

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

**SCHEDULE 14A INFORMATION**

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

Filed by the Registrant  x

Filed by a Party other than the Registrant  o

Check the appropriate box:

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

Isis Pharmaceuticals, Inc.

(Name of Registrant as Specified In Its Charter)

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

Payment of Filing Fee (Check the appropriate box):

- x No fee required.
- o Fee computed on table below per Exchange Act Rules 14a-6(i)(1) and 0-11.
  - (1) Title of each class of securities to which transaction applies:  
\_\_\_\_\_
  - (2) Aggregate number of securities to which transaction applies:  
\_\_\_\_\_
  - (3) Per unit price or other underlying value of transaction computed pursuant to Exchange Act Rule 0-11 (set forth the amount on which the filing fee is calculated and state how it was determined):  
\_\_\_\_\_
  - (4) Proposed maximum aggregate value of transaction:  
\_\_\_\_\_
  - (5) Total fee paid:  
\_\_\_\_\_
- o Fee paid previously with preliminary materials.
- o Check box if any part of the fee is offset as provided by Exchange Act Rule 0-11(a)(2) and identify the filing for which the offsetting fee was paid previously. Identify the previous filing by registration statement number, or the Form or Schedule and the date of its filing.
  - (1) Amount Previously Paid:  
\_\_\_\_\_
  - (2) Form, Schedule or Registration Statement No.:  
\_\_\_\_\_
  - (3) Filing Party:  
\_\_\_\_\_
  - (4) Date Filed:  
\_\_\_\_\_

April 20, 2010

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

**NOTICE OF**  
**2010 ANNUAL MEETING OF STOCKHOLDERS**  
**AND PROXY STATEMENT**

Dear Stockholders,

I am pleased to invite you to Isis Pharmaceuticals' 2010 Annual Meeting of Stockholders. We will host the meeting at our offices in Carlsbad, California on Wednesday, June 2, 2010 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 2010, 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 (the "SEC"). As a result, you will receive in the mail a notice regarding the availability of proxy materials. This notice is important because it contains a control number and instructions that will allow you to access our proxy materials and vote electronically by the Internet or request printed proxy materials so you may vote by telephone or mail.

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

If you plan to attend the meeting and prefer to vote in person, you may still do so even if you have already returned your proxy. If you are unable to attend, please note that a webcast of the presentation will be available at [www.isispharm.com](http://www.isispharm.com).<sup>(1)</sup> In this document, the words "Isis," "we," "our" and "us" refer only to Isis Pharmaceuticals, Inc. and its subsidiaries, including Regulus Therapeutics Inc., and not any other person or entity.

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

We look forward to seeing you at the meeting.

Sincerely,

B. Lynne Parshall  
Secretary

---

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

---

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

**NOTICE OF 2010 ANNUAL MEETING OF STOCKHOLDERS**

Date: Wednesday, June 2, 2010

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

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

Dear Stockholders,

At our 2010 Annual Meeting, we will ask you to:

- elect Stanley T. Crooke, Joseph Klein, III and John C. Reed to serve as a Director for a three-year term;
- approve an amendment to the 2002 Non-Employee Directors' Stock Option Plan to increase the shares reserved for issuance from 850,000 shares to 1,000,000 shares and to extend the term from May 30, 2012 to June 1, 2020;
- approve an increase in shares reserved for issuance under the 1989 Stock Option Plan from 16,700,000 shares to 20,000,000 shares;
- ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2010 fiscal year; and
- transact any other business that may be properly presented at the Annual Meeting.

The foregoing items of business are more fully described in the enclosed Proxy Statement.

If you were an Isis stockholder of record at the close of business on April 6, 2010 you may vote at the Annual Meeting.

By order of the Board of Directors,

B. Lynne Parshall  
Secretary

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

---

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

**PROXY STATEMENT**

**INFORMATION ABOUT THE 2010 ANNUAL MEETING AND VOTING**

**General**

The enclosed proxy materials have been provided to you by the Board of Directors of Isis Pharmaceuticals, Inc., a Delaware corporation, for use at the 2010 Annual Meeting of Stockholders to be held on Wednesday, June 2, 2010, at 2:00 p.m. Pacific Time, or at any adjournment or postponement of the meeting, for the purposes stated in this document. The Annual Meeting will be held at Isis' offices at 1896 Rutherford Road, Carlsbad, California 92008. This Proxy Statement summarizes the information you will need to vote in an informed manner.

**Important Notice Regarding the Availability of Proxy Materials for the Annual Meeting of Stockholders to be held on June 2, 2010.**

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

This Proxy Statement and the accompanying Annual Report are available at [www.proxyvote.com](http://www.proxyvote.com) where you may vote your shares.

Among other things, the Proxy Statement contains information regarding:

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

**Electronic Delivery of Isis Pharmaceuticals, Inc. Stockholder Communications**

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

- delivering the Proxy Statement, Annual Report and related materials by email to our stockholders;
- stockholder voting 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).

**Voting Rights, Outstanding Shares and Quorum**

We will make this Proxy Statement and the accompanying proxy card available on or about April 20, 2010 to all stockholders who are entitled to vote. Only stockholders who owned our common stock at the close of business on April 6, 2010 are entitled to vote at the Annual Meeting. On this record date, we had 99,079,656 shares of our common stock outstanding.

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

Each share of our common stock that you own entitles you to one vote. Your notice of availability of proxy materials and proxy card indicates the number of shares of our common stock that you owned at the close of business on April 6, 2010. The inspector of election will count votes for the meeting, and will separately count "For" and "Against" votes, abstentions and broker non-votes. With respect to the election of Directors, stockholders do not affirmatively vote "Against" Directors. Instead, if you do not want to elect a particular Director, you may simply withhold your "For" vote. The inspector of elections will count abstentions towards the vote total for each proposal, and abstentions will have the same effect as "Against" votes. Broker non-votes have no effect and the inspector of elections will not count them towards the vote total for any proposal.

If your broker holds your shares as your nominee, that is, in "street name," you will need to obtain a proxy form from the institution that holds your shares and follow the instructions included on that form regarding how to instruct your broker to vote your shares. If you do not give instructions to your broker, your broker can vote your shares with respect to "discretionary" items, but not with respect to "non-discretionary" items. Discretionary items are proposals considered routine under the rules of the New York Stock Exchange on which a broker may vote shares held in street name in the absence of your voting instructions. The proposal to ratify Ernst & Young LLP as independent auditors is a discretionary item. Proposal 1, Proposal 2 and Proposal 3 regarding the election of Directors and our stock option plans 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.

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 2010 Annual Meeting and vote in person.

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

We will announce preliminary voting results at the Annual Meeting. 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.

## **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 Shareholder Communications Inc. its customary fee, estimated to be about \$12,000, for rendering solicitation services.

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

If you plan to submit your vote by phone or through the Internet we must receive it by 11:59 p.m., Eastern Time, on June 1, 2010. Submitting your proxy by phone or through the Internet will not affect your right to vote in person should you decide to attend the Annual Meeting.

We provide Internet proxy voting to allow you to vote your shares online, with procedures designed to ensure the authenticity and correctness of your proxy vote instructions. However, please be aware that you must bear any costs associated with your Internet access, such as usage charges from Internet access providers or telephone companies.

### ***For Shares Registered in Your Name***

If you are a stockholder of record, you may go to [www.proxyvote.com](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.

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

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

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

A number of brokers and banks are participating in a program provided by Broadridge Financial Solutions, Inc. which allows proxies to vote shares by means of the telephone and Internet. If your shares are held in an account with a broker or bank participating in the Broadridge program, you may vote your shares by phone or through the Internet by having the voting form in hand and calling the number or going to the website indicated on the form and following the instructions.

A broker non-vote occurs when a broker, bank or other stockholder of record, in nominee name or otherwise, exercising fiduciary powers (typically referred to as being held in "street name") submits a proxy for the Annual Meeting, but does not vote on a particular proposal because that holder does not have discretionary voting power with respect to that proposal and has not received voting instructions from the beneficial owner. Abstentions and broker non-votes have no effect on the determination of whether a nominee or the proposal has received the vote of a majority of the shares of common stock present or represented by proxy and voting at the Annual Meeting. Under the rules that govern brokers who are voting with respect to shares held in street name, brokers have the discretion to vote those shares on routine matters, but not on non-routine matters. Routine matters include ratification of independent public accountants. Non-routine matters include the election of directors and actions on stock plans.

### **Revocability of Proxies**

Once you have submitted your proxy by mail, Internet or telephone, you may revoke it at any time before we exercise it at the Annual Meeting. You may revoke your proxy by any one of the following four ways:

- you may mail another proxy marked with a later date;
- you may revoke it through the Internet;
- you may notify our Secretary in writing that you wish to revoke your proxy before the Annual Meeting takes place; or
- you may vote in person at the Annual Meeting. *Attendance* at the meeting *will not*, by itself, revoke a proxy.

3

---

### **Stockholder Proposals**

If you have a proposal or Director nomination that you would like us to include in our Proxy Statement and form of proxy for, or to present at the 2011 Annual Meeting of Stockholders, you must send the proposal to us by no later than December 21, 2010. Stockholders wishing to submit proposals or Director nominations that are not to be included in such Proxy Statement and proxy must do so no later than the close of business on February 2, 2011. Stockholders should also review our Bylaws, which contain additional requirements with respect to advance notice of stockholder proposals and Director nominations.

4

---

## **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 has been appointed by the Board. As a result, whenever the Board appoints a new member, the Board will submit such new member's directorship for approval at the next regularly scheduled Annual Meeting of Stockholders. If elected by the stockholders, the Board member will serve the remaining term of the class of Directors to which he or she was elected.

The Board represents the interests of our stockholders by overseeing the Chief Executive Officer and other members of senior management in 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 2010 Elections**

The Board has nominated three Directors for election at the 2010 Annual Meeting. Each of the nominees currently serves as one of our Directors. Drs. Crooke, Reed and Mr. Klein have served as a Director since: January 1989 and Chairman of the Board since February 1991; February 2002; and December 2005, respectively, and have been re-elected by our stockholders each successive term. If re-elected, Drs. Crooke, Reed and Mr. Klein will serve until the 2013 Annual Meeting or, in each case, until his successor is elected and has qualified, or until his death, resignation or removal.

Our stockholders elect Directors by a plurality of the votes of the shares represented in person or by proxy at the meeting and entitled to vote in the election of Directors. As a result, the 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 February 26, 2010. Following that report, the Board determined it would be in the best interests of Isis and its stockholders to nominate Stanley T. Crooke, John C. Reed and Joseph Klein, III 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 will be unable to

---

### **Biographies of Nominees for Election for a Three-year Term Expiring at the 2013 Annual Meeting**

**Stanley T. Crooke**, M.D., Ph.D., age 65, 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, and EPIX Pharmaceuticals, Inc., a developer of magnetic resonance imaging contrast agents.

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 49, has served as a Director of Isis since December 2005. Mr. Klein is currently Managing Director of Gauss Capital Advisors, LLC, a financial consulting and investment advisory firm focused on biopharmaceuticals, which he founded in March 1998. From September 2003 to December 2008, Mr. Klein also served as a Venture Partner of Red Abbey Venture Partners, L.P., a life science private equity fund. From September 2001 to September 2002, Mr. Klein was a Venture Partner of MPM Capital, a healthcare venture capital firm. From June 1999 to September 2000 when it merged with WebMD Corporation, Mr. Klein served as Vice President, Strategy, for Medical Manager Corporation, a leading developer of physician office management information systems. For over nine years from 1989 to 1998, Mr. Klein was a health care investment analyst at T. Rowe Price Associates, Inc., where he was the founding portfolio manager of the T. Rowe Price Health Sciences Fund, Inc. Mr. Klein serves on the board of directors of three other publicly-traded biotechnology companies: OSI Pharmaceuticals, Inc. since July 2006; PDL BioPharma, Inc. since July 2007; and Savient Pharmaceuticals, Inc. since May 2006. Mr. Klein serves on the board of directors of The Prospector Funds, Inc., an SEC Registered Investment Company that manages two no-load mutual funds. Mr. Klein also serves on the boards of private and non-profit entities. Within the last five years, Mr. Klein formerly served on the board of directors of five publicly held biotechnology companies: BioMarin Pharmaceutical Inc., Clinical Data, Inc., Genaisance Pharmaceuticals, Inc., Guilford Pharmaceuticals, Inc., and NPS Pharmaceuticals, Inc.

The Board believes that Mr. Klein is uniquely suited to serve on the Board and the Audit Committee because he is a Chartered Financial Analyst (CFA), and because he has extensive venture capital, Board and financial advisory experience in the life sciences industry.

**John C. Reed**, M.D., Ph.D., age 51, has served as a Director of Isis since February 2002. Dr. Reed has been the President and Chief Executive Officer of Sanford-Burnham Medical Research Institute, an independent, nonprofit, public benefit organization dedicated to basic biomedical research, since January 2002. Dr. Reed has been with Sanford-Burnham Medical Research Institute for the past sixteen years, serving as the Deputy Director of the Cancer Center beginning in 1994, as Scientific Director of the Institute beginning in 1995, and as Cancer Center Director in 2002. He also currently serves as an adjunct professor in the medical schools at University of California San Diego School of Medicine and San Diego State University's Biology department. Dr. Reed was recognized as the world's most highly cited scientist in the field of cell biology for the decade 1995-2005. He is the author of over 725 scientific and medical journal publications. 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 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 Medical 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.

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

### **Biographies of Directors Whose Terms Expire at the 2011 Annual Meeting**

**Spencer R. Berthelsen**, M.D., age 58, 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.

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 55, has served as a Director of Isis since September 2000. She has been our Chief Operating Officer since December 2007 and previously served as our Executive Vice President since December 1995. She has served as our Chief Financial Officer since June 1994, and our Secretary since November 1991. From February 1993 to December 1995, she was a Senior Vice President of Isis, and from November 1991 to February 1993, she was a Vice President of Isis. Prior to joining Isis, Ms. Parshall practiced law at Cooley Godward LLP (now Cooley Godward Kronish LLP), outside counsel to Isis, where she was a partner from 1986 to 1991. Ms. Parshall is a member of the American, California and San Diego bar associations. 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 65, has served as a Director of Isis since January 1994. Mr. Wender began with Goldman, Sachs & Co. in 1971 and became a General Partner of that firm in 1982, where he headed the Financial Institutions Group for over a decade. Mr. Wender worked at GSC Group from 2005 through 2007 where he was a Senior Managing Director, member of the Management Committee, and Chairman of the Finance Committee. Since January 2008, he has been a Senior Consultant to Goldman Sachs & Co. He is also an Independent Trustee of the Schwab Family of Funds. Within the last five years, Mr. Wender formerly served on the Board of First Coastal Bancshares, a bank holding company, Neurome, a biopharmaceutical company, and Chairman of GSC Capital Corporation, a Real Estate Investment Trust (REIT).

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.

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

**Richard D. DiMarchi**, Ph.D., age 57, has served as a Director of Isis since December 2004. Dr. DiMarchi has been a Professor and the Jack and Linda Gill Distinguished Chair in Biomolecular Science at Indiana University, Bloomington, Indiana since August 2003. He previously served as Chairman of the Chemistry Department, and is a co-founder of Marcadia Biotech and Ambrx, Inc., privately held biotechnology companies. Prior to joining Indiana University, Dr. DiMarchi worked for 22 years at Eli Lilly and Company in several senior management positions, including Group Vice President, Biotechnology and Product Development, from 1996 to 2003, and Vice President, Endocrine Research and Clinical Investigation, from 1992 to 1996.

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 56, has served as a Director of Isis since March 2001. Mr. Muto joined the law firm of Cooley Godward Kronish LLP, outside counsel to Isis, in 1980 and became a partner in 1986. He is a founding partner of Cooley Godward Kronish LLP's San Diego office and serves as the partner in charge of that office. Mr. Muto also serves on that firm's executive, management and compensation committees.

The 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.

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

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

Consistent with these considerations, after review of all relevant transactions or relationships between each Director, or any of his or her family members, and Isis, its senior management and its independent auditors, the Board affirmatively has determined that all of our Directors are independent Directors within the meaning of the applicable Nasdaq listing standards, except for Dr. Crooke and Ms. Parshall, our Chief Executive Officer and Chief Operating Officer, respectively. In making this determination, the Board found that none of these Directors or nominees for Director had a material or other disqualifying relationship with us. With respect to Mr. Muto who is a partner of Cooley Godward Kronish LLP, our outside legal counsel, and Dr. DiMarchi who had a consulting agreement with us that was terminated in 2008, each is independent for purposes other than serving on the Audit Committee, of which neither is a member.

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

##### *Board Committees and Leadership Structure*

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

- meets the applicable rules and regulations regarding "independence," including, but not limited to, Rule 5605(a)(2) of the Nasdaq listing standards;
- 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 20 years) 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 the execution of 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 "lead independent director." Instead the Chairpersons of the Audit Committee, the Compensation Committee, and the Nominating, Governance and Review Committee each preside over at least one executive session. The Board believes the combined role of Chairman and CEO, together with the executive sessions described above, is in the best interest of stockholders because it provides the appropriate balance between strategy development and independent oversight of 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 10 and 11. While each committee is responsible for evaluating certain risks and overseeing the management of such risks, the entire Board of Directors is regularly informed 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 of Directors met five times in 2009, all regularly scheduled meetings. During 2009, all Directors attended 100% of the aggregate of the meetings of the Board and the committees on which they served, held during the period for which he or she was a Director or committee member. We encourage each member of the Board to attend the Annual Meeting of Stockholders. Last year, Dr. Berthelsen, Dr. Crooke, Mr. Klein, Mr. Muto, Dr. Reed and Ms. Parshall attended our 2009 Annual Meeting of Stockholders.

#### **Board Committee Members**

The table below provides membership and meeting information for fiscal 2009 for each of the Board committees and identifies our current Board and Committee members.

<u>Name</u>	<u>Audit</u>	<u>Compensation</u>	<u>Nominating, Governance and Review</u>
Dr. Spencer R. Berthelsen	X	X*	X*
Dr. Stanley T. Crooke	—	—	—
Dr. Richard D. DiMarchi	—	X	—
Mr. Joseph Klein	X	—	—
Mr. Frederick T. Muto(1)	—	—	—
Ms. B. Lynne Parshall	—	—	—
Dr. John C. Reed	—	X	X
Mr. Joseph H. Wender	X*	—	—
Total meetings in fiscal year 2009	6	2(2)	3

\* Committee Chairperson

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

(2) Acted by written consent 14 times as well. Our Compensation Committee acts by unanimous written consent each month to confirm stock options granted in connection with new hires and promotions.

#### **Audit Committee**

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

The Audit Committee:

- reviews the annual and quarterly financial statements and oversees the annual and quarterly financial reporting processes;
- selects and hires our independent auditors;
- oversees the independence of our independent auditors;
- evaluates our independent auditors' performance; and

- has the authority to hire its own outside consultants and advisors if necessary.

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

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

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

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

In addition, all Audit Committee members must be financially literate and at least one member must be a "financial expert," as defined by SEC regulations. Our Board has determined that the Audit Committee's financial expert is Mr. Wender based on, among other things, his over 35 years of experience as an investment banker with Goldman, Sachs & Co. We provide the Audit Committee with the funding it needs to perform its duties.

In 2009, the Audit Committee met six times and did not act by unanimous written consent. We have attached our Audit Committee charter to this Proxy Statement as Appendix A and you can find the charter on our corporate website at [www.isispharm.com](http://www.isispharm.com).<sup>(2)</sup> Each member meets the membership criteria set forth in the attached Audit Committee charter and as stated above.

#### **Compensation Committee**

The Compensation Committee of the Board of Directors reviews, modifies (as needed) and approves our overall compensation strategy and policies. The Compensation Committee reviews and approves corporate performance goals and objectives relevant to the compensation of our executive officers and other members of senior management; reviews and approves the compensation for our Directors and reviews and approves the compensation

---

(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.

and other terms of employment of our executive officers, including our Chief Executive Officer; evaluates risks associated with the compensation policies and assesses whether risks arising from our compensation policies and practices are reasonably likely to have a material adverse effect on us; and administers our stock option and purchase plans. We also have a Non-Management Stock Option Committee that, as delegated by the Compensation Committee, may award stock options to employees who are below director level in accordance with guidelines adopted by the Compensation Committee. The Non-Management Stock Option Committee has one member, Dr. Crooke.

The Compensation Committee met two times in 2009 and acted by unanimous written consent 14 times. You can find our Compensation Committee charter on our corporate website at [www.isispharm.com](http://www.isispharm.com).<sup>(3)</sup>

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

The charter of the Compensation Committee grants the Compensation Committee full access to all 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 compensation consultants to assist in its evaluation of executive and Director compensation, including the authority to approve the consultant's reasonable fees and other retention terms.

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

As noted above, during the fiscal year ended December 31, 2009, 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 three times during 2009. You can find our Nominating, Governance and Review Committee charter on our corporate website at [www.isispharm.com](http://www.isispharm.com)(3).

---

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

#### *Director Nominations - Quality Standards*

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

The minimum membership requirements are as follows:

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

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

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

#### *Director Nominations - Diversity Discussion*

In considering Director nominations, the Nominating Committee evaluates and considers the total mix of competencies represented on the Board as a whole, as well as the competencies each member, or nominee brings to the Board. In general, the constitution of the Board is diversified across three large categories: (1) investment banking, financial accounting and corporate governance experience; (2) medical and scientific expertise; and (3) employee 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 recommended by stockholders. The Committee does not intend to alter the manner in which it evaluates candidates, including the minimum criteria set forth above, based on whether or not a stockholder recommended the candidate.

The Committee reviews new candidates for Director in the context of the Board's composition, 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 December 21, 2010. 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. You can find our Nominating, Governance and Review Committee charter on our corporate website at [www.isispharm.com](http://www.isispharm.com)(4). 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.

---

(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.

#### **Stockholder Communications with the Board of Directors**

We make every effort to ensure that our Board or individual Directors as applicable, hear the views of stockholders, and provide appropriate responses to stockholders in a timely manner. Stockholders who wish to communicate with the Board, or individual Directors, may do so by sending written communications addressed to the Secretary of Isis at 1896 Rutherford Road, Carlsbad, CA 92008. The Secretary will compile the communications and will submit them to the Board or the individual Directors on a periodic basis. 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. These communications will be reviewed by one or more of our employees designated by the Board, who will determine whether they should be presented to the Board. The purpose of this screening is to allow the Board to avoid having to consider irrelevant or inappropriate communications, such as advertisements, solicitations and hostile communications. All communications directed to the Audit Committee in accordance with our Code of Ethics policy that relates to questionable accounting or auditing matters involving Isis will be promptly and directly forwarded to the Audit Committee. Other than the processes described above, our Board has not adopted a formal written process for stockholder communications with the Board. We believe our Board's responsiveness to stockholder communications has been excellent.

## Code of Ethics and Business Conduct

We have adopted a Code of Ethics that applies to all officers, Directors and employees. We filed the Code of Ethics as an exhibit to our Annual Report on Form 10-K for the fiscal year ended December 31, 2009 by incorporating by reference to the Current Report on Form 8-K we filed with the SEC on December 5, 2008. We also have posted our Code of Ethics on our website. If we make any substantive amendments to the Code of Ethics or grant any waiver from a provision of the Code of Ethics to any executive officer or Director, we will promptly disclose the nature of the amendment or waiver on our website at [www.isispharm.com\(5\)](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\(5\)](http://www.isispharm.com(5)).

---

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

## PROPOSAL 2

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

In this Proposal 2, we are requesting our stockholders approve an amendment to the 2002 Non-Employee Directors' Stock Option Plan (the "Directors' Plan") which the Board of Directors adopted on February 26, 2010, subject to stockholder approval. The amendment to the Directors' Plan is to:

- increase the total number of shares authorized for issuance under the Directors' Plan by 150,000 shares, from 850,000 shares to 1,000,000 shares, which will enable us to continue to grant awards to deserving individuals and remain competitive with our industry peers; and
- extend the term of the Directors' Plan from May 30, 2012 to June 1, 2020.

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

Our request to increase the authorized shares by 150,000 shares considers the following:

- If we do not increase the authorized shares at our 2010 Annual Meeting, we anticipate the share reserve balance will be 37,000 shares at the time of our 2011 annual meeting. This low balance would limit our opportunities to attract unique and highly qualified talent because it would reduce our flexibility and ability to award stock options to a new Director.
- If our stockholders approve our request for 150,000 additional shares at the 2010 Annual Meeting, we do not intend to make the next request for additional shares until the 2013 annual meeting.
- If our stockholders do not approve the extension of the Directors' Plan, the plan will terminate on May 30, 2012. If the Directors' Plan terminates without replacement, our ability to attract and retain high quality Directors will be severely harmed.

The affirmative vote of a majority of the votes cast at the Annual Meeting, at which a quorum is present, either in person or by proxy, is required to approve the proposed amendment to the Directors' Plan discussed above. If you hold your shares in your own name and abstain from voting on this matter, your abstention will have no effect on the vote. If you hold your shares through a broker and you do not instruct the broker on how to vote on this proposal, your broker will not have the authority to vote your shares. Abstentions and broker non-votes will each be counted as present for purposes of determining the presence of a quorum, but will not have any effect on the outcome of the proposal.

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

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

### Purpose

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

### Administration

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

## Stock Subject To The Directors' Plan

An aggregate of 1,000,000 shares of common stock were authorized by the Board for issuance under the Directors' Plan, subject to stockholder approval of this Proposal 2. Subject to stockholder approval of this Proposal 2, as of March 31, 2010, 277,000 shares of common stock were available for future grant under the Directors' Plan, there were options to purchase 610,000 shares of common stock issued and outstanding under the Directors' Plan and Directors had exercised options to purchase 113,000 shares. However, on July 1, 2010, we expect to grant options to purchase a total of 90,000 shares under the Directors' Plan, which would leave only 37,000 shares left for future grant under the plan, if our stockholders do not approve this Proposal.

On March 31, 2010 the last reported sales price of our common stock on the Nasdaq Global Select Market was \$10.93 per share.

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

## Eligibility, Option Grants

The Directors' Plan provides that we may only grant options to a non-employee Director. A "non-employee Director" is defined in the Directors' Plan as a Director of Isis or one of our affiliates who is not otherwise an employee of Isis or any affiliate. Six of our eight current Directors, all except Dr. Crooke and Ms. Parshall, are eligible to participate in the Directors' Plan.

Options granted under the Directors' Plan are nonstatutory stock options, meaning they are not intended to qualify as incentive stock options within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended (the "Code"). Option grants under the Directors' Plan are non-discretionary. The Directors' Plan provides for (i) an initial grant of an option to purchase 30,000 shares of common stock to each person when he or she first becomes a non-employee Director of Isis, and (ii) an annual grant, on July 1, or the next business day should such date be a Saturday, Sunday or holiday, of an option to purchase 15,000 shares of common stock to each non-employee Director.

## Terms of Options

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

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

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

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

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

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

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

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

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

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

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

### **Adjustment Provisions**

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

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

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

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

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

### **Option Repricing Prohibited**

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

### **Duration, Amendment and Termination**

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

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

### **Federal Income Tax Information**

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

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

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

---

### New Plan Benefits Table

The following table presents certain information with respect to options we expect to grant under the Directors' Plan for services rendered during the fiscal year ending December 31, 2010 to our non-employee Directors, assuming stockholder approval of this Proposal 2. This table assumes that each non-employee Director continues as one of our Directors throughout the year and that we do not elect any additional non-employee Directors. This information is for illustration only and may not be indicative of grants that are made in the future under the Directors' Plan.

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

<u>Name of Non-Employee Director</u>	<u>Number of Option Shares</u>
Spencer R. Berthelsen	15,000
Richard D. DiMarchi	15,000
Joseph Klein, III	15,000
Frederick T. Muto	15,000
John C. Reed	15,000
Joseph H. Wender	15,000
<b>Non-Employee Directors as a Group</b>	<b>90,000</b>

---

### PROPOSAL 3

#### AMENDMENT OF THE 1989 STOCK OPTION PLAN TO INCREASE SHARES

In June 1989, our Board of Directors adopted, and our stockholders subsequently approved, our 1989 Stock Option Plan (the "1989 Plan").

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

- Has a term ending on January 31, 2014;
- Prohibits the repricing of any option outstanding under the 1989 Plan unless approved by our stockholders;
- Is limited to the grant of options and does not authorize stock bonuses or restricted stock awards;
- Limits the term of each newly granted option to 7 years;
- Requires that each newly granted option not become fully vested until a date at least two years after the date of grant, except in the case of certain corporate events;
- Limits our ability to accelerate the vesting of stock options to the death, disability, or retirement of the optionee, or a change of control;
- Requires all options outstanding under the 1989 Plan to have an exercise price of not less than 100% of the fair market value of our common stock on the date of grant;
- Is administered by our Compensation Committee, which is composed entirely of independent Directors; and
- Requires that the exercise price for options outstanding under the 1989 Plan can only be paid in cash.

Our management, Board and Compensation Committee believe that stock options are a key aspect of our ability to attract and retain qualified personnel in the face of intense competition for experienced scientists and other personnel among many pharmaceutical and health care companies. The Board, upon the recommendation of the Compensation Committee, has approved an increase in the aggregate number of shares of common stock authorized for issuance under the 1989 Plan by 3,300,000 shares to an aggregate of 20,000,000 shares, in order to ensure that for a period of at least three years, based on our business plans, we can continue to grant stock options to employees and consultants at appropriate levels as determined by the Compensation Committee. If our stockholders do not approve this Proposal 3, and as a consequence, we cannot continue to grant options at competitive levels, we believe that it will negatively affect our ability to meet our needs for highly qualified personnel and our ability to manage future growth. Without these additional shares, management expects that the current shares available for grant under the 1989 Plan will not be sufficient to maintain our option grant practices for new employees or for promotions or merit awards for current employees after January 2011.

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

Subject to stockholder approval of this Proposal 3, a total of 20,000,000 shares are authorized for issuance under the 1989 Plan. As of March 31, 2010, a total of 6,371,807 options were granted and outstanding, 3,494,772 of which were vested and exercisable; and options to purchase a total of 8,623,092 shares

### **Required Vote and Board of Directors Recommendation**

The affirmative vote of the holders of a majority of the shares present in person or represented by proxy and entitled to vote at the 2010 Annual Meeting will be required to approve the amendment to the 1989 Plan.

Should we not obtain stockholder approval, then we will not implement the increase in the aggregate number of shares of common stock authorized for issuance under the 1989 Plan, and no additional stock options will be granted on the basis of such increase. However, the 1989 Plan will remain in effect, and we may continue to make stock option grants and other awards pursuant to the current provisions of the 1989 Plan until we deplete the share reserve.

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

**THEREFORE, THE BOARD UNANIMOUSLY RECOMMENDS A VOTE “FOR” APPROVAL OF THE AMENDMENT TO THE 1989 PLAN TO INCREASE THE SHARES AUTHORIZED FOR ISSUANCE UNDER THE 1989 PLAN FROM 16,700,000 SHARES TO 20,000,000 SHARES.**

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

### **Purpose**

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

Under the 1989 Plan, we cannot grant stock bonuses and restricted stock awards. We have not granted these types of awards in the past.

### **Administration**

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

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

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

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

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

### **Eligibility**

We may only grant incentive stock options under the 1989 Plan to our key employees, including officers. In addition, key employees, including officers, Directors and consultants are eligible to receive supplemental or nonstatutory options. As of March 31, 2010, we had approximately 300 employees and eight Directors who were eligible to receive options under the 1989 Plan.

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

### **Stock Subject to the 1989 Plan**

Subject to stockholder approval of this Proposal 3, a total of 20,000,000 shares of our Common Stock are authorized for issuance under the 1989 Plan. If Options granted under the 1989 Plan expire or otherwise terminate without being exercised, the common stock not purchased pursuant to such Options again becomes available for issuance under the 1989 Plan.

### **Option Budget and Potential Dilution**

Each year the Compensation Committee approves a budget that sets the number of stock options we can grant to our employees for that year. We do not grant options that exceed the budget without the Compensation Committee's approval. The options we grant in any year primarily represent options for new hires and annual merit grants for our existing employees. Over the past five years, the average option budget set by the Compensation Committee has been 1.6% of our outstanding common stock on an issued and outstanding basis. The option budget is a "net" budget, which means that if options expire or otherwise terminate without being exercised, the common stock not purchased pursuant to such options is added to the budget. Since cancelled or terminated options already counted against the budget for the year in which we granted such options, it makes sense to add them to the current budget to avoid double counting. We believe the option budget is an important tool to balance our equity compensation objectives with stockholder interests. Since the option budget has historically been 1.6% of our outstanding common stock on an issued and outstanding basis, we believe we have administered our stock option plans in a way that minimizes the potential dilution to our stockholders.

### **Terms of Options**

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

*Exercise Price; Payment.* The exercise price of Options under the 1989 Plan may not be less than the fair market value of the common stock subject to the Option on the date of the option grant, and in some cases may not be less than 110% of such fair market value (see "Eligibility" above). At March 31, 2010, the closing price of our common stock as reported on the Nasdaq Global Select Market was \$10.93 per share.

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

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

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

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

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

### **Prohibition of Option Repricing**

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

### **Adjustment Provisions**

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

### **Effect of Certain Corporate Events**

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

### **Duration, Amendment and Termination**

The Compensation Committee may suspend or terminate the 1989 Plan without stockholder approval or ratification at any time or from time to time. Unless sooner terminated, the 1989 Plan will terminate on January 31, 2014.

The Compensation Committee may also amend the 1989 Plan at any time or from time to time. However, no amendment will be effective unless approved by our stockholders within 12 months before or after its adoption by the Compensation Committee if such amendment (i) increases the maximum

## No Evergreen

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

## Federal Income Tax Information

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

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

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

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

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

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

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

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

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

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

## New Plan Benefits

The following table presents certain information with respect to merit-based options granted during the fiscal year ended December 31, 2009 to (i) each executive officer named in the Summary Compensation Table under “Executive Compensation—Compensation of Executive Officers”, (ii) all executive

officers as a group, (iii) all non-employee Directors as a group, and (iv) all non-executive officer employees as a group. This information regarding grants for the fiscal year ended December 31, 2009 is for illustration only and may not be indicative of grants that are made in the future under the 1989 Plan.

**NEW PLAN BENEFITS**  
**1989 STOCK OPTION PLAN**

Name and Position	Number of Shares Underlying Options
Stanley T. Crooke Chairman, Chief Executive Officer and President	150,000
B. Lynne Parshall Director, Chief Operating Officer & Chief Financial Officer	78,229
C. Frank Bennett Senior Vice President, Antisense Research	32,909
Richard S. Geary Senior Vice President, Development	28,960
All Executive Officers as a Group	290,098
All Non-Employee Directors as a Group	0
All Non-Executive Officer Employees as a Group	1,594,022

26

**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, 2009.

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)	5,586,426	\$ 10.43	3,371,058(c)
Equity compensation plans not approved by stockholders(b)	3,046,910	\$ 13.62	5,566
Total	<u>8,633,336</u>	\$ 11.56	<u>3,376,624</u>

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

(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, 98,769 remained available for purchase under the Employee Stock Purchase Plan as of December 31, 2009. The Employee Stock Purchase Plan 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 (Expired on January 5, 2010)**

We adopted the 2000 Broad-Based Equity Incentive Plan, or the 2000 Plan, to provide our employees, officers, Directors and consultants an opportunity to benefit from increases in the value of our common stock through the granting of non-statutory stock options, stock bonuses and rights to purchase restricted stock. At the time we adopted the 2000 Plan, we were not required to seek the approval of our stockholders. The Board delegated administration of the 2000 Plan to the Compensation Committee of the Board, and the Compensation Committee delegated administration of the 2000 Plan to the Non-Management Stock Option Committee with respect to certain option grants to employees who do not have a position at the level of director or above. The Board has the power to construe and interpret the 2000 Plan and, subject to the provisions of the 2000 Plan, to select the persons who receive stock awards, designate the number of shares covered by each stock award, establish vesting schedules, and specify the exercise price and the type of consideration we will receive upon exercise or purchase.

As of December 31, 2009, the 2000 Plan had 5,990,000 shares authorized for issuance, options to purchase an aggregate of 3,046,910 shares had been granted and were outstanding under the 2000 Plan, options to purchase an aggregate of 2,937,524 shares had been exercised under the 2000 Plan, and 5,566 shares remained available for grant thereunder. The 2000 Plan expired on January 5, 2010, so we may no longer grant new options under the 2000 Plan.

Options granted under the 2000 Plan generally have a term of seven or ten years, have an exercise price equal to the fair market value at the time of grant, can only be exercised with a cash payment and vest at the rate of 25 percent per year after the first year and then at the rate of 2.08 percent per month thereafter during the option holder's employment or service as a consultant, employee or director. If any change is made in the common stock subject to the 2000 Plan, or subject to any stock award, without the receipt of consideration by us (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by us), we will adjust the 2000 Plan appropriately in the class(es) and maximum number of securities subject to the 2000 Plan, and we will adjust the outstanding stock awards appropriately in the class(es) and number of

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

## **PROPOSAL 4**

### **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 2010 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 2010 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 2010 Annual Meeting will be required to ratify the selection of Ernst & Young LLP.

As of December 31, 2009, 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, 2009 and 2008, 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 \$513,000 and \$506,000, respectively. In addition, Ernst & Young LLP billed us \$28,000 and \$44,000 in 2009 and 2008, respectively, primarily related to accounting consultations for implementing new accounting standards. Furthermore, in 2009 and 2008, Ernst & Young LLP billed us \$86,000 and \$93,000, respectively, for the audit of our subsidiary, Regulus Therapeutics Inc.

#### **Audit Related Fees:**

For the years ended December 31, 2009 and 2008, 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.

#### **Tax Fees:**

For the years ended December 31, 2009 and 2008, there were no tax fees billed by Ernst & Young LLP for tax related matters that were not part of the integrated audit fees. In 2009 and 2008, 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, 2009 and 2008, there were no fees billed by Ernst & Young LLP for information technology consulting.

**All Other Fees:**

During the fiscal years ended December 31, 2009 and 2008, 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, 2009, none of the total hours expended on our financial audit by Ernst & Young LLP were provided by persons other than Ernst & Young LLP’s full-time permanent employees.

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

**SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT**

This table outlines the ownership of our common stock as of March 31, 2010 by:

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

Beneficial Owner	Beneficial Ownership (1)	
	Number of Shares	Percent of Total (2)
FMR LLC (3) 82 Devonshire Street Boston, MA 02109	14,757,143	14.9
BlackRock, Inc. (4) 40 East 52 <sup>nd</sup> Street New York, NY 10022	5,559,341	5.6
Genzyme Corporation (5) 500 Kendall Street Cambridge, MA 02142	5,000,000	5.1
Spencer R. Berthelsen (6)	108,745	*
Stanley T. Crooke (7)	1,659,358	1.7
Richard D. DiMarchi (8)	49,375	*
Joseph Klein, III (9)	47,475	*
Frederick T. Muto (10)	82,875	*
B. Lynne Parshall (11)	357,162	*
John C. Reed (12)	89,375	*
Joseph H. Wender (13)	108,375	*
C. Frank Bennett (14)	185,889	*
Richard S. Geary (15)	90,567	*
All Directors and executive officers as a group (ten persons)(16)	2,779,196	2.8

\*Less than one percent.

- (1) We base this table upon information supplied by officers, Directors, principal stockholders and Form 3s, Schedules 13D and 13G filed with the SEC. Unless otherwise indicated in the footnotes to this table and subject to community property laws where applicable, we believe that each of the stockholders named in this table has sole voting and investment power with respect to the shares indicated as beneficially owned.

31

---

- (2) Applicable percentages are based on 99,077,428 shares of common stock outstanding on March 31, 2010, adjusted as required by rules promulgated by the SEC.
- (3) Fidelity Management & Research Company (“Fidelity”), a wholly-owned subsidiary of FMR LLC and an investment adviser registered under Section 203 of the Investment Advisers Act of 1940, is the beneficial owner of 14,757,143 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 9,832,981 shares. Edward C. Johnson 3d and FMR LLC, through its control of Fidelity, and the funds each has sole power to dispose of the 14,757,143 shares owned by the Funds.
- (4) Represents shares of our common stock formerly beneficially owned by Barclays Global Investors (Deutschland) AG. On December 1, 2009, BlackRock completed its acquisition of Barclays Global Investors from Barclays Bank PLC.
- (5) 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.
- (6) Includes 70 shares owned by Dr. Berthelsen’s daughter for which he disclaims beneficial ownership. Includes 79,375 shares of common stock issuable upon exercise of options held by Dr. Berthelsen that are exercisable on or before May 30, 2010.
- (7) Includes 740,549 shares of common stock issuable upon exercise of options held by Dr. Crooke that are exercisable on or before May 30, 2010. Also includes 43,418 shares of common stock issuable upon exercise of options held by Rosanne Crooke, Dr. Crooke’s wife, that are exercisable on or before May 30, 2010. Dr. Crooke disclaims beneficial ownership of the shares of common stock owned and issuable upon exercise of options held by his wife.
- (8) Includes 49,375 shares of common stock issuable upon exercise of options held by Dr. DiMarchi that are exercisable on or before May 30, 2010.
- (9) Includes 39,375 shares of common stock issuable upon exercise of options held by Mr. Klein that are exercisable on or before May 30, 2010 and 100 shares of common stock indirectly beneficially owned by Mr. Klein’s son.
- (10) Includes 1,500 shares of common stock indirectly beneficially owned through the Cooley Godward Kronish LLP Salary Deferral and Profit Sharing Plan and 81,375 shares of common stock issuable upon exercise of options held by Mr. Muto that are exercisable on or before May 30, 2010.
- (11) Includes 315,177 shares of common stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before May 30, 2010, and an aggregate of 40,000 shares of common stock issuable upon exercise of options which Ms. Parshall transferred to her two daughters that are exercisable on or before May 30, 2010.
- (12) Includes 89,375 shares of common stock issuable upon exercise of options held by Dr. Reed that are exercisable on or before May 30, 2010.
- (13) Includes 67,375 shares of common stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before May 30, 2010.
- (14) Includes 184,718 shares of common stock issuable upon exercise of options held by Dr. Bennett that are exercisable on or before May 30, 2010.
- (15) Includes 88,988 shares of common stock issuable upon exercise of options held by Dr. Geary that are exercisable on or before May 30, 2010.
- (16) Includes an aggregate of 1,819,100 shares issuable upon exercise of options held by all current Directors and executive officers as a group that are exercisable on or before May 30, 2010.

32

---

### 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, 2009, all Section 16(a) filing requirements applicable to our officers, Directors and greater than ten percent beneficial owners were complied with.

33

---

## EXECUTIVE COMPENSATION

### Compensation Discussion and Analysis

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 option 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.

#### *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 2009 we had a Company objective of achieving a positive mipomersen Phase 3 HoFH trial. 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 equity compensation vests over a period of four years, with no vesting during the first year, and we set the option exercise price at the fair market value of our stock on the date of grant. This practice ensures that our 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 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 maximums. It is therefore possible that someone may be in a lower job level, but his/her salary may reach levels which exceed those of someone in a higher job level. We have chosen not to have multiple levels and salary limits because years of experience has shown us that these approaches often create unnecessary bureaucracy and a loss of talented individuals.

We determine base compensation levels throughout 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 Biotechnology Survey to obtain this information targeting the 75<sup>th</sup> percentile and companies of a similar size (150-499 employees). Examples of companies within this group are: Alnylam Pharmaceuticals, Arena Pharmaceuticals, Incyte Corporation, Medarex, Inc., and OSI Pharmaceuticals, Inc. We then look at the salary required to attract a particular candidate. The third step is to determine whether the scope of job responsibilities and internal equity warrant a given base salary.

Base salary is guaranteed to all employees as wages for hours worked. It represents consideration for the performance of job responsibilities. This portion of total cash compensation is not at risk and may increase 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. For the merit increase for all of our employees, including our executive officers, we may increase or decrease the Company-wide merit increase budget percentage depending upon the respective individual’s contribution to Isis.

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

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

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

For example, Dr. Crooke’s 2010 salary of \$710,995 was calculated as follows:

<u>2009 Base Salary</u>	(x)	<u>Merit Increase</u>	=	<u>Increase to Base Salary</u>
\$683,649	(x)	4.0%	=	\$27,346

The average merit increase for all of our other executive officers for 2010 salaries was 4.08%. The 2009 merit budget approved by the Compensation Committee for the entire Company was 4% of salaries. This was a 1.0% decrease over the 2008 merit budget of 5.0%. This decrease was driven by the general decrease we observed in the market balanced against Isis’ strong performance in 2009. 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’ outstanding accomplishments in 2009, as noted in the section entitled “Evaluation of 2009; Business Highlights” below, and competitive information on the planned merit

increases provided by other local biotech companies. Our Executive Director of Human Resources obtained planned merit increases by surveying local companies through the Biotech Employee Development Coalition and by reviewing data provided by AON's Radford Biotechnology Compensation Survey.

As part of the approval process, to ensure that the proposed merit increases are reasonable, the Compensation Committee analyzes the impact of the proposed merit increase on the CEO's salary. In 2010, Dr. Crooke's proposed new base salary of \$710,995 placed him above the 90<sup>th</sup> percentile of Radford (\$690,000); based on this information further analysis was performed. The Compensation Committee reviewed a report of peer group companies obtained by utilizing 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 between 15-26 years; 2) Biotech/Biopharmaceuticals industry; and 3) market capitalization between \$1 billion and \$5 billion, we identified eight peer group CEOs.(6) This information illustrated that Dr. Crooke's base pay was below the CEO average base salary of \$746,500 for these eight companies and, as such, the Compensation Committee believed Dr. Crooke's 4.0% 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 90<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 2009. The average tenure of our executive officers, excluding our CEO, is 17.3 years. The average tenure of our executive officers, including our CEO, is 18 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 that we award bonuses based on Isis' performance, as well as based on the individual's 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%; COO 35% and CEO 40%. An individual's Target MBO percentage does not change unless he or she changes position 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 all prior years to form a comparison for our current year's successes and/or failures.

---

(6) These companies were Cephalon, Inc., Charles River Laboratories International Inc., CV Therapeutics, Inc., Medicis Pharmaceutical Corp., Myriad Genetics, Inc., Onyx Pharmaceuticals, Inc., Regeneron Pharmaceuticals, Inc. and TECHNE Corp.

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

Once the Compensation Committee has determined all of the elements of the formula above, it applies the formula to each individual officer. For example, Dr. Crooke's cash bonus based on his, as well as Isis' performance in 2009, was calculated as follows and equaled \$361,650:

<u>Base Salary</u>	(x)	<u>Target MBO %</u>	(x)	<u>Company Success Factor</u>	(x)	<u>Individual Success Factor</u>
\$683,649	(x)	40%	(x)	115%	(x)	115%

The Compensation Committee reduced the individual success factors for Dr. Crooke and Ms. Parshall because Isis' stock price did not perform well in 2009. The average Target MBO percentage and Individual Success Factor for our other executive officers was 31% and 122%, respectively.

The Compensation Committee set the Company Success Factor for the 2009 MBO at 115% due to our strong achievements for the year, including a positive mipomersen HoFH clinical trial balanced against the performance of the stock price. The section entitled "Evaluation of 2009; Business Highlights" below provides a full review of our accomplishments. This MBO target reflects a decrease of 15 percentage points from the 2008 Company Success Factor of 130%. Although the Board did not set a specific stock price objective for the year, the Compensation Committee did note Isis' stock price did not perform well, and as such was the primary reason for the decrease in the 2009 Company Success Factor.

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 1.7 times greater than that of our other executive officers and 20.3 times that of the average cash compensation for our lowest level employees. This falls within industry standards,

RiskMetrics Group guidelines, and our philosophy. For example, RiskMetrics Group has suggested a ratio of CEO to Executive level compensation of between 2 and 5.

### *Stock Options*

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

Each year the Compensation Committee approves a budget that sets the number of stock options we can grant our employees for annual merit awards. We do not grant options that exceed this budget without the Compensation Committee's approval. Over the past five years, the average option budget set by the Compensation Committee has been approximately 1.6% 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 2009, 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.

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. 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.

38

---

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

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

### *Perquisites*

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

### *Retirement & Other Benefits*

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

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

### *Retention and Change of Control Agreements*

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

Change in Control: As part of our normal course of business, we engage in discussions with other biotechnology and pharmaceutical companies about possible collaborations, licensing and/or other ways in which the companies may work together to further our respective long-term objectives. In addition, many larger established pharmaceutical companies consider companies at similar stages of development to ours as potential acquisition targets. In certain scenarios, the potential for merger or being acquired may be in the best interests of our stockholders. As further described on page 46 of this Proxy Statement, we provide a component of severance compensation for our CEO and COO to promote their ability to act in the best interests of our stockholders even though they could be terminated as a result of the transaction.

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

### *Evaluation of 2009; Business Highlights*

2009 was a strong year for Isis. Isis successfully met its objective for mipomersen, most notably the positive Phase 3 study in HoFH patients. In addition, Isis performed very well financially, where Isis met its operating results guidance and ended 2009 with \$574.3 million of cash, cash equivalents and short-term investments significantly in excess of the \$550 million projected. However, as noted above, the Compensation Committee considered that Isis' stock price did not perform well.

39

---

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:

### Drug Development Highlights

- Mipomersen continued to advance in clinical development and move closer to the market for patients who cannot adequately control their cholesterol levels with current therapies and who need new treatment options. Isis and Genzyme reported positive data from two Phase 3 studies evaluating mipomersen in patients with FH.
- Isis reported positive Phase 2 data on ISIS 113715 in patients with type 2 diabetes on stable doses of sulfonylurea.
- Isis reported positive Phase 1 data in which ISIS-GCGRR<sub>x</sub> produced a significant improvement in glucagon-induced blood glucose levels and was well tolerated.
- In addition, Isis and its partners continued to advance the drugs in Isis' pipeline and reported encouraging clinical results in a broad range of diseases.
- Isis and its partners added four new drugs to its pipeline, including ISIS-FXIR<sub>x</sub> to treat thrombosis, ISIS-SMNR<sub>x</sub> to treat spinal muscular atrophy, or SMA, ISIS-APOCIII<sub>Rx</sub> to treat cardiovascular disease, and ACHN-490 to treat severe bacterial infections.

### Corporate Highlights

- Isis executed its business strategy by successfully selling its Ibis subsidiary to AMI.
- Isis benefited financially as its partners advanced drugs in development.
- Isis also benefited from its partnerships focused on developing and advancing certain RNA-based therapeutic technologies, receiving nearly \$13 million in total.

## Compensation of Executive Officers

The following table shows for the fiscal years ended December 31, 2009, 2008 and 2007 compensation awarded to or paid to, or earned by, our Chief Executive Officer, Chief Financial Officer and our two other most highly compensated executive officers at December 31, 2009 (the "Named Executive Officers").

In 2009, we did not grant any stock awards or non-equity incentive plan compensation and we do not currently offer pension or non-qualified deferred compensation plans.

**Summary Compensation Table for Fiscal 2009, 2008 and 2007**

Name and Principal Position	Year	Salary (\$)	Bonus(1) (\$)	Option Awards (2) (\$)	All Other Compensation(3) (\$)	Total (\$)
Stanley T. Crooke, Chairman, President, Chief Executive Officer	2009	\$ 683,649	\$ 361,650	\$ 1,069,879	\$ 13,258	\$ 2,128,436
	2008	\$ 648,009	\$ 438,054	\$ 1,401,888	\$ 12,248	\$ 2,500,199
	2007	\$ 611,329	\$ 782,501	\$ 1,098,873	\$ 11,625	\$ 2,504,328
B. Lynne Parshall Director, Chief Operating Officer, Chief Financial Officer	2009	\$ 596,613	\$ 276,157	\$ 557,971	\$ 16,567	\$ 1,447,308
	2008	\$ 529,095	\$ 334,499	\$ 914,444(4)	\$ 15,208	\$ 1,793,246
	2007	\$ 484,737	\$ 543,200	\$ 476,177	\$ 14,433	\$ 1,518,547
C. Frank Bennett Senior Vice President, Antisense Research	2009	\$ 369,250	\$ 146,500	\$ 234,725	\$ 16,226	\$ 766,701
	2008	\$ 345,873	\$ 170,625	\$ 339,995	\$ 15,136	\$ 871,629
	2007	\$ 323,959	\$ 291,563	\$ 222,214	\$ 12,359	\$ 850,095
Richard S. Geary(5) Senior Vice President, Development	2009	\$ 364,000	\$ 169,533	\$ 206,559	\$ 12,328	\$ 752,420
	2008	\$ 299,873	\$ 150,150	\$ 345,140(4)	\$ 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; i.e., we paid bonuses for 2009 in January 2010.

(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 5 of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2009 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.

(5) Because Dr. Geary was not a Named Executive Officer in 2007 and did not become an executive officer until August 2008, we are not disclosing compensation for 2007 as permitted by SEC regulations.

## Grants of Plan-Based Awards

The following table shows for the fiscal year ended December 31, 2009, certain information regarding grants of plan-based awards to the Named Executive Officers:

### Grants of Plan-Based Awards in Fiscal 2009

Name	Grant Date	All Other Option Awards: Number of Securities Underlying Options (#)	Exercise or Base Price of Option Awards (\$/Sh)	Grant Date Fair Value of Stock and Option Awards(1) (\$)
Stanley T. Crooke	1/2/09	150,000	\$ 14.47	\$ 1,069,879
B. Lynne Parshall	1/2/09	78,229	\$ 14.47	\$ 557,971
C. Frank Bennett	1/2/09	32,909	\$ 14.47	\$ 234,725
Richard S. Geary	1/2/09	28,960	\$ 14.47	\$ 206,559

(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 5 of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2009 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 2, 2009, the same date on which the committee granted stock options to our other employees.

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

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

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

The following table shows for the fiscal year ended December 31, 2009, 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, 2009. In addition, there were no stock awards outstanding for the individuals named below at December 31, 2009.

### Outstanding Option Awards At December 31, 2009

Name	Number of Securities Underlying Unexercised Options (#) Exercisable	Number of Securities Underlying Unexercised Options (#) Unexercisable	(1)Full Vest Date	Option Exercise Price (\$)	Option Expiration Date
Stanley T. Crooke	50,000	0	1/2/05	\$ 9.625	1/1/2011
	75,720	0	1/3/09	\$ 5.800	1/2/2012
	126,238	2,686	1/3/10	\$ 5.250	1/2/2013
	50,000	0	1/2/07	\$ 6.840	1/1/2013
	40,625	9,375	9/21/10	\$ 7.260	9/20/2013
	130,331	48,409	1/2/11	\$ 11.120	1/1/2014
	80,000	0	1/2/08	\$ 6.810	1/1/2014
	91,279	99,216	1/2/12	\$ 15.380	1/1/2015
	0	150,000	1/2/13	\$ 14.470	1/1/2016
B. Lynne Parshall	28,000(2)	0	1/2/05	\$ 9.625	1/1/2011
	30,263(2)	0	1/3/09	\$ 5.800	1/2/2012
	48,474(2)	1,032	1/3/10	\$ 5.250	1/2/2013
	25,000	0	1/2/07	\$ 6.840	1/1/2013
	24,375	5,625	9/21/10	\$ 7.260	9/20/2013
	38,400	0	1/2/08	\$ 6.810	1/1/2014
	56,477	20,977	1/2/11	\$ 11.120	1/1/2014
	43,853	47,667	1/2/12	\$ 15.380	1/1/2015
	9,375	20,625	9/16/12	\$ 16.450	9/15/2015
	0	78,229	1/2/13	\$ 14.470	1/1/2016
	20,000	0	1/2/05	\$ 9.625	1/1/2011

	19,000	0	1/2/06	\$	21.050	1/1/2012
	17,055	0	1/3/09	\$	5.800	1/2/2012
	11,500	0	1/2/07	\$	6.840	1/1/2013
C. Frank Bennett	19,690	632	1/3/10	\$	5.250	1/2/2013
	28,800	0	1/2/08	\$	6.810	1/1/2014
	26,356	9,789	1/2/11	\$	11.120	1/1/2014
	22,137	24,063	1/2/12	\$	15.380	1/1/2015
	0	32,909	1/2/13	\$	14.470	1/1/2016

	5,000	0	8/1/04	\$	11.563	7/31/2010
	8,480	0	1/2/05	\$	9.625	1/1/2011
	8,000	0	1/2/06	\$	21.050	1/1/2012
	5,044	0	1/3/09	\$	5.800	1/2/2012
	11,253	433	1/3/10	\$	5.250	1/2/2013
Richard S. Geary	13,885	5,157	1/2/11	\$	11.120	1/1/2014
	1,049	0	1/2/08	\$	6.810	1/1/2014
	4,791	5,209	1/1/12	\$	15.750	12/31/2014
	11,500	12,500	1/2/12	\$	15.380	1/1/2015
	3,333	6,667	8/16/12	\$	19.080	8/15/2015
	0	28,960	1/2/13	\$	14.470	1/1/2016

(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 40,000 shares of common stock issuable upon exercise of options which Ms. Parshall transferred to her two daughters.

#### Option Exercises

The following table shows for the fiscal year ended December 31, 2009, certain information regarding option exercises and stock vested during the last fiscal year with respect to the Named Executive Officers:

#### Option Exercises in Fiscal 2009(1)

Name	Option Awards	
	Number of Shares Acquired on Exercise (2) (3) (#)	Value Realized on Exercise (\$)
Stanley T. Crooke	23,465	\$ 77,258.52
	26,535	\$ 85,376.36
	20,000	\$ 60,950.00
	20,000	\$ 63,350.00
	30,000	\$ 100,125.00
	20,000	\$ 68,950.00
	30,000	\$ 111,525.00
	20,000	\$ 66,350.00
	30,000	\$ 112,125.00
	30,000	\$ 111,225.00
B. Lynne Parshall	10,000	\$ 32,175.00
	10,000	\$ 31,675.00
	16,910(4)	\$ 63,877.52
	13,000	\$ 43,387.50
	10,000	\$ 33,175.00
	20,000	\$ 74,350.00
	25,000	\$ 92,687.50
	20,000	\$ 74,750.00
	10,000	\$ 34,475.00
	6,000(4)	\$ 25,515.00
7,090(4)	\$ 31,178.28	
2,000(4)	\$ 8,715.00	
C. Frank Bennett	1,000	\$ 3,780.00
	10,000	\$ 91,100.00
	12,000	\$ 122,587.20
	10,000	\$ 77,930.00
Richard S. Geary	—	—

(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 individual exercised the applicable option because the option otherwise would have expired either on 12/31/09 or 1/5/10.
- (4) Includes options exercised by Ms. Parshall's daughters.

## 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 2009, 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. Crooke and B. Lynne Parshall to clarify the provisions of such agreements in light of Section 409A of the Code.

Specifically, these severance agreements provide the following severance benefits:

- Dr. Crooke will be eligible to receive a lump sum severance payment equal to 36 months of his then-current base salary in the event his employment is terminated as a result of a change of control of Isis; and
- Ms. Parshall will be eligible to receive a lump sum severance payment equal to:
  - 18 months of her then-current base salary in the event that her employment is terminated without cause; and
  - 30 months of her then-current base salary in the event that her employment is terminated as a result of a change of control of Isis.

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

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

### *Conditions*

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

## Potential Payments Upon Termination or Change-Of-Control

The following table estimates the lump sum payments that would be required under the agreements described above that were effective as of December 31, 2008. 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, 2009. The estimates in this table are forward-looking statements. Please see the special note regarding forward-looking statements on page 51 of this Proxy Statement.

Name	Termination Event	
	Termination Without Cause	Termination in a Change of Control
Stanley T. Crooke	—	\$ 2,050,947
B. Lynne Parshall	\$ 894,920	\$ 1,491,533

## 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, 2009, we paid total fees of \$30,000 to each of our non-employee Directors.

In 2009, each non-employee Director also received automatic stock option grants under our Directors' Plan. On July 1, 2009, under the Directors' Plan, each of our non-employee Directors serving at that time received an option to purchase 15,000 shares of our common stock, at an exercise price of \$16.32 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, 2009 certain information with respect to the compensation of all our non-employee Directors:

#### Director Compensation for Fiscal 2009

Name	Fees Earned or Paid in Cash (\$)	Option Awards(1) (\$)	All Other Compensation (\$)	Total (\$)
Spencer R. Berthelsen	\$ 30,000	\$ 159,479	—	\$ 189,479
Richard D. DiMarchi	\$ 30,000	\$ 159,479	—	\$ 189,479
Joseph Klein	\$ 30,000	\$ 159,479	—	\$ 189,479
Frederick T. Muto	\$ 30,000	\$ 159,479	—	\$ 189,479
John C. Reed	\$ 30,000	\$ 159,479	—	\$ 189,479
Joseph H. Wender	\$ 30,000	\$ 159,479	—	\$ 189,479

(1) These amounts represent the estimated fair values of stock option grants we recognized pursuant to ASC 718 as share-based compensation expense in fiscal 2009 because service was provided during fiscal 2009. The estimated fair value amounts were determined using option-pricing models and are not indicative of whether the director will realize the estimated fair value or any financial benefits from the award.

46

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

The following table shows for the fiscal year ended December 31, 2009, certain information regarding outstanding awards at fiscal year-end of all our non-employee Directors:

Name	Number of Securities Underlying Unexercised Options (#)	
	Exercisable	Unexercisable
Spencer R. Berthelsen	79,375	35,625
Richard D. DiMarchi	49,375	35,625
Joseph Klein	39,375	35,625
Frederick T. Muto	81,375	35,625
John C. Reed	89,375	35,625
Joseph H. Wender	67,375	35,625

#### Option Exercises in Fiscal 2009

Name	Option Awards	
	Number of Shares Acquired on Exercise (#)	Value Realized on Exercise (\$)
Joseph H. Wender	10,000(1)	\$ 44,500

(1) Option exercised because it otherwise would have expired on 1/5/10.

#### 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 employee 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 2009, 2008, and 2007, she received the following compensation:

Name	Year	Salary (\$)	Bonus(1) (\$)	Option Awards(2) (\$)	All Other Compensation(3) (\$)	Total (\$)
Rosanne Crooke,	2009	\$ 147,002	\$ 42,263	\$ 49,929	\$ 336	\$ 239,530
Executive Director,	2008	\$ 140,002	\$ 45,501	\$ 61,416	\$ 3,331	\$ 250,250
Cardiovascular Disease	2007	\$ 132,452	\$ 74,173	\$ 62,984	\$ 2,622	\$ 272,231

(1) We present cash bonuses in the years they were earned, not in the year paid. Cash bonuses represent compensation for achievements and are not necessarily paid in the year they are earned; i.e., we paid bonuses for 2009 in January 2010.

47

(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 amount represents an option to purchase 5,958 shares of our common stock at an exercise price of \$11.12 per share that Dr. Rosanne Crooke received on January 2, 2007 and 5,000 shares of the our common stock at an exercise price of \$9.92 per share that Dr. Rosanne Crooke received on May 1, 2007 for her promotion; represents an option to purchase 8,300 shares of our common stock at an exercise price of \$15.38 per share that Dr. Rosanne Crooke received on January 2, 2008, and represents an option to purchase 7,000 shares of our common stock at an exercise price of \$14.47 per shares that Dr. Rosanne Crooke received on January 2, 2009.

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

One of our Directors, Mr. Muto, who was elected by the Board in March 2001, is a partner at Cooley Godward Kronish LLP, our outside legal counsel. We paid Cooley Godward Kronish LLP an aggregate of \$243,516 for Isis and \$48,923 for Regulus in fees in 2009 for legal services, which amount is substantially less than five percent of Cooley's gross revenues for its 2009 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 CEO or COO (for non-executive officers) to determine that no conflict of interest exists.

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

---

### **COMPENSATION COMMITTEE REPORT\***

The Compensation Committee has:

- reviewed and discussed the Compensation Discussion and Analysis included in this Proxy Statement with management; and
- based on this review and discussion, the Compensation Committee recommended to the Board of Directors that the Compensation Discussion and Analysis be included in our Proxy Statement relating to the 2010 Annual Meeting of stockholders.

#### *The Compensation Committee*

Spencer R. Berthelsen, *Chairman*

Richard D. DiMarchi

John C. Reed

---

\* 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.

---

### **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, 2009 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, 2009 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 2010.

*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.

---

\* 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, 2009 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](http://www.isispharm.com)) to view our 2010 Annual Report. Any information that is included on or linked to our website is not part of this Proxy Statement or any registration statement or report that incorporates this Proxy Statement by reference. The Annual Report is not incorporated into this Proxy Statement and is not considered soliciting material.

By Order of the Board of Directors,

B. Lynne Parshall  
Secretary

April 20, 2010

## Special Note Regarding Forward-Looking Statements

**This Proxy Statement includes forward-looking statements regarding Isis Pharmaceuticals’ business, the financial position and outlook for Isis as well as Regulus, its majority-owned subsidiary, and the therapeutic and commercial potential of our technologies and products in development. Any statement describing our 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. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning our programs are described in additional detail in our**

---

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

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

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

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

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

A-1

---

10. The Audit Committee will review the interim financial statements with management and the independent auditors prior to the filing of the Company's Quarterly Reports on Form 10-Q. The Audit Committee will also discuss the results of the quarterly reviews and any other matters required to be communicated to the Audit Committee by the independent auditors under generally accepted auditing standards. The Chair of the Audit Committee may represent the entire committee for the purposes of this review.
11. The Audit Committee will review with management and the independent auditors the financial statements to be included in the Company's Annual Report on Form 10-K (or the annual report to stockholders if distributed prior to the filing of Form 10-K), including their judgment about the quality, not just acceptability, of accounting principles, the reasonableness of significant judgments, and the clarity of the disclosures in the financial statements. Also, the Audit Committee will discuss the results of the annual audit and any other matters required to be communicated to the Audit Committee by the independent auditors under generally accepted auditing standards.
12. The Audit Committee will review and, if appropriate, approve, transactions that would qualify as a related party transaction under the Securities Act of 1933.
13. The Audit Committee will review the Company's annual budget with management and, if acceptable, recommend such budget to the Board for approval.
14. The Audit Committee will review and evaluate and, if appropriate, make recommendations to Board of Directors on any matters related to stockholder protection and takeover preparedness, equity or debt financing plans and opportunities, and the selection and evaluation of money managers or investment advisors for the Company.

15. The Audit Committee will establish procedures for the receipt, retention, and treatment of complaints received by the Company regarding accounting, internal accounting controls, or auditing matters, and the confidential, anonymous submission by employees of the Company of concerns regarding questionable accounting or auditing matters.
16. The Audit Committee will maintain free and open communication between the Audit Committee, directors who are not members of the Audit Committee, the Company's management, the internal auditors, and the independent auditors.
17. The Audit Committee shall have adequate resources and authority to discharge its responsibilities and duties including the following:
  - a. The Audit Committee will have full authority at its own discretion to institute investigations of any matter brought to its attention, with full access to all books, records, facilities and personnel of the Company, and the authority to engage independent counsel and other advisors it deems necessary to conduct its duties.
  - b. The Audit Committee will have the authority to review all aspects of the Company's financial operations on a planned basis.
  - c. The Audit Committee will have the authority to review the Company's policies and procedures and the actual implementation of such policies and procedures with respect to officers' expenses and perquisites.
18. The Audit Committee will report annually to the Board of Directors, outlining the Audit Committee's activities for the past year and its plans for the coming year. In addition, the Audit Committee shall report to the Board of Directors any significant matters as they occur during the year.

A-2

---

Appendix B

**AMENDMENT  
TO  
ISIS PHARMACEUTICALS, INC.  
2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN  
ADOPTED BY THE BOARD OF DIRECTORS FEBRUARY 26, 2010  
SUBJECT TO APPROVAL BY STOCKHOLDERS**

These Amendments to the Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan (the "Amendments"), is effective as of June 2, 2010.

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

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

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

ARTICLE 1. AMENDMENT

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

**4. SHARES SUBJECT TO THE PLAN.**

**"(a) Share Reserve.** Subject to the provisions of Section 11(a) relating to Capitalization Adjustments, the Common Stock that may be issued pursuant to Options shall not exceed in the aggregate 1,000,000 shares of Common Stock."

- 1.2 Amendment of Section 13(a). Section 13(a) of the Plan is hereby amended, restated and replaced in its entirety by the following language:

**13. TERMINATION OR SUSPENSION OF THE PLAN.**

**"(a) Plan Term.** The Board may suspend or terminate the Plan at any time. Unless sooner terminated, the Plan shall terminate on June 1, 2020. No Options may be granted under the Plan while the Plan is suspended or after it is terminated."

B-1

---

**ISIS PHARMACEUTICALS, INC.  
2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN  
ADOPTED BY THE BOARD OF DIRECTORS SEPTEMBER 11, 2001  
APPROVED BY STOCKHOLDERS MAY 31, 2002  
EFFECTIVE DATE: MAY 31, 2002**

**AMENDED: APRIL 20, 2006**(Amendment approved by Board on

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

**1. PURPOSES.**

- (a) **Amendment and Restatement.** This Plan is an amendment and restatement of the Isis Pharmaceuticals, Inc. 1992 Non-Employee Directors' Stock Option Plan.
- (b) **Eligible Option Recipients.** The persons eligible to receive Options are the Non-Employee Directors of the Company.
- (c) **Available Options.** The purpose of the Plan is to provide a means by which Non-Employee Directors may be given an opportunity to benefit from increases in value of the Common Stock through the granting of Nonstatutory Stock Options.
- (d) **General Purpose.** The Company, by means of the Plan, seeks to retain the services of its Non-Employee Directors, to secure and retain the services of new Non-Employee Directors and to provide incentives for such persons to exert maximum efforts for the success of the Company and its Affiliates.

**2. DEFINITIONS.**

- (a) **"Affiliate"** means any parent corporation or subsidiary corporation of the Company, whether now or hereafter existing, as those terms are defined in Sections 424(e) and (f), respectively, of the Code.
- (b) **"Annual Grant"** means an Option granted annually to all Non-Employee Directors who meet the criteria specified in subsection 6(b) of the Plan.
- (c) **"Board"** means the Board of Directors of the Company.
- (d) **"Capitalization Adjustment"** has the meaning ascribed to that term in Section 11(a).

B-2

---

- (e) **"Change in Control"** means the occurrence, in a single transaction or in a series of related transactions, of any one or more of the following events:
  - (i) any Exchange Act Person becomes the Owner, directly or indirectly, of securities of the Company representing more than 50% of the combined voting power of the Company's then outstanding securities other than by virtue of a merger, consolidation or similar transaction and other than by a purchase of securities directly from the Company;

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

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

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

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

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

B-3

---

Notwithstanding the foregoing or any other provision of this Plan, the definition of Change in Control (or any analogous term) in an individual written agreement between the Company or any Affiliate and the Optionholder shall supersede the foregoing definition with respect to Options subject to

such agreement (it being understood, however, that if no definition of Change in Control or any analogous term is set forth in such an individual written agreement, the foregoing definition shall apply).

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

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

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

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

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

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

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

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

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

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

B-4

---

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

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

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

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

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

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

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

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

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

(s) **“Initial Grant”** means an Option granted to a Non-Employee Director who meets the criteria specified in subsection 6(a) of the Plan.

(t) **“Non-Employee Director”** means a Director who is not an Employee.

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

B-5

---

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

(w) **“Option”** means a Nonstatutory Stock Option granted pursuant to the Plan.

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

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

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

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

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

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

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

### 3. ADMINISTRATION.

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

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

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

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

B-6

---

(iii) To amend the Plan or an Option as provided in Section 12.

(iv) To terminate or suspend the Plan as provided in Section 13.

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

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

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

### 4. SHARES SUBJECT TO THE PLAN.

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

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

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

### 5. ELIGIBILITY.

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

## 6. NON-DISCRETIONARY GRANTS.

(a) **Initial Grants.** Without any further action of the Board, each person who is elected or appointed for the first time after the effective date of this amendment and restatement of the Plan to be a Non-Employee Director automatically shall, upon the date of his or her initial election or appointment to be a Non-Employee Director by the Board or stockholders of the Company, as applicable, be granted an Initial Grant to purchase **30,000** shares of Common Stock on the terms and conditions set forth herein.

B-7

---

(b) **Annual Grants.** Without any further action of the Board, after the effective date of this amendment and restatement of the Plan, a Non-Employee Director shall be granted an Annual Grant as follows: On July 1 of each year, beginning on July 1, 2002, each person who is then a Non-Employee Director automatically shall be granted an Annual Grant to purchase **15,000** shares of Common Stock on the terms and conditions set forth herein. Should the date of grant set forth above be a legal holiday, then such grant shall be made on the next business day.

## 7. OPTION PROVISIONS.

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

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

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

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

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

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

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

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

B-8

---

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

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

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

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

(j) **Death of Optionholder.** In the event that (i) an Optionholder's Continuous Service terminates as a result of the Optionholder's death or (ii) the Optionholder dies within the period (if any) specified in the Option Agreement after the termination of the Optionholder's Continuous Service for a reason other than death, then the Option may be exercised (to the extent the Optionholder was entitled to exercise such Option as of the date of death) by the Optionholder's estate, by a person who acquired the right to exercise the Option by bequest or inheritance or by a person designated to exercise the Option upon the Optionholder's death pursuant to subsection 7(d), but only within the period ending on the earlier of (1) the date 18 months following the date of

death (or such longer or shorter period specified in the Option Agreement) or (2) the expiration of the term of such Option as set forth in the Option Agreement. If, after death, the Option is not exercised within the time specified herein, the Option shall terminate.

B-9

---

## 8. COVENANTS OF THE COMPANY.

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

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

## 9. USE OF PROCEEDS FROM STOCK.

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

## 10. MISCELLANEOUS.

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

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

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

(d) **Investment Assurances.** The Company may require an Optionholder, as a condition of exercising or acquiring Common Stock under any Option, (i) to give written assurances satisfactory to the Company as to the Optionholder's knowledge and experience in financial and business matters and/or to employ a purchaser representative reasonably satisfactory to the Company who is knowledgeable and experienced in financial and business matters and that he or she is capable of evaluating, alone or together with the purchaser

B-10

---

representative, the merits and risks of exercising the Option; and (ii) to give written assurances satisfactory to the Company stating that the Optionholder is acquiring the Common Stock subject to the Option for the Optionholder's own account and not with any present intention of selling or otherwise distributing the Common Stock. The foregoing requirements, and any assurances given pursuant to such requirements, shall be inoperative if (1) the issuance of the shares of Common Stock upon the exercise or acquisition of Common Stock under the Option has been registered under a then currently effective registration statement under the Securities Act or (2) as to any particular requirement, a determination is made by counsel for the Company that such requirement need not be met in the circumstances under the then applicable securities laws. The Company may, upon advice of counsel to the Company, place legends on stock certificates issued under the Plan as such counsel deems necessary or appropriate in order to comply with applicable securities laws, including, but not limited to, legends restricting the transfer of the Common Stock.

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

## 11. ADJUSTMENTS UPON CHANGES IN STOCK.

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

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

B-11

---

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

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

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

B-12

---

the following order unless the Optionholder elects in writing a different order (*provided, however*, that such election shall be subject to Company approval if made on or after the effective date of the event that triggers the Payment): reduction of cash payments; cancellation of accelerated vesting of Options or other equity-based awards; reduction of employee benefits. In the event that acceleration of vesting of Options or other equity-based compensation is to be reduced, such acceleration of vesting shall be cancelled in the reverse order of the date of grant of the Optionholder's Options or other equity-based awards unless the Optionholder elects in writing a different order for cancellation.

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

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

## 12. AMENDMENT OF THE PLAN AND OPTIONS.

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

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

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

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

B-13

(e) **Option Repricing Prohibited.** The Board will not have the authority, at any time, without obtaining the approval of a majority of the shares present or represented and entitled to vote at a duly convened meeting of stockholders, to (1) reduce the exercise price of any Options under the Plan that are currently outstanding; or (2) cancel any outstanding Options under the Plan and grant in substitution therefore new Options under the Plan at a lower exercise price (including entering into any “6 month and 1 day” cancellation and re-grant scheme), regardless of whether or not the cancelled Options revert to and again become available for issuance under the Plan This Section 12(e) may not be amended without the affirmative vote of the holders of a majority of the shares present or represented and entitled to vote at a duly convened meeting of the stockholders of the Company. Notwithstanding the foregoing, this paragraph will not be construed to apply to “issuing or assuming a stock option in a transaction to which section 424(a) applies,” within the meaning of Section 424 of the Code.”

**13. TERMINATION OR SUSPENSION OF THE PLAN.**

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

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

**14. EFFECTIVE DATE OF PLAN.**

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

**15. CHOICE OF LAW.**

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

B-14

---

Appendix C

**AMENDMENT TO  
ISIS PHARMACEUTICALS, INC.  
1989 STOCK OPTION PLAN  
ADOPTED BY THE BOARD OF DIRECTORS FEBRUARY 26, 2010**

**SUBJECT TO APPROVAL BY STOCKHOLDERS**

This Amendment to the Isis Pharmaceuticals, Inc. 1989 Stock Option Plan (the “Amendment”), is effective as of June 2, 2010.

A. WHEREAS, the Board of Directors of Isis approved an amendment to the Isis Pharmaceuticals, Inc. 1989 Stock Option Plan (the “Plan”), as more fully described below.

NOW THEREFORE, the Plan is hereby amended as follows:

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

ARTICLE 1. AMENDMENT

1.1 Amendment and Restatement of Section 3(a). Section 3(a) of the Plan is hereby amended, restated and replaced in its entirety by the following language:

3. SHARES SUBJECT TO THE PLAN.

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

C-1

---

**ISIS PHARMACEUTICALS, INC.  
1989 STOCK OPTION PLAN**

As Amended September 5, 1991  
As Amended September 4, 1992  
As Amended January 4, 1993

As Amended December 2, 1993 and January 20, 1994

1. PURPOSE.

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

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

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

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

C-2

---

2. ADMINISTRATION.

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

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

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

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

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

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

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

3. SHARES SUBJECT TO THE PLAN.

(a) Subject to the provisions of paragraph 10 relating to adjustments upon changes in stock, the stock that may be issued pursuant to Options granted under the Plan will not exceed in the aggregate **16,700,000** shares of the Company's common stock. If any Option granted under the Plan will for any reason expire or otherwise terminate without having been exercised in full, the stock not purchased under such Option will again become available for the Plan.

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

C-3

---

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

is determined that an entire Option or any portion thereof does not qualify for treatment as an Incentive Stock Option by reason of exceeding such maximum, such Option or the applicable portion will be considered a Supplemental Stock Option.

#### 4. ELIGIBILITY.

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

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

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

#### 5. OPTION PROVISIONS.

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

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

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

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

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

C-4

---

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

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

(g) An Option will terminate 3 months after termination of the optionee's employment or relationship as a consultant or director with the Company or an Affiliate, unless (i) such termination is due to such person's permanent and total disability, within the meaning of Section 422(c)(6) of the Code, in which case the Option may, but need not, provide that it may be exercised at any time within 1 year following such termination of employment or relationship as a consultant or director; or (ii) the optionee dies while in the employ of or while serving as a consultant or director to the Company or an Affiliate, or within not more than 3 months after termination of such relationship, in which case the Option may, but need not, provide that it may be exercised at any time within 18 months following the death of the optionee by the person or persons to whom the optionee's rights under such Option pass by will or by the laws of descent and distribution; or (iii) the Option by its terms specifies either (a) that it will terminate sooner than 3 months after termination of the optionee's employment or relationship as a consultant or director or (b) that it may be exercised more than 3 months after termination of the relationship with the Company or an Affiliate. This subparagraph 5(g) will not be construed to extend the term of any Option or to permit anyone to exercise the Option after expiration of its term, nor will it be construed to increase the number of shares as to which any Option is exercisable from the amount exercisable on the date of termination of the optionee's employment or relationship as a consultant or director.

C-5

---

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

6. COVENANTS OF THE COMPANY.

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

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

7. USE OF PROCEEDS FROM STOCK.

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

8. MISCELLANEOUS.

(a) Subject to the limitation set forth in Section 5(e), and *solely* in connection with (i) an optionee's death, permanent and total disability within the meaning of Section 422(c)(6) of the Code or retirement from the Company; or (ii) a Change in Control, the Committee will have the power to accelerate the time during which an Option may be exercised or the time during which an Option or any part thereof will vest, notwithstanding the provisions in the Option stating the time during which it may be exercised or the time during which it will vest. For purposes of this Section 8(a), Change in Control means: (i) a sale of all or substantially all of the assets of the Company; (ii) a merger or consolidation in which the Company is not the surviving corporation and in which beneficial ownership of securities of the Company representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of Directors has changed; (iii) a reverse merger in which the Company is the surviving corporation but the shares of Common Stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or

C-6

---

otherwise, and in which beneficial ownership of securities of the Company representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of the Company's Board of Directors has changed; or (iv) an acquisition by any person, entity or group within the meaning of Section 13(d) or 14(d) of the Exchange Act, or any comparable successor provisions (excluding any employee benefit plan, or related trust, sponsored or maintained by the Company or subsidiary of the Company or other entity controlled by the Company) of the beneficial ownership (within the meaning of Rule 13d-3 promulgated under the Exchange Act, or comparable successor rule) of securities of the Company representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of the Company's Board of Directors.

(b) Neither an optionee nor any person to whom an Option is transferred under subparagraph 5(d) will be deemed to be the holder of, or to have any of the rights of a holder with respect to, any shares subject to such Option unless and until such person has satisfied all requirements for exercise of the Option pursuant to its terms.

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

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

9. OPTION REPRICING PROHIBITED.

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

C-7

---

10. ADJUSTMENTS UPON CHANGES IN STOCK.

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

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

11. AMENDMENT OF THE PLAN.

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

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

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

C-8

---

12. TERMINATION OR SUSPENSION OF THE PLAN.

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

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

13. EFFECTIVE DATE OF PLAN.

The Plan is effective April 19, 1991.

C-9

---

**\*\*\* Exercise Your *Right to Vote* \*\*\***  
**Important Notice Regarding the Availability of Proxy Materials for the**  
**Shareholder Meeting to Be Held on June 2, 2010.**

ISIS PHARMACEUTICALS, INC.



**Meeting Information**

**Meeting Type:** Annual Meeting

**For holders as of:** April 6, 2010

**Date:** June 2, 2010 **Time:** 2:00 p.m., Pacific Time

**Location:** Isis Pharmaceuticals, Inc.

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

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

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

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

---

— Before You Vote —  
How to Access the Proxy Materials

**Proxy Materials Available to VIEW or RECEIVE:**

NOTICE AND PROXY STATEMENT          FORM 10-K

**How to View Online:**

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

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

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

- |                         |  |
|-------------------------|--|
| 1) <i>BY INTERNET:</i>  | <a href="http://www.proxyvote.com">www.proxyvote.com</a>                   |
| 2) <i>BY TELEPHONE:</i> | 1-800-579-1639   |
| 3) <i>BY E-MAIL*:</i>   | <a href="mailto:sendmaterial@proxyvote.com">sendmaterial@proxyvote.com</a> |

---

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

Requests, instructions and other inquiries sent to this e-mail address will NOT be forwarded to your investment advisor. Please make the request as instructed above on or before May 19, 2010 to facilitate timely delivery.

— How To Vote —  
Please Choose One of the Following Voting Methods

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

**Vote By Internet:** To vote now by Internet, go to [www.proxyvote.com](http://www.proxyvote.com). Have the 12-Digit Control Number available and follow the instructions.

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

---

**Voting Items**

**THE BOARD OF DIRECTORS RECOMMENDS A VOTE “FOR” ITEMS 1 THROUGH 4.**

- To elect as Directors of Isis Pharmaceuticals, Inc. the nominees listed below.  
    - Stanley T. Crooke
    - Joseph Klein, III
    - John C. Reed
  - To approve an amendment to the 2002 Non-Employee Directors’ Stock Option Plan to increase the shares authorized for issuance under the plan from 850,000 shares to 1,000,000 shares and to extend the term from May 30, 2012 to June 1, 2020;
  - To approve an amendment to the 1989 Stock Option Plan to increase the shares authorized for issuance under the plan from 16,700,000 shares to 20,000,000 shares;
  - To ratify the Audit Committee’s selection of Ernst & Young LLP as independent auditors for our 2010 fiscal year.
-



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

**VOTE BY INTERNET - www.proxyvote.com**

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

**ELECTRONIC DELIVERY OF FUTURE STOCKHOLDER COMMUNICATIONS**

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

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

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

**VOTE BY MAIL**

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

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

M24186-P90973

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

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

**ISIS PHARMACEUTICALS, INC.**

**For All Withhold For All Except**

**THE BOARD OF DIRECTORS RECOMMENDS A VOTE "FOR" ITEMS 1 THROUGH 4.**

o o o

**Vote On Directors**

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

- 01) Stanley T. Croke
- 02) Joseph Klein, III
- 03) John C. Reed

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

**Vote On Proposals**

**For Against Abstain**

- |    |   |   |   |   |
|----|---|---|---|---|
| 2. | To approve an amendment to the 2002 Non-Employee Directors' Stock Option Plan to increase the shares authorized for issuance under the plan from 850,000 shares to 1,000,000 shares and to extend the term from May 30, 2012 to June 1, 2020; | o | o | o |
| 3. | To approve an amendment to the 1989 Stock Option Plan to increase the shares authorized for issuance under the plan from 16,700,000 shares to 20,000,000 shares;  | o | o | o |
| 4. | To ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2010 fiscal year.  | o | o | o |

The shares represented by this proxy, when properly executed, will be voted in the manner directed herein by the undersigned Stockholder(s). **If no direction is made, this proxy will be voted FOR items 1 through 4.** If any other matters properly come before the meeting, or if cumulative voting is required, the persons named in this proxy will vote in their discretion.

\_\_\_\_\_  
 Signature [PLEASE SIGN WITHIN BOX]

\_\_\_\_\_  
 Date

\_\_\_\_\_  
 Signature (Joint Owners)

\_\_\_\_\_  
 Date

## Directions

### From Los Angeles and Points North:

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



### From San Diego Airport, Downtown and Points South:

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

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

The Notice and Proxy Statement and Form 10-K are available at [www.proxyvote.com](http://www.proxyvote.com).

## ISIS PHARMACEUTICALS, INC.

### **THIS PROXY IS SOLICITED ON BEHALF OF THE BOARD OF DIRECTORS**

### **ANNUAL MEETING OF STOCKHOLDERS**

**JUNE 2, 2010**

The stockholder(s) hereby appoint(s) Stanley T. Crooke and B. Lynne Parshall, or either of them, as proxies, each with the power to appoint his or her substitute, and hereby authorizes them to represent and to vote, as designated on the reverse side of this ballot, all of the shares of Common Stock of Isis Pharmaceuticals, Inc. (the "Company") that the stockholder(s) is/are entitled to vote at the Annual Meeting of Stockholders to be held at 2:00 p.m., Pacific Time on June 2, 2010, at the Company's offices at 1896 Rutherford Road, Carlsbad, California 92008, and any adjournment or postponement thereof.

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

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

**CONTINUED AND TO BE SIGNED ON REVERSE SIDE**

---