

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

SCHEDULE 14A

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

Filed by the Registrant x
Filed by a Party other than the Registrant o

Check the appropriate box:

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

Isis Pharmaceuticals, Inc.

(Name of Registrant as Specified In Its Charter)

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

Payment of Filing Fee (Check the appropriate box):

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

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

NOTICE OF

2007 ANNUAL MEETING OF STOCKHOLDERS

AND PROXY STATEMENT

Dear Stockholders,

I am pleased to invite you to Isis Pharmaceuticals' 2007 Annual Meeting of Stockholders. We will host the meeting at our offices in Carlsbad, California on Thursday, May 17, 2007 at 9:00 a.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 2007, 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 complete, date, sign and return the enclosed proxy as soon as possible to ensure your representation at the meeting. We have provided a postage-paid envelope for your convenience. If you plan to attend the meeting and prefer to

vote in person, you may still do so even if you have already returned your proxy. If you are unable to attend, please note that a webcast of the presentation will be available at www.isispharm.com.(1)

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 ADP Investor Communication Services 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.

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 2007 ANNUAL MEETING OF STOCKHOLDERS

Date: Thursday, May 17, 2007
Time: 9:00 a.m., Pacific Time
Place: Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008

Dear Stockholders,

At our 2007 Annual Meeting, we will ask you to:

- elect three Directors each to serve for a three-year term;
- ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2007 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 March 19, 2007 you may vote at the Annual Meeting.

By order of the Board of Directors,

B. Lynne Parshall
Secretary

Carlsbad, California
April 5, 2007

ALL STOCKHOLDERS ARE CORDIALLY INVITED TO ATTEND THE MEETING IN PERSON. WHETHER OR NOT YOU EXPECT TO ATTEND THE MEETING, PLEASE COMPLETE, DATE, SIGN AND RETURN THE ENCLOSED PROXY AS PROMPTLY AS POSSIBLE IN ORDER TO ENSURE YOUR REPRESENTATION AT THE MEETING. A RETURN ENVELOPE (WHICH IS POSTAGE PREPAID IF MAILED IN THE UNITED STATES) IS ENCLOSED FOR THAT PURPOSE. ALTERNATIVELY, YOU MAY VOTE BY PHONE OR INTERNET BY FOLLOWING THE INSTRUCTIONS INCLUDED IN THIS PROXY STATEMENT AND WITH YOUR PROXY CARD. 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 2007 ANNUAL MEETING AND VOTING

General

The enclosed proxy card has been sent to you by the Board of Directors of Isis Pharmaceuticals, Inc., a Delaware corporation, for use at the 2007 Annual Meeting of Stockholders to be held on Thursday, May 17, 2007, at 9:00 a.m. Pacific Time, or at any adjournment or postponement of the meeting, for the purposes stated in this document. The Annual Meeting will be held at the Company's offices at 1896 Rutherford Road, Carlsbad, California. This Proxy Statement summarizes the information you will need to vote in an informed manner.

Voting Rights, Outstanding Shares and Quorum

We will begin mailing this Proxy Statement and the accompanying proxy card on or about April 5, 2007 to all stockholders who are entitled to vote. Only stockholders who owned our common stock at the close of business on March 19, 2007 are entitled to vote at the Annual Meeting. On this record date, we had 82,484,960 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. Your shares will be counted towards the quorum only if you submit a valid proxy vote or vote at the meeting. Abstentions and broker non-votes will be counted towards the quorum requirement.

Each share of our common stock that you own entitles you to one vote. The proxy card indicates the number of shares of our common stock that you own. 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 a stockholder does not want to elect a particular director, the stockholder may simply withhold their "For" vote. Abstentions will be counted towards the vote total for each proposal, and will have the same effect as "Against" votes. Broker non-votes have no effect and will not be counted towards the vote total for any proposal.

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

You may vote in one of the following ways:

- attend the 2007 Annual Meeting and vote in person;
- complete, sign, date and return the enclosed proxy card in the postage paid envelope provided; or
- vote by phone or through the Internet by following the instructions included with your proxy card.

If you receive more than one proxy card, 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 proxy card so that your shares are properly voted.

We will announce preliminary voting results at the annual meeting and publish final voting results in our quarterly report on Form 10-Q for the second quarter of 2007.

Solicitation

The Board of Directors of Isis is soliciting your proxy to vote at the Annual Meeting. Isis will bear the entire cost of soliciting proxies, including preparing, assembling, printing and mailing this Proxy Statement, the proxy card and any additional information furnished to stockholders. Copies of solicitation materials will be furnished to banks, brokerage houses, fiduciaries and custodians holding in their names 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. Original solicitation of proxies by mail may be supplemented by telephone, electronic mail or personal solicitation by Directors, officers or other employees of Isis. We will not pay our Directors and employees any additional compensation for soliciting proxies.

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

Votes submitted by phone or through the Internet must be received by 11:59 p.m., Eastern Time, on May 16, 2007. Submitting your proxy by phone or through the Internet will not affect your right to vote in person should you decide to attend the Annual Meeting.

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

For Shares Registered in Your Name

If you are a stockholder of record, you may go to <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. If you are using a touch-tone telephone

you may also vote your shares by calling 1-800-690-6903 and following the recorded instructions. Please have your proxy card available at the time you are voting.

For Shares Registered in the Name of a Broker or Bank

Most beneficial owners whose stock is held in street name receive instructions for voting their shares from their bank, broker or other agent, rather than from our proxy card.

A number of brokers and banks are participating in an ADP Investor Communication Services program 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 ADP Investor Communication Services program, you may vote your shares by phone or through the Internet by having the voting form in hand and calling the number or going to the website indicated on the form and following the instructions.

Revocability of Proxies

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

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

2

Stockholder Proposals

If you have a proposal or director nomination that you would like included in our proxy statement and form of proxy for, or to be presented at the 2008 Annual Meeting of Stockholders, you must send the proposal to Isis by no later than December 7, 2007. Stockholders wishing to submit proposals or director nominations that are not to be included in such proxy statement and proxy must do so no earlier than the close of business on January 18, 2008 and no later than the close of business on February 17, 2008. Stockholders are also advised to review our Bylaws, which contain additional requirements with respect to advance notice of stockholder proposals and director nominations.

3

PROPOSAL 1

ELECTION OF DIRECTORS

Information about our Board of Directors

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

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

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

Information about the 2007 Elections

The Board has nominated three Directors for election at the 2007 Annual Meeting. Each of the nominees currently serves as one of our Directors. As a founder of the Company, Dr. Crooke has served as a Director since its formation and has been re-elected by our stockholders each successive term. Mr. Klein and Dr. Reed were initially appointed to the Board by the then existing members of the Board, and each was subsequently elected by our stockholders. If re-elected, the nominees, Dr. Crooke, Mr. Klein and Dr. Reed, will serve until the 2010 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. Shares represented by executed proxies will be voted for the election of the three nominees listed below, unless authority to vote in favor of the nominees is withheld. Each person nominated for election has agreed to serve if elected, and we have no reason to believe that any of the nominees will be unable to serve. However, if any nominee cannot serve, your proxy may be voted for another nominee proposed by the Board, or the Board may reduce the number of authorized Directors.

We provide below a short biography of each of the nominees and of each Director whose term of office will continue after the Annual Meeting.

Biographies of Nominees for Election for a Three-year Term Expiring at the 2010 Annual Meeting

Stanley T. Crooke, M.D., Ph.D., age 62, was 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 was employed by SmithKline Beckman Corporation, a pharmaceutical company, where his titles included President of Research and Development of SmithKline and French Laboratories.

Joseph Klein, III, age 46, 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. In addition to his investment advisory and financial consulting activities, Mr. Klein currently serves as a Venture Partner of Red Abbey Venture Partners, LP, a life sciences 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. Mr. Klein serves on the board of directors of four publicly held biotechnology companies: BioMarin Pharmaceutical Inc. since June 2005; NPS Pharmaceuticals, Inc. since 1998, but does not intend to stand for reelection to NPS' board at its annual meeting in May 2007; OSI Pharmaceuticals, Inc. since July 2006; and Savient Pharmaceuticals, Inc. since May 2006.

John C. Reed, M.D., Ph.D., age 48, has served as a Director of Isis since February 2002. Dr. Reed has been the President and Chief Executive Officer of Burnham Institute for Medical Research, an independent, nonprofit, public benefit organization dedicated to basic biomedical research, since January 2002. Dr. Reed has been with The Burnham Institute for the past thirteen 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 University of California, San Diego's (UCSD) Department of Molecular Pathology and in San Diego State University's Biology department. In addition, Dr. Reed is an associate member of UCSD's Cancer Center. Dr. Reed serves on the board of directors of two publicly held biotechnology companies: Stratagene, Inc. and Pharmion Corporation.

The Nominating, Governance and Review Committee made its report to the Board on March 1, 2007. Following that report, the Board determined it would be in the best interests of Isis and its stockholders to nominate Messrs. Crooke, Klein and Reed as directors to be elected at the Annual Meeting.

THE BOARD OF DIRECTORS RECOMMENDS THAT YOU VOTE IN FAVOR OF THE ELECTION OF EACH OF THE ABOVE NOMINEES

Biographies of Directors Whose Terms Expire at the 2008 Annual Meeting

Spencer R. Berthelsen, M.D., age 55, has served as a Director of Isis since May 2002. Since 1980, he has practiced Internal Medicine with the Kelsey Seybold Clinic, a 310 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 and Medical Director. He has been Chairman of the Board of Directors since October 2001 and Managing Director since August 2005. He is a Clinical Professor of Medicine at Baylor College of Medicine. Dr. Berthelsen has served on the Board of the Texas Academy of Internal Medicine in the past and the Caremark National Pharmacy and Therapeutics Committee from 1999 through 2005.

B. Lynne Parshall, age 52, has served as a Director of Isis since September 2000. She has served as our Executive Vice President since December 1995, 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 on the Board of Trustees of the Bishops School and is also a member of the American, California and San Diego bar associations. Ms. Parshall serves on the board of directors of two publicly held biotechnology companies: Corautus Genetics Inc. and CardioDynamics International Corporation.

Joseph H. Wender, age 62, has served as a Director of Isis since January 1994. Mr. Wender joined GSC Group in 2005 where he is a Senior Managing Director, member of the Management Committee, and Chairman of the Finance Committee. He is a former member of the GSC Advisory Board. Prior to this, he 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. He sits on the Board of First Coastal Bancshares, a bank holding company, Affinity Financial, an Internet financial institution and Vintrust, a wine management company. He also is Chairman of the Board of GSC Capital Corporation, a Real Estate Investment Trust (REIT).

Biographies of Directors Whose Terms Expire at the 2009 Annual Meeting

Richard D. DiMarchi, Ph.D., age 54, 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 currently serves as Chairman of the Chemistry Department, and is a co-founder and the Chief Scientific Officer of Marcadia Biotech, a privately held biotechnology company. Prior to joining Indiana University, Dr. DiMarchi worked for 22 years at Eli Lilly and Company in several senior management positions, including Group Vice President, Biotechnology and Product Development, from 1996 to 2003, and Vice President, Endocrine Research and Clinical Investigation, from 1992 to 1996.

Frederick T. Muto, age 53, 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 management committee.

Independence of the Board of Directors

As required under The NASDAQ Global Market ("Nasdaq") listing standards, a majority of the members of a listed Company's Board of Directors must qualify as "independent," as affirmatively determined by the Nominating, Governance and Review Committee of the Board of Directors. The Nominating,

Governance and Review Committee consults with our 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 Executive Vice President, respectively. In making this determination, the Board found that none of these directors or nominees for director had a material or other disqualifying relationship with Isis. With respect to Mr. Muto who is a partner of Cooley Godward Kronish LLP, our outside counsel, and Dr. DiMarchi who has a consulting agreement with Isis, each is independent for purposes other than serving on the Audit Committee, of which neither is a member.

Information Regarding the Board of Directors and its Committees

As part of each Board meeting, our independent Directors meet in executive session without the presence of our employee Directors. The Chairpersons of the Audit Committee, the Compensation Committee, and the Nominating, Governance and Review Committee will each preside over at least one executive session. Persons interested in communicating with the independent Directors about their concerns or issues may address correspondence to a particular Director or to the independent Directors generally, in care of Isis Pharmaceuticals, Inc., 1896 Rutherford Road, Carlsbad, CA 92008. If no particular Director is named, letters will be forwarded, depending on the subject matter, to the Chair of the Audit, Compensation, or Nominating, Governance and Review Committee.

6

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

- meets the applicable rules and regulations regarding "independence," including but not limited to, Rule 4200(a)15 of the Nasdaq listing standards;
- is not an officer or employee of the Company; and
- is free of any relationship that would interfere with his or her individual exercise of independent judgment with regard to Isis.

Meetings and Attendance; Committee Members

The Board of Directors met six times in 2006, four regularly scheduled meetings and two special meetings, and acted by unanimous written consent four times. During 2006, all Directors, except Dr. Reed, attended at least 75% of the meetings of the Board and the committees on which they served. Dr. Reed attended 75% of all the regularly scheduled meetings and 50% of all of the special meetings, due to scheduling conflicts. We encourage each member of the Board to attend the Annual Meeting of Stockholders. Last year, Dr. Crooke, Mr. Klein, Ms. Parshall and Dr. Reed attended our 2006 Annual Meeting of Stockholders.

2006 Board Committee Members

The following table provides membership and meeting information for fiscal 2006 for each of the Board committees:

Name	Audit	Compensation	Nominating, Governance and Review
Dr. Spencer R. Berthelsen	X	X*	X*
Dr. Stanley T. Crooke	—	—	—
Dr. Richard D. DiMarchi	—	X	—
Mr. Christopher F. O. Gabrieli	X(1)	—	X(1)
Mr. Joseph Klein	X	—	—
Mr. Frederick T. Muto(2)	—	—	—
Ms. B. Lynne Parshall	—	—	—
Dr. John C. Reed	—	X	X
Mr. Joseph H. Wender	X*	X(3)	—
Total meetings in fiscal year 2006	5(4)	3(5)	3

* Committee Chairperson

- (1) Mr. Gabrieli resigned from the Board on 4/10/06 and from the Audit Committee on 2/28/06
- (2) Mr. Muto served as counsel to the Nominating, Governance & Review Committee
- (3) Mr. Wender was no longer a member of the Compensation Committee effective 11/29/06
- (4) Acted by written consent one time as well
- (5) Acted by written consent 13 times as well

7

2007 Board Committee Members

The following table provides membership information for fiscal 2007 for each of the Board committees:

Name	Audit	Compensation	Nominating, Governance and Review
Dr. Spencer R. Berthelsen	X	X *	X *
Dr. Stanley T. Crooke	—	—	—
Dr. Richard D. DiMarchi	—	X	—
Mr. Joseph Klein	X	—	—
Mr. Frederick T. Muto	—	—	X **
Ms. B. Lynne Parshall	—	—	—
Dr. John C. Reed	—	X	X
Mr. Joseph H. Wender	X *	—	—

* Committee Chairperson

** Mr. Muto serves as counsel to the Nominating, Governance and Review Committee

Audit Committee

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

The Audit Committee:

- reviews the annual and quarterly financial statements and oversees the annual and quarterly financial reporting processes;
- selects and hires our independent auditors;
- oversees the independence of our independent auditors;
- evaluates our independent auditors' performance; and
- has the authority to hire its own outside consultants and advisors if necessary.

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

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

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

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

In addition, all Audit Committee members must be financially literate and at least one member must be a "financial expert," as defined by Securities and Exchange Commission ("SEC") regulations. Our Board has determined that the Audit Committee's financial expert is Mr. Wender based on, among other things, his over 30 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 2006, the Audit Committee met five times and acted by unanimous written consent once. Our Audit Committee charter can be found on our corporate website at www.isispharm.com.(2) Each member meets the membership criteria set forth in the Audit Committee charter and as stated above.

Compensation Committee

The Compensation Committee of the Board of Directors reviews, modifies (as needed) and approves the overall compensation strategy and policies of Isis. The Compensation Committee reviews and approves corporate performance goals and objectives relevant to the compensation of our executive officers and other members of senior management; reviews and approves the compensation for our Directors and reviews and approves the compensation and other terms of employment of our executive officers, including our Chief Executive Officer; and administers our stock option and purchase plans. We also have a

Non-Management Stock Option Committee that may award stock options to employees who are below director level in accordance with guidelines adopted by the Compensation Committee, which consists of one member, Dr. Crooke.

The Compensation Committee met three times in 2006 and acted by unanimous written consent thirteen times. Our Compensation Committee charter can be found on our corporate website at www.isispharm.com.(2)

Beginning this year, the Compensation Committee reviews with management Isis' Compensation Discussion and Analysis to consider whether to recommend that it be included in proxy statements and other filings.

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

Compensation Committee Interlocks and Insider Participation

As noted above, during the fiscal year ended December 31, 2006, our Compensation Committee was composed of Drs. Berthelsen, DiMarchi and Reed and Mr. Wender, except that Mr. Wender's service on the Committee ended on November 11, 2006. None of the members of the Committee has ever been an employee or officer of Isis. None of our executive officers serves as a member of the Board of Directors or Compensation Committee of any other entity that has one or more executive officers serving as a member of our Board of Directors or Compensation Committee.

Nominating, Governance and Review Committee

Role and Responsibilities

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

- interviewing, evaluating, nominating and recommending individuals for membership on Isis' Board of Directors. As part of this process, the Nominating, Governance and Review Committee will consider nominees recommended by Isis' stockholders;

(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.

-
- on an annual basis, reviewing the performance of the Board and its committees, including evaluating the Board's ability to function as a group and the integrity, independence and competency of the individual Board members;
 - annually reviewing and assessing the adequacy of Isis' corporate governance guidelines and recommending any proposed changes to the Board for approval; and
 - performing such other functions as may be necessary or convenient for the efficient discharge of the foregoing.

The Nominating, Governance and Review Committee met three times during 2006. You can find our Nominating, Governance and Review Committee charter on our corporate website at www.isispharm.com.(3)

Director Nominations - Quality Standards

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

The minimum membership requirements are as follows:

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

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

- possessing relevant expertise to offer advice and guidance to management;
- having sufficient time to devote to the affairs of Isis;
- demonstrating excellence in his or her field;

- having sound business judgment; and
- having commitment to rigorously represent the long-term interests of our stockholders.

Director Nominations - Process

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

New candidates for Director are reviewed in the context of the current composition of the Board, the operating requirements of Isis and the long-term interests of our stockholders. 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

(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.

to compile a list of potential candidates, but may also engage, if it deems appropriate, a paid professional search firm. The Committee conducts any appropriate and necessary inquiries into the backgrounds and qualifications of possible candidates after considering the function and needs of the Board.

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

Stockholder Recommendations for Directors

Stockholders who wish to recommend individuals for consideration by the Nominating, Governance and Review Committee to become nominees for election to the Board may do so by delivering a written recommendation to the Secretary of Isis at the following address: 1896 Rutherford Road, Carlsbad, CA 92008, by December 7, 2007. Submissions must include the full name of the proposed nominee, a description of the proposed nominee's business experience for at least the previous five years, complete biographical information, a description of the proposed nominee's qualifications as a Director and a representation that the nominating stockholder is a beneficial or record owner of our stock. Any such submission must be accompanied by the written consent of the proposed nominee to be named as a nominee and to serve as a Director if elected.

Stockholder Communications with the Board of Directors

We make every effort to ensure that the views of stockholders are heard by the Board or individual Directors, as applicable, and that appropriate responses are provided 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. Communications will be compiled by the Secretary and submitted to the Board or the individual Directors on a periodic basis. These communications will be reviewed by one or more employees of Isis designated by the Board, who will determine whether they should be presented to the Board. The purpose of this screening is to allow the Board to avoid having to consider irrelevant or inappropriate communications (such as advertisements, solicitations and hostile communications). All communications directed to the Audit Committee in accordance with our Code of Ethics policy that relate to questionable accounting or auditing matters involving Isis will be promptly and directly forwarded to the Audit Committee. Other than the processes described above, our Board has not adopted a formal written process for stockholder communications with the Board. We believe our Board's responsiveness to stockholder communications has been excellent.

Code of Ethics and Business Conduct

Isis has adopted a Code of Ethics that applies to all officers, Directors and employees. We filed the Code of Ethics as an exhibit to our Annual Report on Form 10-K for the fiscal year ended December 31, 2003 and posted the Code of Ethics on our website. If we make any substantive amendments to the Code of Ethics or grant any waiver from a provision of the Code of Ethics to any executive officer or Director, we will promptly disclose the nature of the amendment or waiver on our website at www.isispharm.com. (4)

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

PROPOSAL 2

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 2007 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 2007 Annual Meeting to answer any questions and make a statement should they be asked 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.

We require 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 annual meeting to ratify the selection of Ernst & Young LLP. Abstentions will be counted toward the tabulation of votes cast on proposals presented to the stockholders and will have the same effect as negative votes. Broker non-votes are counted towards a quorum, but are not counted for any purpose in determining whether this matter has been approved.

As of December 31, 2006, none of our finance or accounting employees had been employed by Ernst & Young LLP during the past six years.

Independent Auditors' Fees

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

Audit Fees:

For the fiscal years ended December 31, 2006 and 2005, the aggregate fees billed by Ernst & Young LLP related to the integrated audit of our financial statements for such fiscal years and for the reviews of our interim financial statements were \$404,199 and \$367,000, respectively. In addition, the 2006 audit fees for Symphony GenIsis Inc. were \$67,362.

Audit Related Fees:

During the fiscal years ended December 31, 2006 and 2005, the aggregate fees billed by Ernst & Young LLP for assurance and related services that were reasonably related to the performance of the audit or review of our financial statements that are not included under "Audit Fees" above were \$88,690 and \$0, respectively. The fees billed during 2006 were primarily for services related to Ernst & Young LLP's consultations related to accounting for a number of our business transactions.

12

Tax Fees:

During the fiscal years ended December 31, 2006 and 2005, the aggregate fees billed by Ernst & Young LLP for professional services rendered for tax compliance, tax advice and tax planning were \$31,023 and \$23,894, respectively. The fees for 2006 and 2005 were for services related to the preparation of information requested in connection with a Franchise Tax Board audit. In 2005 and 2006, we utilized Deloitte & Touche LLP for the majority of our tax services.

Financial Information Systems Design and Implementation Fees:

During the fiscal years ended December 31, 2006 and 2005, there were no fees billed by Ernst & Young LLP for information technology consulting.

All Other Fees:

During the fiscal years ended December 31, 2006 and 2005, all other fees billed by Ernst & Young LLP were \$2,472 and \$1,765, respectively. These fees were for a subscription to an online accounting and tax information service.

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

During the fiscal year ended December 31, 2006, 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 OF DIRECTORS RECOMMENDS A VOTE IN FAVOR OF PROPOSAL 2

13

SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

This table outlines the ownership of our common stock as of March 15, 2007 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)
Federated Investors, Inc. (3) Federated Investors Tower Pittsburgh, PA 15222-3779	10,368,830	12.4
Spencer R. Berthelsen (4)	74,370	*
Stanley T. Crooke (5)	1,586,059	1.9
Richard D. DiMarchi (6)	12,500	*
Joseph Klein, III (7)	23,100	*
Frederick T. Muto (8)	48,500	*
B. Lynne Parshall (9)	370,201	*
John C. Reed (10)	55,000	*
Joseph H. Wender (11)	86,000	*
David J. Ecker (12)	153,956	*
Michael J. Treble (13)	67,989	*
Mark K. Wedel (14)	89,844	*
All Directors and executive officers as a group (14 persons)(15)	2,828,500	3.4

* Less than one percent.

- (1) This table is based upon information supplied by officers, Directors, principal stockholders and Form 3s, Schedules 13D and 13G filed with the SEC. Unless otherwise indicated in the footnotes to this table and subject to community property laws where applicable, we believe that each of the stockholders named in this table has sole voting and investment power with respect to the shares indicated as beneficially owned.
- (2) Applicable percentages are based on 82,484,960 shares of common stock outstanding on March 15, 2007, adjusted as required by rules promulgated by the SEC.

- (3) Represents shares of our Common Stock beneficially owned by registered investment companies and separate accounts advised by Federated Equity Management Corp. (the “Investment Advisers”) as of December 31, 2006. The Investment Advisers are wholly owned subsidiaries of FH Holdings, Inc., which is a wholly owned subsidiary of Federated Investors, Inc. The beneficial ownership also includes 1,176,470 shares of common stock issuable upon exercise of warrants and 4,705,882 shares of Common Stock issued to Federated Kaufmann Fund, a portfolio of Federated Equity Funds, pursuant to the August 2005 Private Placement.
- (4) Includes 70 shares owned by Dr. Berthelsen’s daughter for which he disclaims beneficial ownership. Includes 45,000 shares of common stock issuable upon exercise of options held by Dr. Berthelsen that are exercisable on or before May 14, 2007.
- (5) Includes 676,143 shares of common stock issuable upon exercise of options held by Dr. Crooke that are exercisable on or before May 14, 2007. Also includes 36,625 shares of common stock issuable upon exercise of options held by Rosanne Crooke, Dr. Crooke’s wife, that are exercisable on or before May 14, 2007, and 1,050 shares owned by her. Dr. Crooke disclaims beneficial ownership of the shares of common stock owned and issuable upon exercise of options held by his wife.
- (6) Includes 12,500 shares of common stock issuable upon exercise of options held by Dr. DiMarchi that are exercisable on or before May 14, 2007.
- (7) Includes 5,000 shares of common stock issuable upon exercise of options held by Mr. Klein that are exercisable on or before May 14, 2007 and 100 shares of common stock indirectly beneficially owned by Mr. Klein’s son.
- (8) Includes 1,500 shares of common stock indirectly beneficially owned through the Cooley Godward LLP Salary Deferral and Profit Sharing Plan and 47,000 shares of common stock issuable upon exercise of options held by Mr. Muto that are exercisable on or before May 14, 2007.
- (9) Includes 335,532 shares of common stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before May 14, 2007, and an aggregate of 30,090 shares of common stock issuable upon exercise of options which Ms. Parshall transferred to her two daughters that are

exercisable on or before May 14, 2007.

- (10) Includes 55,000 shares of common stock issuable upon exercise of options held by Dr. Reed that are exercisable on or before May 14, 2007.
- (11) Includes 55,000 shares of common stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before May 14, 2007.
- (12) Includes 116,602 shares of common stock issuable upon exercise of options held by Dr. Ecker that are exercisable on or before May 14, 2007.
- (13) Includes 67,989 shares of common stock issuable upon exercise of options held by Mr. Treble that are exercisable on or before May 14, 2007.
- (14) Includes 79,530 shares of common stock issuable upon exercise of options held by Dr. Wedel that are exercisable on or before May 14, 2007.
- (15) Includes an aggregate of 1,820,185 shares issuable upon exercise of options held by all current Directors and executive officers as a group that are exercisable on or before May 14, 2007.

Section 16(a) Beneficial Ownership Reporting Compliance

Section 16(a) of the Securities Exchange Act of 1934, as amended (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 common stock and other equity securities of Isis. Officers, Directors and greater than ten percent stockholders are required by SEC regulation to furnish us with copies of all Section 16(a) forms they file.

To our knowledge, based solely on a review of the copies of such reports furnished to us and written representations that no other reports were required, during the fiscal year ended December 31, 2006, all Section 16(a) filing requirements applicable to our officers, Directors and greater than ten percent beneficial owners were complied with.

EXECUTIVE COMPENSATION

Compensation Discussion and Analysis

Compensation Overview and the Role of the Compensation Committee

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

The Compensation Committee's responsibilities include:

- overall compensation strategy;
- reviewing and approving corporate performance goals and objectives relevant to the compensation of Isis' executive officers;
- evaluating and recommending to the Board the compensation plans and programs advisable for Isis, as well as modifying or terminating existing plans and programs;
- establishing policies with respect to equity compensation arrangements;
- reviewing and approving compensation arrangements for Isis' executive officers, including its Chief Executive Officer;
- reviewing and approving compensation arrangements for Isis' Directors;
- administering Isis' benefit plans, including stock option and employee stock purchase plans;
- performing other functions as may be necessary or convenient in the efficient discharge of the foregoing; and
- reporting to the Board of Directors from time to time, or whenever it shall be called upon to do so.

Compensation Philosophy & Objectives

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

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

Elements of Executive Compensation

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

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

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

Base Salary

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

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

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

Each year we evaluate how our employees have performed their jobs and reward them for this performance with an appropriate merit salary increase. Our executive officers are eligible to receive this increase based both on a combination of Isis' performance and the officer's respective individual contribution to Isis. At the end of each year,

The Compensation Committee meets to evaluate the overall performance of the Company as well as the individual performance of each of the executive officers. They measure Company performance based upon the achievement of goals that were set at the beginning of the year and agreed upon by our Board and upper management. The Committee may also consider unexpected accomplishments, as well as failures, that occurred through the year. The Compensation Committee sets a Company-wide merit increase budget (percentage) based on the performance of the Company as well as external factors (the average merit increase being used by comparable companies). This serves as the basis for each individual salary increase.

As noted above, the Compensation Committee also evaluates each individual officer's performance. With respect to all executive officers, other than the CEO, the Compensation Committee gives great deference to our senior management's written evaluation of each individual executive officer. The Compensation Committee gives this 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 executive officer's new salaries for the upcoming year are calculated as follows:

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

For example, Dr. Crooke's 2007 salary was calculated as follows:

$$\frac{2006 \text{ Base Salary}}{\$582,218} \times \frac{\text{Merit Increase}}{(x) \quad 5\%} = \frac{2007 \text{ Base Salary}}{\$611,329}$$

Cash Bonus — At Risk

The next component of an executive officer's salary, as well as the salary of our employees at the director and above level, is a cash bonus through our management by objective bonus program. While we design individual salary to compensate an employee for his or her continued service with us, we designed our cash bonus portion of total compensation to compensate employees for reaching their objectives and for the judgment they use in making decisions. This portion of compensation is totally at risk. As such, bonus represents an opportunity for reward based upon the individual's level of accountability and depends on the relative success of both Isis and the individual.

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

$$\text{Base Salary} \times \text{Target MBO \%} \times \text{Company Success Factor} \times \text{Individual Success Factor}$$

Using this formula (the multipliers) ensures that we award bonuses based on the Company's performance, as well as based on the individual's performance. For example, in 1999, the Company Success Factor was 0% due to the failures the Company faced at the time. This resulted in no cash bonuses for executive officers and director level and above employees. Conversely, if Isis has a good year, we reward our employees proportionately using the Company Success Factor.

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

The Compensation Committee sets the Company Success Factor based on Isis' achievement of set objectives for the year, in the same manner the Committee sets the Company-wide merit increase budget described above.

Finally, the Committee assigns each individual officer an individual success factor, based on the same elements it used to evaluate the individual success factor for salary increases.

Once the Committee has determined all of the elements of the formula above, they apply the formula to each individual officer. For example, Dr. Crooke's cash bonus based on his performance in 2006 was calculated as follows and equated to \$423,855:

<u>Base Salary</u>	<u>(x)</u>	<u>Target MBO%</u>	<u>(x)</u>	<u>Company Success Factor</u>	<u>(x)</u>	<u>Individual Success Factor</u>
\$582,218	(x)	40%	(x)	130%	(x)	140%

An executive officer's salary plus bonus represents such 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. Recently, Institutional Shareholder Services (ISS) has become very active in this area and defined a ratio of 20-30 as ideal. Also, ISS has suggested a ratio of CEO to Executive level compensation of about 3.0. Dr. Crooke's total cash compensation is an average of 1.9 times greater than that of our other executive officers and 21.7 times that of the average cash compensation for our lowest level employees. This falls within industry standards, ISS guidelines, and our philosophy.

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 that year. We do not grant options that exceed the budget without the Compensation Committee's approval. The options we grant in any year represent options for new hires, promotions and annual merit grants for our existing employees. Over the past five years, the average option budget set by the Compensation Committee has been approximately 2.4% of our outstanding Common Stock on an as-issued basis. We believe the option budget is an important tool to balance our equity compensation objectives with stockholder interests. For 2006, the Compensation Committee set the option budget at 1.5 million shares, which represented 1.8% of our outstanding Common Stock on an as-issued 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 Company sets a vesting schedule that is typically over a 4-year period 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. We have historically had low employee turnover, particularly in our management team and our employees typically hold their options for a long period of time before exercise (on average over 5 years). The low turnover is indicative of our employees' commitment to Isis and its technology. As such, we believe our officers see the long term value of our stock and therefore we do not require our employees to own a minimum number of shares of our stock, or hold shares of our stock they acquire for minimum periods of time.

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

Finally, we have a Rule 10b5-1 Program. When there is no material non-public information available, our Rule 10b5-1 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

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 Employee Stock Purchase Plan (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 Executive Vice Presidents and CEO 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. We provide a component of severance compensation for our CEO and Executive Vice Presidents 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 Executive Vice Presidents "without cause" we will pay them the benefits described under "Post-Employment Compensation — Retention and Change of Control Agreements" of this proxy Statement. These agreements provide 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 2006; Business Highlights

2006 was a strong year for Isis. Highlights below are some of the key accomplishments for the year:

Cardiovascular Program

- In November 2006, at the American Heart Association meeting, we reported Phase 2 results from two studies: a monotherapy study and an add-on study with statins. Patients in both of these studies experienced potent, linear, dose-dependent reductions in all harmful lipids and triglycerides, and these reductions were comparable when ISIS 301012 was administered as a single agent or when it was added to ongoing statin therapy. ISIS 301012 was well tolerated in these studies. We are looking at higher dose groups in both studies as well as longer dosing in the add-on study.
- We secured \$75 million of financing from Symphony Capital to fund development of ISIS 301012 through the completion of registration-supporting clinical studies in patients with familial hypercholesterolemia and through the completion of Phase 2b development in routine high cholesterol patients as well as to develop through proof-of-concept clinical trials two new metabolic disease drugs. Consistent with our strategy, these funds will enable us to fund and control the development of ISIS 301012 to key value inflection points prior to partnering.

Metabolic Program

- We reported positive Phase 2 results for ISIS 113715, which inhibits production of PTP-1b. In the single-agent, dose-escalation study in treatment-naïve patients with type 2 diabetes, we reported at the American Diabetes Association 2006 Scientific Sessions that ISIS 113715 reduced glucose levels, and also lowered cholesterol. In this small, short-term study we did not see a statistically significant improvement in glycosylated hemoglobin, or HbA1c, which is a measure of long-term glucose control. The single-agent treatment was well tolerated in all dose cohorts.
- We also advanced the first of two new metabolic disease program drugs funded by Symphony Capital, ISIS 325568, into toxicology and pharmacokinetic studies in animals to support the initiation of human clinical studies. ISIS 325568 targets the receptor for glucagon, or GCGR, which is a hormone that opposes the action of insulin and stimulates the liver to produce glucose. Reducing the expression of GCGR using antisense drugs, and thereby reducing excessive liver glucose production, should lower blood sugar and help control type 2 diabetes.
- We recently advanced the second new diabetes drug funded by Symphony Capital, ISIS 377131, targeting the glucocorticoid receptor, or GCCR, into our development pipeline. Glucocorticoids promote breakdown of protein and fat from storage and ultimately result in increased liver glucose production. Reducing GCCR levels should reduce glucocorticoid action and have a beneficial effect on glucose control, blood lipid levels and body fat.

Partner Development Pipeline

- OncoGenex showed encouraging Phase 1 activity in patients with non-small cell lung cancer for OGX-011, an antisense inhibitor of clusterin now in five Phase 2 trials. We are co-developing this drug with OncoGenex, which has a second antisense drug, OGX-427, targeting Hsp27, that it expects to begin testing in Phase 1 clinical trials in 2007.
- Lilly highlighted two of our cancer drugs in its pipeline: LY2181308, targeting survivin, is poised to enter a broad Phase 2 program in 2007, and LY2275796, targeting eIF-4E, continues in Phase 1.

Intellectual Property, Licensing and Partnering Activity

- We were awarded several key U.S. patents, including a patent protecting our antisense drugs with modified sugars until 2023, a patent that broadly covers certain chemical modifications of oligonucleotides and the first issued patent protecting our core Ibis business. Additionally, the European Patent Office upheld on appeal a key Isis patent covering antisense drugs with gapmer structures.
- We licensed our aminoglycoside antibiotics program to Achaogen, Inc.
- We licensed an aptamer drug, ISIS 5320, to ImQuest Pharmaceuticals, Inc. to be developed as an anti-HIV topical microbicide.
- We and Rosetta Genomics Ltd. entered into a research collaboration to discover and develop antisense drugs that regulate microRNAs.
- We received a \$1 million milestone payment from Merck & Co., Inc. for the initiation of clinical trials of a compound that was discovered during a research collaboration between the companies.
- Alnylam Pharmaceuticals, Inc. paid us \$750,000 related to its sublicense of our technology to a pharmaceutical company.
- We received \$8 million from Drug Royalty USA, Inc. related to Macugen.
- We received a milestone payment from iCo Therapeutics Inc. based on its filing of an Investigational New Drug, or IND, application for iCo-007.
- We and Pfizer Inc. extended our research agreement, adding to the scope of target validation activities.

Ibis Biosciences, Inc.

2006 marked the transition of Ibis Biosciences from research and development to initial commercialization.

- Ibis announced a strategic alliance with Bruker Daltonics Inc., a subsidiary of Bruker Biosciences Corporation. Bruker Daltonics will provide Ibis T5000 instrument manufacturing along with global installation and support services.
- Ibis earned revenue from its first commercial orders for Ibis T5000 Biosensor Systems and assay services.

Financing Activity

- We received \$75 million from our collaboration with Symphony GenIsis to fund continued development of ISIS 301012 and two preclinical metabolic disease program drugs targeting GCGR and GCCR.
- We raised \$75 million by selling approximately 8.0 million shares of our common stock at an average price of \$9.41 per share under our equity line of credit with Azimuth Opportunity Ltd.

Based on Isis' successful achievement of these objectives for the year, the Compensation Committee set the Company Success Factors for salary and bonus as described above.

Taxes

Under Section 162(m) of the Code, we can only deduct up to \$1 million of compensation we pay to certain executive officers each taxable year. However, we may deduct compensation above \$1 million if it is "performance based compensation" within the meaning of the Internal Revenue Code. The Compensation Committee has determined that stock options granted under the 1989 Plan and the 2000 Plan with an exercise price at least equal to the fair market value of our common stock on the date of grant is performance-based compensation.

Compensation of Executive Officers

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

In 2006, 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 2006

Name and Principal Position	Year	Salary (\$)	Bonus(1) (\$)	Option Awards (2) (\$)	All Other Compensation(3) (\$)	Total (\$)
Stanley T. Crooke, Chairman, President and CEO	2006	\$ 582,218	\$ 423,855	\$ 411,091	\$ 11,213	\$ 1,428,377
B. Lynne Parshall, Director, Executive VP, CFO	2006	\$ 458,898	\$ 292,318	\$ 174,096	\$ 13,905	\$ 939,217
David J. Ecker, VP, Chief Scientific Officer of Ibis Biosciences, Inc.	2006	\$ 327,178	\$ 178,639	\$ 121,509	\$ 11,113	\$ 638,439
Michael J. Treble, VP, President of Ibis Biosciences, Inc.	2006	\$ 340,795	\$ 146,201	\$ 173,127	\$ 11,142	\$ 671,265
Mark K. Wedel, SVP, Development and Chief Medical Officer	2006	\$ 359,426	\$ 182,229	\$ 97,343	\$ 11,181	\$ 650,179

- Bonuses are included here in the years they were earned, not in the year in which they were paid. Bonuses represent compensation for achievements and are not necessarily paid in the year they are earned; i.e., bonuses for 2006 were paid in January 2007.
- Non-cash amounts calculated utilizing the provisions of Statement of Financial Accounting Standards ("SFAS") No. 123R, "Share-based Payment." For more information, please see Note 4 of the consolidated financial statements in our Annual Report for the year ended December 31, 2006 regarding assumptions underlying valuation of equity awards.
- Includes AD&D, Basic Life, Medical, Dental, Vision, and 401(k) company contributions which are available to all employees.

Grants of Plan-Based Awards

The following table shows for the fiscal year ended December 31, 2006, certain information regarding grants of plan-based awards to the Named Executive Officers:

Grants of Plan-Based Awards in Fiscal 2006

Name	Grant Date	All Other Option Awards: Number of Securities Underlying Options (#)	Exercise or Base Price of Option Awards (\$/Sh)	Grant Date Fair Value of Stock and Option Awards(1) (\$)
Stanley T. Crooke	1/3/06	128,924	\$ 5.25	\$ 391,305
	9/21/06	50,000	\$ 7.26	\$ 211,541
B. Lynne Parshall	1/3/06	49,506	\$ 5.25	\$ 150,258
	9/21/06	30,000	\$ 7.26	\$ 126,924
David J. Ecker	1/3/06	36,098	\$ 5.25	\$ 109,563
Michael J. Treble	1/3/06	40,842	\$ 5.25	\$ 123,962
Mark K. Wedel	1/3/06	25,784	\$ 5.25	\$ 78,259

- Non-cash amounts calculated utilizing the provisions of Statement of Financial Accounting Standards ("SFAS") No. 123R, "Share-based Payment." For more information, please see Note 4 of the consolidated financial statements in our Annual Report for the year ended December 31, 2006 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 at a previously scheduled meeting, which was held on January 3, 2007, the same date on which they granted stock awards to our other employees.

The Compensation Committee granted non-statutory stock options to Dr. Crooke and Ms. Parshall on September 21, 2006 at a regularly scheduled meeting as a result of a promotion within their job level at Isis. The options were priced using the closing price on the date of the Compensation Committee meeting.

All of these stock options were granted out of our 1989 Stock Option Plan. The options have a term of seven years, have an exercise price equal to the closing price on the Nasdaq on the date of grant 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.

We grant our annual merit stock option awards on the first trading day of the new year and set the option price at 100% of the closing price on the date of grant. For new hires and promotions, the Board has pre-approved standing resolutions that set the number of shares to be granted. The stock option price is set at 100% of the closing price on the date of hire or promotion, as applicable.

Outstanding Equity Awards at Fiscal Year — Executive Officers

The following table shows for the fiscal year ended December 31, 2006, 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 at December 31, 2006. In addition, there were no stock awards outstanding for the individuals named below at December 31, 2006.

Outstanding Option Awards At December 31, 2006

Name	Number of Securities Underlying Unexercised Options (#)	Number of Securities Underlying Unexercised Options (#)	(1) Full Vest Date	Option Exercise Price (\$)	Option Expiration Date
	Exercisable	Unexercisable			
Stanley T. Crooke	70,000	0	1/1/2002	\$ 12.3125	12/31/2007
	35,000	0	1/1/2003	\$ 12.9375	12/31/2008
	250,000	0	1/2/2002	\$ 6.8125	1/5/2010
	50,000	0	1/2/2005	\$ 9.6250	1/1/2011
	48,958	1,042	1/2/2007	\$ 6.8400	1/1/2013
	67,333	0	1/1/2006	\$ 5.1500	12/31/2008
	58,333	21,667	1/2/2008	\$ 6.8100	1/1/2014
	36,282	39,438	1/3/2009	\$ 5.8000	1/2/2012
	0	128,924	1/3/2010	\$ 5.2500	1/2/2013
	0	50,000	9/21/2010	\$ 7.2600	9/20/2013
B. Lynne Parshall	45,000	0	1/1/2002	\$ 12.3125	12/31/2007
	25,000	0	1/1/2003	\$ 12.9375	12/31/2008
	139,910	0	1/6/2000	\$ 6.8125	1/5/2010
	30,090(2)	0	1/6/2001	\$ 6.8125	1/5/2010
	28,000	0	1/2/2005	\$ 9.6250	1/1/2011
	24,479	521	1/2/2007	\$ 6.8400	1/1/2013
	6,466	0	1/1/2006	\$ 5.1500	12/31/2008
	28,000	10,400	1/2/2008	\$ 6.8100	1/1/2014
	14,501	15,762	1/3/2009	\$ 5.8000	1/2/2012
	0	49,506	1/3/2010	\$ 5.2500	1/2/2013
0	30,000	9/21/2010	\$ 7.2600	9/20/2013	
David J. Ecker	30,000	0	1/6/2004	\$ 6.8100	1/5/2010
	18,000	0	1/2/2005	\$ 9.6250	1/1/2011
	12,239	261	1/2/2007	\$ 6.8400	1/1/2013
	23,800	8,840	1/2/2008	\$ 6.8100	1/1/2014
	13,857	15,061	1/3/2009	\$ 5.8000	1/2/2012
0	36,098	1/3/2010	\$ 5.2500	1/2/2013	
Michael J. Treble	45,000	45,000	12/6/2008	\$ 5.9500	12/5/2011
	0	40,842	1/3/2010	\$ 5.2500	1/2/2013
Mark K. Wedel	24,479	521	1/1/2007	\$ 6.5900	12/31/2012
	4,406	94	1/2/2007	\$ 6.8400	1/1/2013
	10,500	0	1/1/2006	\$ 5.1500	12/31/2008
	12,236	4,545	1/2/2008	\$ 6.8100	1/1/2014
	9,989	10,859	1/3/2009	\$ 5.8000	1/2/2012
3,958	6,042	5/25/2009	\$ 3.9400	5/24/2012	
0	25,784	1/3/2010	\$ 5.2500	1/2/2013	

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

(2) Includes an aggregate of 30,090 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, 2006, certain information regarding option exercises and stock vested during the last fiscal year with respect to the Named Executive Officers:

Option Exercises in Fiscal 2006(1)

Name	Option Awards	
	Number of Shares Acquired on Exercise (2) (#)	Value Realized on Exercise (\$)
Stanley T. Crooke	—	—
B. Lynne Parshall	20,000	\$ 131,900
	30,000(3)	\$ 214,000

David J. Ecker	80,365	\$	316,347
	30,000	\$	158,298
Michael J. Treble	—		—
Mark K. Wedel	—		—

- (1) The Company currently does not utilize stock awards as part of its compensation plan. As such, the Company does not include information regarding stock awards that would otherwise appear as blank columns in this table.
- (2) All exercises and resulting sales were made pursuant to the Named Executive Officers' Rule 10b5-1 trading plan.
- (3) Exercise of transferred stock options by Ms. Parshall's two daughters pursuant to Ms. Parshall's Rule 10b5-1 trading plan.

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, up to a maximum matching contribution of \$3,300. 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, details of which are provided below.

Retention and Change of Control Agreements

In February 2006, we amended agreements with Stanley T. Crooke and B. Lynne Parshall to continue their April 2003 retention agreements. Specifically, we agreed to continue to provide the following severance benefits:

- Dr. Crooke will be eligible to receive a 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; and
- Ms. Parshall will be eligible to receive a severance payment equal to (i) 18 months of her then-current base salary in the event that her employment is terminated without cause and (ii) 30 months of her then-current base salary in the event that her employment is terminated as a result of a Change of Control.

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

On February 1, 2007, Jeffrey M. Jonas started his employment with Isis as Executive Vice President. As part of his employment, Isis entered into a severance benefit agreement with Dr. Jonas.

Dr. Jonas' severance agreement provides the following:

- In the event his employment is terminated without cause by Isis on or before February 1, 2008, he will be eligible to receive salary continuation equal to his then-current base salary, less payroll deductions and withholdings until the sooner to occur of the date he secures new employment or the twelve-month anniversary of the date of his termination; and
- If within the first twelve months of a specified change in control, his employment is terminated without cause by Isis or the acquirer, or he elects to terminate his employment because in his sole judgment his job responsibilities are significantly reduced, he will receive a severance payment equal to a total of 24 months of his then-current base salary, less payroll deductions and withholdings.

In connection with our recent recruitment of Dr. Jonas as Executive Vice President responsible for development, to whom Dr. Mark K. Wedel now reports, to affirm our commitment to Dr. Wedel as a senior contributor to Isis long term and to assure effective integration of Dr. Jonas, Isis entered an employee retention agreement with Dr. Wedel.

Isis designed the retention agreement in recognition of the significant change represented by the recruitment of Dr. Jonas and to present Dr. Wedel with an opportunity to contribute as an Isis employee for the long term. However, should Dr. Wedel decide the change is unsatisfactory, he may resign, and may be eligible to receive a salary continuation benefit depending on the date of his termination. If Dr. Wedel remains an employee of Isis through July 31, 2007, but terminates his employment before November 1, 2007 by providing at least 2 months prior notice, he will be eligible to receive a salary continuation benefit equal to 12 months plus two additional months of salary continuation for every month he remains an employee after August 1, 2007, not to exceed a maximum of 18 months salary continuation.

Conditions

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

Potential Payments Upon Termination or Change-In-Control

The following table estimates the payments that would be required under the agreements described above that were effective as of December 31, 2006. This table estimates the payments based upon either a termination without cause or a termination in connection with a change of control assuming either

occurred on December 31, 2006. The estimates in this table are forward-looking statements. Please see special note regarding forward-looking statements on page 33 of this Proxy Statement.

Name	Termination Event	
	Termination Without Cause	Termination in a Change of Control
Stanley T. Croke	\$ 0	\$ 1,746,654
B. Lynne Parshall	\$ 688,347	\$ 1,147,245

27

Director Compensation

We pay our non-employee Directors a fee of \$25,000 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, 2006, we paid total fees of \$25,000 to each of our non-employee Directors, excluding Mr. Gabrieli who received only \$12,500 as he retired from our Board in April 2006.

In 2006, each non-employee Director also received automatic stock option grants under our 2002 Non-Employee Directors' Stock Option Plan. On July 3, 2006, under the 2002 Non-Employee Directors' Stock Option Plan, each of our non-employee Directors serving at that time received an option to purchase 12,500 shares of our common stock, at an exercise price of \$5.93 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, 2006 certain information with respect to the compensation of all non-employee directors of the Company:

Director Compensation for Fiscal 2006

Name	Fees Earned or Paid in Cash (\$)	Option Awards (\$)	All Other Compensation (\$)	Total (\$)
Spencer R. Berthelsen	\$ 25,000	\$ 57,689	—	\$ 82,689
Richard D. DiMarchi	\$ 25,000	\$ 57,689	\$ 12,000(1)	\$ 94,689
Christopher F. O. Gabrieli(2)	\$ 12,500	—	—	\$ 12,500
Joseph Klein	\$ 25,000	\$ 57,689	—	\$ 82,689
Frederick T. Muto	\$ 25,000	\$ 57,689	—	\$ 82,689
John C. Reed	\$ 25,000	\$ 57,689	—	\$ 82,689
Joseph H. Wender	\$ 25,000	\$ 57,689	—	\$ 82,689

- (1) Fees paid to Dr. DiMarchi for consulting services. Please see "Certain Relationships and Related Transactions" for more information.
(2) Mr. Gabrieli ceased being a director on April 10, 2006.

28

Outstanding Equity Awards at Fiscal Year End — Directors

The following table shows for the fiscal year ended December 31, 2006, certain information regarding outstanding awards at fiscal year end of all non-employee directors of the Company:

Name	Number of Securities Underlying Unexercised Options (#)	
	Exercisable	Unexercisable
Spencer R. Berthelsen	45,000	27,500
Richard D. DiMarchi	12,500	30,000
Joseph Klein	5,000	27,500
Frederick T. Muto	47,000	27,500
John C. Reed	55,000	27,500
Joseph H. Wender	55,000	27,500

Certain Relationships and Related Transactions

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

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

Name	Year	Salary (\$)	Bonus(1) (\$)	Option Awards(2) (\$)	All Other Compensation(3) (\$)	Total (\$)
------	------	-------------	---------------	-----------------------	--------------------------------	------------

Dr. Rosanne Crooke	2006	\$ 114,951	\$ 15,144	\$ 18,211	\$ 2,226	\$ 150,532
--------------------	------	------------	-----------	-----------	----------	------------

- (1) Bonuses are included here in the years they were earned, not in the year in which they were paid. Bonuses represent compensation for achievements and are not necessarily paid in the year they are earned; i.e., bonuses for 2006 were paid in January 2007.
- (2) Non-cash amounts calculated utilizing the provisions of Statement of Financial Accounting Standards ("SFAS") No. 123R, "Share-based Payment." For more information, please see Note 4 of the consolidated financial statements in our Annual Report for the year ended December 31, 2006 regarding assumptions underlying valuation of equity awards. Represents an option to purchase 6,000 shares of the Company's common stock at an exercise price of \$5.25 per share Dr. Rosanne Crooke received on January 3, 2006.
- (3) Includes AD&D, Basic Life, Medical, Dental, Vision, and 401(k) company contributions which are available to all employees.

Prior to his joining the Board, Isis engaged Dr. Richard DiMarchi as a consultant. With over 22 years of experience in drug discovery and development, Dr. DiMarchi provides consulting to Isis regarding Isis' research projects and drugs in clinical development that is above and beyond the scope of his duties as a member of the Board. As such, Isis pays Dr. DiMarchi an additional \$12,000 a year for his consulting services.

One of our Directors, Mr. Muto, who was elected by the Board in March 2001, is a partner at Cooley Godward Kronish LLP, our outside counsel. We paid Cooley Godward Kronish an aggregate of \$108,494 in fees in 2006 for legal services, which amount is substantially less than five percent of Cooley's gross revenues for its 2006 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.

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

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

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

COMPENSATION COMMITTEE REPORT(5)

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 discussions, the Compensation Committee recommended to the Board of Directors that the Compensation Discussion and Analysis be included in the Company's proxy statement relating to the 2007 annual meeting of shareholders.

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

- (5) This Section is not "soliciting material," is not deemed filed with the SEC and is not to be incorporated by reference in any filing of Isis under the 1933 Act or the Exchange Act.

AUDIT COMMITTEE REPORT (6)

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, 2006 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 Independence Standards Board Standard No. 1. The Audit Committee also discussed with our independent auditors the matters required by the Statement on Auditing Standards No. 61.

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, 2006 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.

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

HOUSEHOLDING OF PROXY MATERIALS

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

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

(6) This Section is not "soliciting material," is not deemed filed with the SEC and is not to be incorporated by reference in any filing of Isis under the 1933 Act or the Exchange Act.

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, 2006 that we filed with the SEC, and is available free of charge. Please send written requests to:

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

You may also visit the Company's website (www.isispharm.com) to view our 2007 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

Special Note Regarding Forward-Looking Statements

This proxy statement includes forward-looking statements regarding Isis Pharmaceuticals' business, the financial position and outlook for Isis and Ibis Biosciences, and the therapeutic and commercial potential of the Company's technologies and products in development. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' goals or projections. 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, in developing and commercializing systems to identify infectious organisms that are effective and commercially attractive, and in the endeavor of building a business around such products. Isis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2006, which are on file with the SEC. Copies of these and other documents are available from the Company.

Isis Pharmaceuticals, Ibis Biosciences and Ibis T5000 are registered trademarks or trademarks of Isis Pharmaceuticals, Inc.



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

AUTO DATA PROCESSING
INVESTOR COMM SERVICES
ATTENTION:
TEST PRINT
51 MERCEDES WAY
EDGEWOOD, NY
11717

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 ADP; 51 Mercedes Way; Edgewood, NY 11717.

123,456,789,012.0000
0000 0000 0000

TO VOTE, MARK BLOCKS BELOW IN BLUE OR BLACK INK AS FOLLOWS: x ISISP1 KEEP THIS PORTION FOR YOUR RECORDS

THIS PROXY CARD IS VALID ONLY WHEN SIGNED AND DATED. DETACH AND RETURN THIS PORTION ONLY

ISIS PHARMACEUTICALS, INC.

THE BOARD OF DIRECTORS RECOMMEND A VOTE 02 000000000 214958298819
"FOR" ITEMS 1 and 2.

Vote On Directors	For All	Withhold All	For All Except	To withhold authority to vote for any individual nominee(s); mark "For All Except" and write the numbers(s) of the nominees(s) on the line below.
-------------------	------------	-----------------	-------------------	---------------------------------------------------------------------------------------------------------------------------------------------------

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

