**” means the Securities Exchange Act of 1934, as amended, and the rules and regulations promulgated thereunder.

(u) “**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 (i) the Company or any Subsidiary of the Company, (ii) 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, (iii) an underwriter temporarily holding securities pursuant to a registered public offering of such securities, (iv) 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; or (v) any natural person,

Entity or “group” (within the meaning of Section 13(d) or 14(d) of the Exchange Act) that, as of the Effective Date, is 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.

(v) “**Executive Officer**” means a person who is an officer of the Company within the meaning of Section 16 of the Exchange Act.

(w) “**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 any established market, the Fair Market Value of a share of Common Stock shall be the closing sales price for such stock as quoted on such exchange or market (or the exchange or market with the greatest volume of trading in the Common Stock) on the date of determination, as reported in a source the Board deems reliable.

(ii) Unless otherwise provided by the Board, if there is no closing sales price for the Common Stock on the date of determination, then the Fair Market Value shall be the closing selling price on the last preceding date for which such quotation exists.

(iii) In the absence of such markets for the Common Stock, the Fair Market Value shall be determined by the Board in good faith and in a manner that complies with Sections 409A and 422 of the Code.

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(x) “**Non-Employee Director**” means a Director who either (i) is not a current employee or officer of the Company or an Affiliate, does not receive compensation, either directly or indirectly, from the Company or an Affiliate for services rendered as a consultant or in any capacity other than as a Director (except for an amount as to which disclosure would not be required under Item 404(a) of Regulation S-K promulgated pursuant to the Securities Act (“**Regulation S-K**”)), does not possess an interest in any other transaction for which disclosure would be required under Item 404(a) of Regulation S-K, and is not engaged in a business relationship for which disclosure would be required pursuant to Item 404(b) of Regulation S-K; or (ii) is otherwise considered a “non-employee director” for purposes of Rule 16b-3.

(y) “**Option**” means a stock option granted pursuant to Section 5 of the Plan to purchase shares of Common Stock granted pursuant to the Plan.

(z) “**Option Agreement**” means a written agreement between the Company and an Optionholder evidencing the terms and conditions of an Option grant. Each Option Agreement shall be subject to the terms and conditions of the Plan.

(aa) “**Optionholder**” means a person to whom an Option is granted pursuant to the Plan or, if applicable, such other person who holds an outstanding Option.

(bb) “**Outside Director**” means a Director who either (i) is not a current employee of the Company or an “affiliated corporation” (within the meaning of Treasury Regulations promulgated under Section 162(m) of the Code), is not a former employee of the Company or an “affiliated corporation” who receives compensation for prior services (other than benefits under a tax-qualified retirement plan) during the taxable year, has not been an officer of the Company or an “affiliated corporation,” and does not receive remuneration from the Company or an “affiliated corporation,” either directly or indirectly, in any capacity other than as a Director, or (ii) is otherwise considered an “outside director” for purposes of Section 162(m) of the Code.

(cc) “**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.

(dd) “**Participant**” means a person to whom an Award is granted pursuant to the Plan or, if applicable, such other person who holds an outstanding Stock Award.

(ee) “**Performance Cash Award**” means an award of cash granted pursuant to the terms and conditions of Section 6(c)(ii).

(ff) “**Performance Criteria**” means the one or more criteria that the Board shall select for purposes of establishing the Performance Goals for a Performance Period. The Performance Criteria that shall be used to establish such Performance Goals may be based on any one of, or combination of, the following as determined by the Board: (i) earnings (including earnings per share and net earnings); (ii) earnings before interest, taxes and depreciation; (iii) earnings before interest, taxes, depreciation and amortization; (iv) total stockholder return; (v) return on equity or average stockholder’s equity; (vi) return on assets, investment, or capital employed; (vii) stock price; (viii) margin (including gross margin); (ix) income (before or after taxes); (x) operating income; (xi) operating income after taxes; (xii) pre-tax profit; (xiii) operating cash flow; (xiv) sales or revenue targets; (xv) increases in revenue or product revenue; (xvi) expenses and cost

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reduction goals; (xvii) improvement in or attainment of working capital levels; (xviii) economic value added (or an equivalent metric); (xix) market share; (xx) cash flow; (xxi) cash flow per share; (xxii) share price performance; (xxiii) debt reduction; (xxiv) implementation or completion of projects or processes (including, but not limited to development and regulatory milestones); (xxv) customer satisfaction; (xxvi) stockholders’ equity; (xxvii) capital expenditures; (xxviii) debt levels; (xxix) operating profit or net operating profit; (xxx) workforce diversity; (xxxi) growth of net income or operating income; (xxxii) billings; and (xxxiii) to the extent that an Award is not intended to comply with Section 162(m) of the Code, other measures of performance selected by the Board.

(gg) “**Performance Goals**” means, for a Performance Period, the one or more goals established by the Board for the Performance Period based upon the Performance Criteria. Performance Goals may be based on a Company-wide basis, with respect to one or more business units, divisions, Affiliates, or business segments, and in either absolute terms or relative to the performance of one or more comparable companies or the performance of one or more relevant indices. Unless specified otherwise by the Board (i) in the Award Agreement at the time the Award is granted or (ii) in such other document setting forth the Performance Goals at the time the Performance Goals are established, the Board shall appropriately make adjustments in the method of calculating the attainment of Performance Goals for a Performance Period as follows: (1) to exclude restructuring and/or other nonrecurring charges; (2) to exclude exchange rate effects, as applicable, for non-U.S. dollar denominated Performance Goals; (3) to exclude the effects of changes to generally accepted

accounting principles; (4) to exclude the effects of any statutory adjustments to corporate tax rates; (5) to exclude the effects of any “extraordinary items” as determined under generally accepted accounting principles; and (6) to exclude accounting expenses relating to share-based compensation.

(hh) “**Performance Period**” means the period of time selected by the Board over which the attainment of one or more Performance Goals will be measured for the purpose of determining a Participant’s right to and the payment of a Stock Award or a Performance Cash Award. Performance Periods may be of varying and overlapping duration, at the sole discretion of the Board.

(ii) “**Performance Stock Award**” means a Stock Award granted under the terms and conditions of Section 6(c)(i).

(jj) “**Plan**” means this Isis Pharmaceuticals, Inc. 2011 Equity Incentive Plan.

(kk) “**Restricted Stock Award**” means an award of shares of Common Stock which is granted pursuant to the terms and conditions of Section 6(a).

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

(mm) “**Restricted Stock Unit Award**” means a right to receive shares of Common Stock which is granted pursuant to the terms and conditions of Section 6(b).

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

(oo) “**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.

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

(qq) “**Stock Appreciation Right**” or “**SAR**” means a right to receive the appreciation on Common Stock that is granted pursuant to the terms and conditions of Section 5.

(rr) “**Stock Appreciation Right Agreement**” means a written agreement between the Company and a holder of a Stock Appreciation Right evidencing the terms and conditions of a Stock Appreciation Right grant. Each Stock Appreciation Right Agreement shall be subject to the terms and conditions of the Plan.

(ss) “**Stock Award**” means any right to receive Common Stock granted under the Plan, including an Option, a Restricted Stock Award, a Restricted Stock Unit Award, a Stock Appreciation Right, or a Performance Stock Award.

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

(uu) “**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, limited liability company or other entity 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%.

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

**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 cut-off date or meeting date. Have your proxy card in hand when you access the web site and follow the instructions to obtain your records and to create an electronic voting instruction form.

**ELECTRONIC DELIVERY OF FUTURE PROXY MATERIALS**

If you would like to reduce the costs incurred by our company in mailing proxy materials, you can consent to receiving all future proxy statements, proxy cards and annual reports electronically via e-mail or the Internet. To sign up for electronic delivery, please follow the instructions above to vote using the Internet and, when prompted, indicate that you agree to receive or access proxy materials electronically in future years.

**VOTE BY PHONE - 1-800-690-6903**

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

**VOTE BY MAIL**

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

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

M35755-P04756

KEEP THIS PORTION FOR YOUR RECORDS

THIS PROXY CARD IS VALID ONLY WHEN SIGNED AND DATED.

DETACH AND RETURN THIS PORTION ONLY

|   |   |                              |                          |  |   |   |
|---|---|------------------------------|--------------------------|--|---|---|
| <b>ISIS PHARMACEUTICALS, INC.</b>   |   | <b>For All</b>               | <b>Withhold All</b>      | <b>For All Except</b>                            | To withhold authority to vote for any individual nominee(s), mark "For All Except" and write the number(s) of the nominee(s) on the line below. |   |
| <b>The Board of Directors recommends you vote FOR Proposals 1, 2 and 3:</b> |   |                              |                          |  |   |   |
| 1.  | Election of Directors   | <input type="checkbox"/>     | <input type="checkbox"/> | <input type="checkbox"/>                         | _____   |   |
|   | <b>Nominees:</b>  |                              |                          |  |   |   |
|   | To be elected for terms expiring in 2014:   |                              |                          |  |   |   |
|   | 01) Spencer R. Berthelsen   |                              |                          |  |   |   |
|   | 02) B. Lynne Parshall   |                              |                          |  |   |   |
|   | 03) Joseph H. Wender  |                              |                          |  |   |   |
|   |   |                              |                          |  |   | <b>For Against Abstain</b>  |
| 2.  | To approve the Isis Pharmaceuticals, Inc. 2011 Equity Incentive Plan.   |                              |                          |  |   | <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>                          |
| 3.  | To approve, by non-binding vote, executive compensation.  |                              |                          |  |   | <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>                          |
|   | <b>The Board of Directors recommends you vote for 1 year:</b>   |                              |                          |  |   | <b>1 Year 2 Years 3 Years Abstain</b>   |
| 4.  | To recommend, by non-binding vote, the frequency of executive compensation votes.   |                              |                          |  |   | <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> |
|   | <b>The Board of Directors recommends you vote FOR Proposal 5:</b>   |                              |                          |  |   | <b>For Against Abstain</b>  |
| 5.  | Ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for the 2011 fiscal year.   |                              |                          |  |   | <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>                          |
|   | <b>NOTE:</b> Such other business that may be properly presented at the meeting or any adjournment thereof.  |                              |                          |  |   |   |
|   | <b>NOTE:</b> Please sign as the name appears hereon. Joint owners should each sign. When signing as attorney, executor, administrator, trustee or guardian, please give full title as such. |                              |                          |  |   |   |
| <input type="text"/><br>Signature [PLEASE SIGN WITHIN BOX]                  |   | <input type="text"/><br>Date |                          | <input type="text"/><br>Signature (Joint Owners) |   | <input type="text"/><br>Date  |

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

The Notice and Proxy Statement and Annual Report are available at [www.proxyvote.com](http://www.proxyvote.com).

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**PROXY**

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

The undersigned hereby appoints B. Lynne Parshall and Stanley T. Crooke, and each of them, with power to act without the other and with power of substitution, as proxies and attorneys-in-fact and hereby authorizes them to represent and vote, as provided on the other side, all the shares of Isis Pharmaceuticals, Inc. Common Stock which the undersigned is entitled to vote and, in their discretion, to vote upon such other business as may properly come before the Annual Meeting of Stockholders of the Company to be held June 16, 2011 or any adjournment thereof, with all powers which the undersigned would possess if present at the Meeting.

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

**(Continued and to be marked, dated and signed, on the other side)**