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SCHEDULE 14A INFORMATION

Proxy Statement Pursuant to Section 14(a) of the Securities Exchange Act of 1934

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

Check the appropriate box:

- Preliminary Proxy Statement
- Confidential, for Use of the Commission Only (as permitted by Rule 14a-6(e)(2))**
- Definitive Proxy Statement
- Definitive Additional Materials
- Soliciting Material under Rule 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)(4) 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.
2292 Faraday Avenue
Carlsbad, CA 92008

NOTICE OF

2002 ANNUAL MEETING OF STOCKHOLDERS

AND PROXY STATEMENT

Dear Stockholders,

I am pleased to invite you to Isis Pharmaceuticals' 2002 Annual Meeting of Stockholders. We will host the meeting at our offices in Carlsbad, California on Friday, May 31 at 2:30 P.M. In addition to covering the formal items on the agenda, we will review the major developments of the past year 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 general information about Isis Pharmaceuticals.

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 a stockholder of record (that is, if your stock is registered with us in your own name), you may 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 allows you to vote by phone or 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 nominee.

We look forward to seeing you at the meeting.

Sincerely,

B. Lynne Parshall
Secretary

ISIS PHARMACEUTICALS, INC.
2292 Faraday Avenue
Carlsbad, CA 92008

NOTICE OF 2002 ANNUAL MEETING OF STOCKHOLDERS

Date: Friday, May 31
Time: 2:30 P.M.
Place: Isis Pharmaceuticals
2292 Faraday Avenue
Carlsbad, CA 92008

Dear Stockholders,

At our 2002 Annual Meeting, we will ask you to:

- Elect two Directors to each serve for a three-year term;
- Approve the 2002 Non-Employee Directors' Stock Option Plan;
- Ratify the selection of Ernst & Young LLP as independent auditors for 2002; and
- Transact any other business that may properly be presented at the Annual Meeting.

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

If you were an Isis stockholder of record at the close of business on April 1, 2002 you may vote at the Annual Meeting.

By order of the Board of Directors,

B. Lynne Parshall
Secretary

Carlsbad, California
April 22, 2002

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 RECORD HOLDER A PROXY ISSUED IN YOUR NAME.

ISIS PHARMACEUTICALS, INC.
2292 Faraday Avenue
Carlsbad, CA 92008

PROXY STATEMENT

INFORMATION ABOUT THE 2002 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 2002 Annual Meeting of Stockholders to be held on Friday, May 31, 2002, at 2:30 P.M. local time, or at any adjournment or postponement thereof, for the purposes stated herein. The Annual Meeting will be held at 2292 Faraday Avenue, Carlsbad, California. This Proxy Statement summarizes the information you will need to know to vote in an informed manner.

Voting Rights and Outstanding Shares

We will begin mailing this Proxy Statement and accompanying proxy card on or about April 22, 2002 to all stockholders who are entitled to vote. Only stockholders who owned our Common Stock at the close of business on April 1, 2002 are entitled to vote at the Annual Meeting. On this record date, we had 53,977,317 shares of our Common Stock outstanding.

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 separately tabulate affirmative and negative votes, abstentions and broker non-votes. Abstentions will count as a cast vote that has the same effect as a negative vote. The inspector of election will count broker non-votes towards a quorum. Broker non-votes will not count towards whether the stockholders have approved a proposal.

You may vote in one of three ways:

- Attend the 2002 Annual Meeting and vote in person;
- Complete, sign, date and return the enclosed proxy card; or
- Vote by telephone or the Internet by following the instructions included with your proxy card.

Solicitation

We will bear the entire cost of solicitation of proxies, including preparation, assembly, printing and mailing of 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, telegram or personal solicitation by directors, officers or other employees of Isis. No additional compensation will be paid to directors, officers or other employees for such services.

General Information for all Shares Voted via the Internet or by Telephone

Votes submitted via the Internet or by telephone must be received by 12:00 midnight, Eastern Daylight Time, on May 30, 2002. Submitting your proxy via the Internet or by telephone will not affect your right to vote in person should you decide to attend the Annual Meeting.

For Shares Registered in Your Name

If you are a stockholder of record, you may go to <http://www.voteproxy.com> to vote your shares by means of the Internet. The votes represented by such 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-PROXIES (1-800-776-9437) and following the recorded instructions. You will be required to provide the control number contained on your proxy card when you vote either by telephone or the Internet, so please have it 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 our proxy card.

A number of brokers and banks are participating in a program provided through ADP Investor Communication Services that allows proxies to vote shares to be granted 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 telephonically by calling the telephone number shown on the instruction form received from your broker or bank, or via the Internet at ADP Investor Communication Services' web site at <http://www.proxyvote.com>.

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. You may revoke your proxy in any one of three ways:

- You may send in by mail another proxy marked with a later date;
- You may revoke it via 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.

Stockholder Proposals

If you have a proposal or director nomination that you would like to be included in our proxy statement and form of proxy for, or to be presented at, the 2003 Annual Meeting of Stockholders, you must send the proposal to Isis by no later than December 22, 2002. 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 31, 2003 and no later than the close of business on March 2, 2003. Stockholders are also advised to review our Bylaws, which contain additional requirements with respect to advance notice of stockholder proposals and director nominations.

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PROPOSAL 1

ELECTION OF DIRECTORS

Information about our Board of Directors

The Board is divided into three classes, each consisting as nearly as possible of one third of the total number of directors. Presently, the Board has eight members, two classes consisting of three directors and one class consisting of two. Each class serves a three-year term, and we hold elections each year at the Annual Meeting to elect the directors whose terms have expired.

During the course of a term, 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. The new director will finish out the term of the director he or she replaced. Frederick T. Muto was elected by the Board in March 2001 and John C. Reed was elected by the Board in February 2002. Mr. Muto and Dr. Reed are scheduled for election by the stockholders at the 2003 Annual Meeting and 2004 Annual Meeting, respectively.

Information about the 2002 Elections

The Board has nominated two directors for election at the 2002 Annual Meeting. Each of the nominees currently serves as one of our directors. If re-elected, each will serve until the 2005 Annual Meeting or until his or her successor is elected and has qualified.

Our stockholders elect directors by a plurality of the votes of the shares present in person or represented 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 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 either nominee will be unable to serve. However, if either nominee cannot serve, your proxy may be voted for another nominee proposed by the Board, or the Board may reduce the number of directors.

We provide below a short biographical description 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 2005 Annual Meeting

B. Lynne Parshall, age 47, 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, outside counsel to Isis, where she was a partner from 1986 to 1991. Ms. Parshall is on the Board of Visitors at Stanford University Law School. Ms. Parshall is also a member of the Licensing Executives Society and a member of the American, California and San Diego bar associations.

Joseph H. Wender, age 57, has served as a director of Isis since January 1994. Mr. Wender is currently Senior Director of the Financial Institutions Group at Goldman, Sachs & Co., an investment banking firm. He joined Goldman, Sachs & Co. in 1971 and became a General Partner of that firm in 1982 and a Limited Partner in 1992. He is also a director of First Coastal Bancshares, a bank holding company, and Event 411, an Internet event planning company.

The Board recommends that you vote IN FAVOR of the election of each of the above nominees

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Biographies of Board Members Continuing Until the 2003 Annual Meeting

William R. Miller, age 73, has served as a director of Isis since March 1991. In January 1991, he retired as Vice Chairman of the Board of Directors of Bristol-Myers Squibb Company, a position he had held since 1985. He is Chairman of the Board of Trustees of the Cold Spring Harbor Laboratory. Mr. Miller is also Chairman of the Board of Vion Pharmaceuticals, Inc., a biopharmaceutical company. He is a director of ImClone Systems, Inc. and Transkaryotic Therapies, Inc., both biopharmaceutical companies.

Christopher F.O. Gabrieli, age 42, has served as a director of Isis since May 1994. Mr. Gabrieli was a founder of Isis and served as a director from January 1989 to May 1992. He is currently a manager of the general partners of Bessemer Venture Partners II L.P., Bessemer Venture Partners III L.P., Bessemer Venture Partners IV L.P. and related venture capital partnerships, where he has worked since 1986. He is Chairman of the Board of EPIX Medical, Inc., a developer of magnetic resonance imaging contrast agents. He is also the Co-Founder and Chairman of Massachusetts 2020, a non-profit education public policy organization.

Frederick T. Muto, age 48, has served as a director of Isis since March 2001. Mr. Muto joined the law firm of Cooley Godward LLP, outside counsel to Isis, in 1980 and became a partner in 1986. He is a founding partner of Cooley's San Diego office and serves as the partner in charge of that office. Mr. Muto also serves on Cooley's firmwide management committee.

Biographies of Board Members Continuing Until the 2004 Annual Meeting

Stanley T. Crooke, M.D., Ph.D., age 57, was a founder of Isis and has been Chief Executive Officer and a director since January 1989. He served as our President from January 1989 to May 1994, and was elected Chairman of the Board in February 1991. SmithKline Beckman Corporation, a pharmaceutical company, employed Dr. Crooke from 1980 until January of 1989, where his titles included President of Research and Development of SmithKline and French Laboratories. Dr. Crooke is Chairman of the Board of Idun Pharmaceuticals, Inc., a pharmaceuticals company. He also serves as a director of SYNSORB Biotech Inc. and Antisense Therapeutics Ltd., both biopharmaceutical companies, Axon Instruments, Inc., a developer and manufacturer of novel high-technology devices and software for drug discovery, Applied Molecular Evolution Inc., a biopharmaceutical company, and EPIX Medical, Inc., a developer of magnetic resonance imaging contrast agents. Dr. Crooke is also an adjunct professor of pharmacology at the Baylor College of Medicine and the University of California, San Diego.

John C. Reed, M.D., Ph.D., age 43, has served as a director of Isis since February 2002. Dr. Reed has been the President and Chief Executive Officer of The Burnham Institute, 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 ten years, serving as Director, Oncogene and Tumor Suppressor Gene Program, as the Deputy Director of the Cancer Center beginning in 1994, as Scientific Director beginning in 1995, and as Cancer Center Director in 2002. He also currently serves as 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. Prior to these positions, from 1989 to 1992, Dr. Reed worked as Assistant Director, Laboratory of Molecular Diagnosis at the hospital of the University of Pennsylvania and Assistant Professor, Department of Pathology and Laboratory Medicine at the University of Pennsylvania School of Medicine.

Mark B. Skaletsky, age 53, has served as a director of Isis since January 1989. Mr. Skaletsky is currently the Chairman, Chief Executive Officer and President of Essential Therapeutics, a biopharmaceutical company. From May 1993 to January 2001, Mr. Skaletsky served as President and

Chief Executive Officer of GelTex Pharmaceuticals, Inc., a biopharmaceutical company. From 1989 to 1993, Mr. Skaletsky was Chairman of Enzytech, Inc., a biopharmaceutical company, and Chief Executive Officer of Enzytech from 1988 to 1993. Mr. Skaletsky is also a director of ConjuChem, Inc. and ImmunoGen, Inc., both biopharmaceutical companies, and Paradigm Genetics, Inc., an integrated life science company. He is a director and past Chairman of the Biotechnology Industry Organization. In addition, Mr. Skaletsky is a member of the Board of Trustees of Bentley College located in Waltham, Massachusetts.

The Board of Director Committees and Meetings

The Board of Directors met seven times in 2001, including four regularly scheduled meetings and three special telephone meetings, and acted by unanimous written consent six times. The Board of Directors also has Audit, Compensation and Nominating committees. During 2001, all directors attended over 75% of the meetings of the Board and the committees on which they served.

As of June 5, 2001, the Audit Committee members are Mr. Wender (Chairman), Mr. Miller and Mr. Muto. Prior to that, the Audit Committee members were Mr. Skaletsky, Mr. Miller and Mr. Wender. None of the members of our Audit Committee are officers or employees of Isis and all are independent directors under currently applicable rules. The Audit Committee has adopted a formal written Audit Committee Charter, which was filed as an appendix to our 2000 Proxy Statement. The Audit Committee met five times in 2001.

The Audit Committee:

- Reviews the annual and quarterly financial statements and oversees the annual and quarterly financial reporting processes;
- Selects our independent auditors;
- Oversees the independence of our independent auditors;
- Evaluates our independent auditors' performance; and
- Receives and considers our independent auditors' comments as to controls, adequacy of staff and management performance and procedures in connection with audit and financial controls.

The members of the Compensation Committee are Mr. Skaletsky (Chairman), Mr. Miller and Mr. Wender, all of whom are non-employee directors of Isis. The committee met two times in 2001 and acted by unanimous written consent fourteen times. The Compensation Committee:

- Makes recommendations concerning executive salaries and incentive compensation;
- Awards stock options, bonus stock and rights to purchase restricted stock under our 1989 Stock Option Plan and 2000 Broad-Based Equity Incentive Plan;
-

Administers our 1989 Stock Option Plan, 2000 Broad-Based Equity Incentive Plan and 2000 Employee Stock Purchase Plan; and

- Determines executive compensation levels and performs other functions regarding compensation as the Board requests.

The Nominating Committee currently consists of two non-employee directors: Mr. Gabrieli (Chairman) and Mr. Muto. The committee informally discussed Board composition on a number of occasions but did not conduct any formal meetings in 2001. The Nominating Committee:

- Interviews, evaluates, nominates and recommends individuals for membership on our Board of Directors and its committees; and
- Considers nominees whom our stockholders may recommend.

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PROPOSAL 2

APPROVAL OF THE 2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN

Stockholders are requested in this Proposal 2 to approve the 2002 Non-Employee Directors' Stock Option Plan (the "Directors' Plan") which was adopted by the Board of Directors on September 11, 2001, subject to stockholder approval. This Plan amends, restates and retitles our 1992 Non-Employee Directors' Stock Option Plan previously approved by our stockholders.

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 2002 Annual Meeting will be required to approve the Directors' Plan.

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

Purpose

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

Administration

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

Stock Subject To The Directors' Plan

Subject to stockholder approval of this proposal, an aggregate of 600,000 shares of Common Stock is reserved for issuance under the Directors' Plan. As of February 28, 2002, 28,000 shares of Common Stock were reserved for issuance under the 1992 Non-Employee Directors' Plan. Therefore, if approved, the Directors' Plan will require approval of an additional 572,000 shares of Common Stock to create the 600,000 share reserve.

If options granted under the Directors' Plan expire or otherwise terminate without being exercised, the shares of Common Stock not acquired pursuant to such options again become available for issuance under the Directors' Plan. If we reacquire unvested stock issued under the Directors' Plan, the reacquired stock will not again become available for reissuance under the Directors' Plan.

Eligibility, Option Grants

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

Options granted under the Directors' Plan are nonstatutory stock options, meaning that they are not intended to qualify as incentive stock options within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended (the "Code"). Option grants under the Directors' Plan are non-discretionary. The Directors' Plan provides for (i) an initial grant of an option to purchase 20,000 shares of Common Stock to each person when he or she first becomes a non-employee director, and (ii) an annual grant, on July 1 or the next business day should such date be a Saturday, Sunday or holiday, of an option to purchase 10,000 shares of Common Stock to each non-employee director,

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commencing July 1, 2002. Prior to the proposed amendment and restatement, the 1992 Non-Employee Directors' Stock Option Plan provided for similar grants to each non-employee director, except that the initial grant was for 18,000 shares of Common Stock and each annual grant was for 4,000 shares of Common Stock.

As of February 28, 2002, we had granted options to purchase 391,000 shares of Common Stock under the 1992 Non-Employee Directors' Stock Option Plan and directors had exercised options to purchase 69,000 shares. No options have yet been granted under the Directors' Plan. On February 28, 2002, the last reported sales price of our Common Stock on the Nasdaq National Market was \$14.67 per share.

Terms of Options

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

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

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

An option granted under the Directors' Plan may be exercised by giving written notice of exercise to Isis, specifying the number of full shares of Common Stock to be purchased accompanied by payment of the purchase price.

Exercise Price; Payment. The exercise price of options granted under the Directors' Plan is equal to 100% of the fair market value of the Common Stock on the date granted; however, an option may be granted with a lower exercise price if the option is granted pursuant to an assumption or substitution for another option in a manner which satisfies the provision of Section 424(a) of the Code. The exercise price of options granted under the Directors' Plan must be paid in cash. To the extent provided by the terms of an option, an optionholder may satisfy any federal, state or local tax withholding obligation relating to the exercise of such option by a cash payment upon exercise, by authorizing Isis to withhold a portion of the stock otherwise issuable to the optionholder, by delivering already-owned shares of our Common Stock or by a combination of these means.

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

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

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

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

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

Adjustment Provisions

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

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

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

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

the options will terminate on the earlier of 12 months following the date of the Change of Control or the expiration date set forth in the option grant.

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

Duration, Amendment and Termination

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

Subject to stockholder approval, unless sooner terminated, the Directors' Plan will terminate on the day before the tenth anniversary of the date the Directors' Plan is approved by our stockholders.

Federal Income Tax Information

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

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

Upon disposition of the stock, the optionholder will recognize a capital gain or loss equal to the difference between the selling price and the sum of the amount paid for such stock plus any amount recognized as ordinary income upon exercise of the option (or vesting of the stock). Such gain or loss will be long-term or short-term depending on whether the stock was held for more than one year. Slightly different rules may apply to optionholders who are subject to Section 16(b) of the Exchange Act.

New Plan Benefits Table

The following table presents certain information with respect to options we expect to grant under the Directors' Plan for the fiscal year ending December 31, 2002 to our non-employee directors. This table assumes that each non-employee director continues as one of our directors throughout the year

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and that we do not elect any additional non-employee directors. This information is for illustration only and may not be indicative of grants that are made in the future under the Directors' Plan.

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

| Name of Non-Employee Director | Number of Option Shares |
|-----------------------------------|-------------------------|
| Christopher F. O. Gabrieli | 10,000 |
| William R. Miller | 10,000 |
| Frederick T. Muto | 10,000 |
| John C. Reed | 10,000 |
| Mark B. Skaletsky | 10,000 |
| Joseph H. Wender | 10,000 |
| Non-Employee Directors as a Group | 60,000 |

The Board of Directors recommends a vote IN FAVOR of Proposal 2

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PROPOSAL 3

RATIFICATION OF SELECTION OF INDEPENDENT AUDITORS

The Board of Directors has selected Ernst & Young LLP as our independent auditors for the fiscal year ending December 31, 2002, 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 2002 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 auditors, the Board would like to hear the stockholders' opinion as a matter of good corporate practice. If the stockholders vote against Ernst & Young LLP, the Board will reconsider whether or not to keep the firm. However, even if the stockholders ratify the selection, 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 Isis and its stockholders.

To ratify the selection of Ernst & Young LLP, the holders of a majority of shares present in person or represented by proxy and entitled to vote at the 2002 Annual Meeting must vote in favor of Proposal 3.

As of December 31, 2001, none of our finance or accounting employees had been employed by Ernst & Young LLP during the past six years.

Audit Fees:

For the fiscal year ended December 31, 2001, the aggregate fees paid to or due to Ernst & Young LLP related to the audit of our financial statements for such fiscal year and for the reviews of our interim financial statements was \$64,050.

Financial Information Systems Design and Implementation Fees:

During the fiscal year ended December 31, 2001, there were no fees billed by Ernst & Young LLP for information technology consulting fees.

All Other Fees:

During the fiscal year ended December 31, 2001, the aggregate fees billed by Ernst & Young LLP for professional services other than audit and information technology consulting fees were \$133,493 which were primarily for services provided in support of our secondary offering in October 2001 and tax and accounting advice.

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

During the fiscal year ended December 31, 2001, 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 3

SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

This table outlines the ownership of our Common Stock as of February 28, 2002 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) |
| Citigroup Inc. (3) 399 Park Avenue New York, NY 10043 | 7,523,924 | 13.9 |
| Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285 | 4,166,167 | 7.7 |
| Stanley T. Croke (4) | 1,573,918 | 2.9 |
| Christopher F. O. Gabrieli (5) | 1,265,349 | 2.3 |
| William R. Miller (6) | 69,000 | * |
| Frederick T. Muto (7) | 6,000 | * |
| B. Lynne Parshall (8) | 453,744 | * |
| John C. Reed (9) | 10,000 | * |
| Mark B. Skaletsky (10) | 56,000 | * |
| Joseph H. Wender (11) | 80,000 | * |
| C. Frank Bennett (12) | 127,142 | * |
| F. Andrew Dorr (13) | 102,699 | * |
| David J. Ecker (14) | 224,269 | * |
| All directors and executive officers as a group (17 persons)(15) | 4,563,654 | 8.1 |

* Less than one percent.

- (1) This table is based upon information supplied by officers, directors and principal stockholders and Schedules 13D and 13G filed with the Securities and Exchange Commission (the "SEC"). Unless otherwise indicated in the footnotes to this table and subject to community property laws where applicable, Isis believes 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 53,958,465 shares of Common Stock outstanding on February 28, 2002, adjusted as required by rules promulgated by the SEC.
- (3) Includes 6,015,469 shares held by Salomon Smith Barney Inc., 1,439,950 shares held by Smith Barney Fund Management LLC, all directly or indirectly wholly-owned subsidiaries of Citigroup Inc., and 68,505 shares held by Citigroup Inc. through other wholly-owned subsidiaries.
- (4) Includes 578,204 shares of Common Stock issuable upon exercise of options held by Dr. Crooke that are exercisable on or before April 29, 2002 and 23,473 shares of Common Stock issuable upon exercise of options held by Rosanne Crooke, Dr. Crooke's wife, that are exercisable on or before

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April 29, 2002. Dr. Crooke disclaims beneficial ownership of the shares of Common Stock issuable upon exercise of options held by his wife.

- (5) Includes 759,566 shares of Common Stock held of record by Bessemer Venture Partners II L.P. ("BVP II"), 329,479 shares of Common Stock held of record by Bessemer Venture Partners III L.P. ("BVP III") and 740 shares of Common Stock held of record by the Gabrieli Family Foundation ("GFF"). Mr. Gabrieli is a Manager of Deer II & Co. LLC and of Deer III & Co. LLC, the General Partners of BVP II and BVP III, respectively, and disclaims beneficial ownership of the shares of Common Stock held of record by or issuable to BVP II and BVP III, except to the extent of his respective interests therein. Mr. Gabrieli is a trustee of GFF and disclaims beneficial ownership of the shares of Common Stock held of record by or issuable to GFF. Also includes 49,000 shares of Common Stock issuable upon exercise of options held by Mr. Gabrieli that are exercisable on or before April 29, 2002.
- (6) Includes 6,500 shares of Common Stock issuable upon exercise of options held by Mr. Miller that are exercisable on or before April 29, 2002.
- (7) Includes 1,500 shares of Common Stock indirectly beneficially owned through the Cooley Godward LLP Salary Deferral and Profit Sharing Plan and 4,500 shares of Common Stock issuable upon exercise of options held by Mr. Muto that are exercisable on or before April 29, 2002.
- (8) Includes 440,600 shares of Common Stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before April 29, 2002, and an aggregate of 10,090 shares of Common Stock issuable upon exercise of options which Ms. Parshall transferred to her daughters that are exercisable on or before April 29, 2002.
- (9) Includes 10,000 shares of Common Stock issuable upon exercise of options held by Dr. Reed that are exercisable on or before April 29, 2002, granted to him under a previous consulting agreement.
- (10) Includes 34,000 shares of Common Stock issuable upon exercise of options held by Mr. Skaletsky that are exercisable on or before April 29, 2002.
- (11) Includes 49,000 shares of Common Stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before April 29, 2002.
- (12) Includes 126,287 shares of Common Stock issuable upon exercise of options held by Dr. Bennett that are exercisable on or before April 29, 2002.
- (13) Includes 102,699 shares of Common Stock issuable upon exercise of options held by Dr. Dorr that are exercisable on or before April 29, 2002.
- (14) Includes 39,034 shares of Common Stock held by the Ecker Family Revocable Trust in which Dr. Ecker is a trustee, and an aggregate of 5,382 shares of Common Stock held by Dr. Ecker's son and daughter. Also includes 179,853 shares of Common Stock issuable upon exercise of options held by Dr. Ecker that are exercisable on or before April 29, 2002.
- (15) Includes an aggregate of 2,205,050 shares issuable upon exercise of options held by all current directors and executive officers as a group that are exercisable on or before April 29, 2002.

Section 16(a) Beneficial Ownership Reporting Compliance

Section 16(a) of the Exchange Act requires Isis' directors and 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.

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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, 2001, all Section 16(a) filing requirements applicable to our officers, directors and greater than ten percent beneficial owners were complied with.

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EXECUTIVE COMPENSATION

Compensation of Directors

We pay our non-employee directors a fee of \$15,000 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, 2001, we paid a total of \$67,500 to our non-employee directors. Mr. Frederick T. Muto joined the Board in March 2001 and therefore only received \$7,500. Dr. Reed joined the Board in February 2002 and therefore did not receive any compensation for 2001.

Each non-employee director also received automatic stock option grants under our 1992 Non-Employee Directors' Stock Option Plan. Under the 1992 Non-Employee Directors' Stock Option Plan, each of our non-employee directors at that time received an option to purchase 4,000 shares of our Common Stock, at an exercise price of \$12.00 per share, on July 2, 2001. On March 6, 2001, Mr. Muto, upon his election to the Board, was granted an option to purchase 18,000 shares of stock under our 1992 Non-Employee Directors' Stock Option Plan, at an exercise price of \$10.625, the fair market value on the date of grant. The exercise price of each of the stock option grants mentioned above was equal to 100% of the fair market value of the Common Stock on the date of the grant (based on the closing sales price reported on the Nasdaq National Market). The options vest over a four year period in equal annual installments.

In addition, if the Directors' Plan is approved by the stockholders, future automatic grants for each non-employee director will be under the Directors' Plan, rather than the 1992 Non-Employee Directors' Stock Option Plan, as follows: (i) upon election to the Board, each new non-employee director will receive an automatic grant of an option to purchase 20,000 shares of our Common Stock, and (ii) on July 1 of each year (or the next business day should this date fall on a weekend or holiday), each non-employee director will receive an automatic annual grant of an option to purchase 10,000 shares of our Common Stock, as described in Proposal 2.

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Compensation of Executive Officers

The following table outlines the compensation paid to or earned by our Chief Executive Officer and each of our four other highest paid executive officers whose total annual salary and bonus exceeded \$100,000, for the fiscal years ending December 31, 2001, 2000, and 1999.

Summary Compensation Table

| Name and Principal Position | Year | Annual Compensation | | | Long-Term Compensation Awards | All Other Compensation (\$) |
|--|------|---------------------|-------------------|---|--|-----------------------------------|
| | | Salary (\$) | Bonus (\$) (1) | Other Annual Compensation (\$ (2) | Securities Underlying Options (#) | |
| Stanley T. Crooke Chairman, CEO and President | 2001 | 450,009 | 432,000 | 0 | 50,000 | 0 |
| | 2000 | 400,008 | 257,605 | 0 | 250,000(3) | 0 |
| | 1999 | 400,008 | 0 | 0 | 35,000 | 0 |
| B. Lynne Parshall Director, Executive VP & Chief Financial Officer | 2001 | 358,883 | 282,620 | 0 | 28,000 | 0 |
| | 2000 | 330,168 | 172,760 | 0 | 170,000(3) | 0 |
| | 1999 | 307,723 | 0 | 0 | 25,000 | 0 |
| C. Frank Bennett Vice President, Antisense Research | 2001 | 244,260 | 153,884 | 0 | 20,000 | 0 |
| | 2000 | 210,187 | 100,913 | 0 | 80,000 | 0 |
| | 1999 | 179,152 | 0 | 0 | 15,000 | 0 |
| F. Andrew Dorr Vice President, Chief Medical Officer | 2001 | 290,125 | 163,195 | 0 | 14,400 | 0 |
| | 2000 | 261,372 | 109,106 | 0 | 118,749(4) | 0 |
| | 1999 | 238,225 | 0 | 0 | 20,000 | 0 |
| David J. Ecker President, Ibis Therapeutics | 2001 | 241,125 | 150,964 | 0 | 18,000 | 0 |
| | 2000 | 209,249 | 93,150 | 0 | 70,000 | 0 |
| | 1999 | 186,727 | 0 | 0 | 15,000 | 0 |

- (1) Bonuses are included here in the years they were earned. Bonuses represent compensation for achievements and are not necessarily paid in the year they are earned; i.e., bonuses for 2001 were paid in January 2002.
- (2) As permitted by rules promulgated by the SEC, no amounts are shown for any executive officers where the amounts constitute perquisites and do not exceed the lesser of 10% of the sum of the aggregate amount in the Salary and Bonus columns or \$50,000.
- (3) Options were to fully vest on January 2, 2006; provided, however, that the options would fully vest on January 2, 2002 if certain performance objectives were met prior to that date. As of January 2, 2002, all of the objectives had been met and therefore the options fully vested.
- (4) Includes 10,000 options granted to Dr. Dorr in August 2000 in association with his promotion and 48,749 options issued in a 2 for 1 stock exchange offered to all non-executive officer employees. At the time of the exchange, Dr. Dorr was not an executive officer.

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Stock Option Grants and Exercises

Executive officers are granted stock options under our 1989 Stock Option Plan and 2000 Broad-Based Equity Incentive Plan (the "2000 Plan"). During 2001, options to purchase a total of 1,126,855 shares of our Common Stock had been granted under the 1989 Stock Option Plan and options to purchase 722,895 shares of our Common Stock had been granted under the 2000 Plan.

We implemented a stock trading program for our Board of Directors, corporate executive officers and other insiders, under Rule 10b5-1 of the Exchange Act. When there is no material non-public information available, Rule 10b5-1 allows corporate insiders to establish plans that permit prearranged future sales of his or

her securities.

The following tables show certain information regarding options granted to, exercised by, and held at year end December 31, 2001 by each of the executive officers named in the Summary Compensation Table:

Option Grants in Last Fiscal Year

| Name | Individual Grants | | | | Potential Realizable Value at Assumed Annual Rates of Stock Price Appreciation for Option Term (3) | |
|-------------------|--|---|------------------------|-----------------|--|----------|
| | Number of Securities Underlying Options Granted (#)(1) | % of Total Options Granted to Employees in Fiscal Year(2) | Exercise Price (\$/Sh) | Expiration Date | 5% (\$) | 10% (\$) |
| | | | | | | |
| Stanley T. Crooke | 50,000 | 2.7 | 9.625 | 01-01-11 | 302,551 | 766,663 |
| B. Lynne Parshall | 28,000 | 1.5 | 9.625 | 01-01-11 | 169,428 | 429,331 |
| C. Frank Bennett | 20,000 | 1.1 | 9.625 | 01-01-11 | 121,020 | 306,665 |
| F. Andrew Dorr | 14,400 | 0.8 | 9.625 | 01-01-11 | 87,135 | 220,799 |
| David J. Ecker | 18,000 | 1.0 | 9.625 | 01-01-11 | 108,918 | 275,999 |

- (1) Options granted in 2001 vest over a four-year period: 25% after the first year and 2.08% per month thereafter.
- (2) Based on options to purchase an aggregate of 1,849,750 shares granted in 2001 under our 1989 Stock Option Plan and our 2000 Plan. This is not necessarily indicative of the number of options that will be granted in the future.
- (3) The potential realizable value is calculated based on the term of the option at its time of grant, based on the assumption that the market value of the underlying stock increases at the stated values, compounded annually.

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Aggregated Option Exercises in Last Fiscal Year and FY-End Option Values

| Name | Shares Acquired on Exercise | Value Realized (1) | Number of Securities Underlying Unexercised Options at Fiscal Year End | Value of Unexercised In-the-Money Options at Fiscal Year End (2) |
|-------------------|-----------------------------|--------------------|--|--|
| | | | Exercisable/Unexercisable | Exercisable/Unexercisable |
| Stanley T. Crooke | 0 | \$ 0 | 308,203/310,939 | \$ 3,756,675/\$4,574,750 |
| B. Lynne Parshall | (3)32,600 | (3)\$ 524,078 | 268,918/205,710 | \$ 3,038,716/\$3,037,919 |
| C. Frank Bennett | 2,950 | \$ 18,658 | 133,828/66,022 | \$ 1,471,460/\$938,449 |
| F. Andrew Dorr | 5,000 | \$ 52,550 | 95,717/60,016 | \$ 1,326,992/\$812,090 |
| David J. Ecker | 0 | \$ 0 | 166,936/60,189 | \$ 2,276,696/\$813,139 |

- (1) Fair market value of our Common Stock on the date of exercise minus the exercise price.
- (2) Fair market value of our Common Stock at December 31, 2001 (\$22.19) multiplied by the applicable number of shares minus the aggregate exercise price of the options for the number of shares.
- (3) Includes an aggregate of 18,554 options exercised by Ms. Parshall's daughters that she had transferred to them.

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COMPENSATION COMMITTEE REPORT¹

The Compensation Committee of the Board of Directors consists of Mark B. Skaletsky, Chairman, William R. Miller and Joseph H. Wender, none of whom has ever been an officer or employee of Isis. The Compensation Committee's responsibilities include:

- Making recommendations concerning executive officer salaries and incentive compensation;
- Awarding employee stock options, bonus stock and rights to purchase restricted stock under our 1989 Stock Option Plan and the 2000 Broad-Based Equity Incentive Plan;
- Administering our 2000 Employee Stock Purchase Plan; and

- Determining executive officer compensation levels and performing other functions regarding compensation as the Board of Directors requests.

The full Board of Directors reviews the Compensation Committee's recommendations regarding the compensation of executive officers.

Compensation Committee Interlocks and Insider Participation

As noted above, during the fiscal year ended December 31, 2001, our Compensation Committee was composed of Messrs. Skaletsky, Miller and Wender, none of whom have ever been employees or officers 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.

Executive Compensation

We design our executive compensation programs to attract and retain executives who can help us meet our business objectives and to motivate them to enhance long-term stockholder value. The executive officers' annual compensation consists of three elements: cash salary, a cash incentive bonus and stock option grants.

To determine fair compensation, the Compensation Committee reviews historical and current salary, bonus and stock award information for other comparable companies in similar geographic areas and at similar stages of growth and development. The group of comparable companies is not necessarily the same as the companies included in the market indices included in the performance graph in this Proxy Statement. The Compensation Committee also reviews a variety of industry surveys throughout the year, which provide additional information about short and long-term executive compensation. Based in part on this information, the Compensation Committee generally sets salaries, including that of our Chief Executive Officer, at levels comparable to competitive companies of comparable size in similar industries. We structure our management bonus program around both individual and Isis' performance. We base the total size of the cash bonus pool on our success in meeting performance goals for the year, accounting for changes the Compensation Committee discusses and agrees to during the course of the year.

We use our stock option program to give management employees a substantial economic interest in the long-term appreciation of our Common Stock. We grant existing members of management new options on an annual basis to provide a continuing financial incentive. The size of the individual annual option grants is related to the executive's position and performance in the previous year. The Compensation Committee does consider the number of options held by executive officers when awarding new grants.

¹ The material in this report is not "soliciting material," is not deemed filed with the SEC and is not to be incorporated by reference in any filing of Isis under the Securities Act of 1933, as amended (the "1933 Act"), or the Exchange Act.

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 Stock Option 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 will be treated as performance-based compensation.

Assessment of 2001

We set extremely challenging objectives for 2001. In achieving the majority of those objectives, we made significant progress in the following areas:

- Ended the year with \$312.0 million in cash, including \$130.7 million from our strategic alliance with Eli Lilly and Company ("Lilly") and \$107.7 million from a secondary public offering;

Antisense Drug Discovery and Development

- Positive data from first clinical study of antisense drug based on second-generation chemistry
- Continued progress in developing oral formulations for antisense drugs
- Positive clinical data from four Phase II programs:
 - In non-small cell lung cancer, with ISIS 3521 (LY900003) plus chemotherapy, now partnered with Lilly
 - In Hepatitis C, with ISIS 14803, partnered with Elan Corporation, plc.
 - In psoriasis, with a topical cream formulation of alicaforsen (ISIS 2302)
- Initiation of a Phase III trial of alicaforsen (ISIS 2302) in Crohn's disease
- Initiation of new partnerships:
 - Lilly—License of ISIS 3521 (LY900003) and initiation of antisense drug discovery program in metabolic and inflammatory diseases

- Merck—License of ISIS 113715 preclinical drug for Type 2 diabetes
- Amgen—initiation of antisense drug discovery program
- OncoGenex Technologies, Inc.—collaboration to develop ISIS 112989 / OGX-011 in prostate cancer
- Antisense Therapeutics, Limited—collaboration to develop ISIS 107248 in multiple sclerosis and to discover antisense drugs

GeneTrove

- Initiation of new collaborations with Celera, Lilly, Chiron, Amgen
- Extension of Abbott collaboration
- Introduction of the Human Gene Function Database

Ibis Therapeutics

- Achievement of two milestones for drug discovery progress in Pfizer collaboration

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- Receipt of a nearly \$9 million contract to develop a diagnostic device to detect infectious agents used in biological warfare attacks

Intellectual Property

- Licensing of functional genomics patents to Chiron and Amgen with GeneTrove collaboration
- Licensing of non-antisense patents to Eyetech
- Licensing of antisense intellectual property to and from Hybridon and to and from Integrated DNA Technologies, Inc. (IDT)

Recent Developments

- Completion of enrollment of our 600-patient Phase III clinical trial of ISIS 3521 (LY900003) in combination with chemotherapy in patients with non-small cell lung cancer

As a result, the Compensation Committee recommended, and the Board approved, a corporate bonus guideline of 150%. Individual executive officer base salary increases were based on individual executive officer performance.

Compensation for Our CEO

Dr. Crooke's compensation is determined in accordance with the criteria described above for all executive officers. The Compensation Committee recommended that Dr. Crooke receive a salary increase of 8%, to \$486,000 for 2002. Dr. Crooke received a salary increase in 2001 of 12.5% and did not receive an increase in 2000. In January 2002, Dr. Crooke received a bonus of \$432,000 for accomplishments in 2001. In January 2001, the Committee also approved an option grant of 50,000 shares of Common Stock for Dr. Crooke, pursuant to our 2000 Plan, at an exercise price of \$9.625 per share, the fair market value on the date of grant.

Mark B. Skaletsky, Chairman
 William R. Miller
 Joseph H. Wender

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AUDIT COMMITTEE REPORT¹

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, 2001 with management, including a discussion of the quality, not just the acceptability, of the accounting principles, the reasonableness of significant judgments, and the clarity of disclosures in the financial statements.

The Audit Committee reviewed with our independent auditors, who are responsible for expressing an opinion on the conformity of our audited financial statements with generally accepted accounting principles, their judgments as to the quality, not just the acceptability, of our accounting principles and any other matters as are required to be discussed with the Audit Committee under generally accepted auditing standards. In addition, the Audit Committee has discussed with the independent auditors the auditors' independence from management and Isis, including the matters in the written disclosures required by the Independence Standards Board. The Audit Committee received from Ernst & Young LLP written disclosure and the letter regarding its independence as required by 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 the Annual Report on Form 10-K for the fiscal year ended December 31, 2001 for filing with the SEC. The Audit Committee and the Board have also recommended, subject to stockholder approval, the selection of our independent auditors.

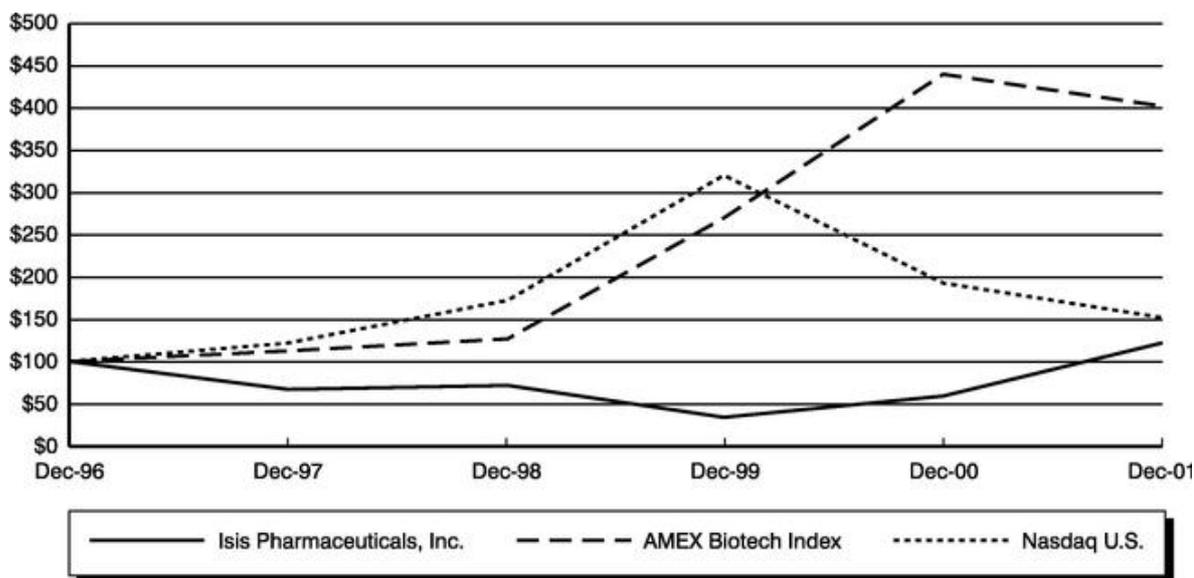
Joseph H. Wender, Audit Committee Chairman
 William R. Miller, Audit Committee Member
 Frederick T. Muto, Audit Committee Member

1 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.

Performance Measurement Comparison¹

**COMPARISON OF 5 YEAR CUMULATIVE TOTAL RETURN AMONG ISIS PHARMACEUTICALS, INC.,
 THE NASDAQ COMPOSITE INDEX (TOTAL RETURN) AND
 THE AMEX BIOTECH INDEX**

CUMULATIVE TOTAL RETURN
Based upon an initial investment of \$100 on December 31, 1996
with dividends reinvested



SOURCE: GEORGESON SHAREHOLDER COMMUNICATIONS INC.

| | Dec-96 | Dec-97 | Dec-98 | Dec-99 | Dec-00 | Dec-01 |
|---------------------------|--------|--------|--------|--------|--------|--------|
| Isis Pharmaceuticals Inc. | \$ 100 | \$ 68 | \$ 72 | \$ 35 | \$ 59 | \$ 123 |
| AMEX Biotech Index | \$ 100 | \$ 113 | \$ 128 | \$ 271 | \$ 440 | \$ 402 |
| Nasdaq U.S. | \$ 100 | \$ 122 | \$ 173 | \$ 321 | \$ 193 | \$ 153 |

The above table and chart assume \$100 invested on December 31, 1996 in our Common Stock, the NASDAQ Composite Index (Total Return) and the AMEX Biotech Index. Total return assumes reinvestment of dividends.

1 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.

Certain Transactions

In August 2001, we entered into a strategic alliance with Lilly in which we licensed our investigational drug, ISIS 3521, for non-small cell lung cancer, and formed a four-year research collaboration with Lilly. As part of the agreement, Lilly paid us an upfront fee of \$25.0 million for the license, provided a \$100 million interest free loan to fund the research collaboration's expenses, agreed to reimburse us for costs we had incurred related to our development of ISIS 3521, and purchased \$75 million of our Common Stock at \$18 per share. The loan is due in four years and is payable at

anytime in cash or our Common Stock at \$40 per share, at our option. At December 31, 2001, Lilly owned approximately 7.75% of our outstanding Common Stock. Additionally, Lilly agreed to reimburse us for costs we incur related to the ongoing trials for ISIS 3521, including the Phase III trial.

One of our directors, Mr. Frederick T. Muto, who was elected by the Board in March 2001, is a partner at Cooley Godward LLP, our outside counsel.

We have entered into indemnity agreements with certain officers and directors 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.

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, please request a copy of our Annual Report. The report is the Form 10-K for the year ended December 31, 2001 that we filed with the SEC, and is available free of charge. Please send written requests to:

B. Lynne Parshall, Secretary
Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008

By Order of the Board of Directors

B. Lynne Parshall
Secretary

April 22, 2002

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

1. PURPOSES.

(a) Amendment and Restatement. This Plan is an amendment and restatement of the Isis Pharmaceuticals, Inc. 1992 Non-Employee Directors' Stock Option Plan.

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

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

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

2. DEFINITIONS.

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

(b) "Annual Grant" means an Option granted annually to all Non-Employee Directors who meet the criteria specified in subsection 6(b) of the Plan.

(c) "Board" means the Board of Directors of the Company.

(d) "Capitalization Adjustment" has the meaning ascribed to that term in Section 11(a).

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

- (i)** any Exchange Act Person becomes the Owner, directly or indirectly, of securities of the Company representing more than 50% of the combined voting power of the Company's then outstanding securities other than by virtue of a merger, consolidation or similar transaction and other than by a purchase of securities directly from the Company;

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

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- (ii) there is consummated a merger, consolidation or similar transaction involving (directly or indirectly) the Company and, immediately after the consummation of such merger, consolidation or similar transaction, the stockholders of the Company immediately prior thereto do not Own, directly or indirectly, outstanding voting securities representing more than 50% of the combined outstanding voting power of the surviving Entity in such merger, consolidation or similar transaction or more than 50% of the combined outstanding voting power of the parent of the surviving Entity in such merger, consolidation or similar transaction;
- (iii) the stockholders of the Company approve or the Board approves a plan of complete dissolution or liquidation of the Company, or a complete dissolution or liquidation of the Company shall otherwise occur;
- (iv) there is consummated a sale, lease, license or other disposition of all or substantially all of the consolidated assets of the Company and its Subsidiaries, other than a sale, lease, license or other disposition of all or substantially all of the consolidated assets of the Company and its Subsidiaries to an Entity, more than 50% of the combined voting power of the voting securities of which are Owned by stockholders of the Company in substantially the same proportions as their Ownership of the Company immediately prior to such sale, lease, license or other disposition; or
- (v) individuals who, on the date this Plan is adopted by the Board, are members of the Board (the "Incumbent Board") cease for any reason to constitute at least a majority of the members of the Board; (*provided, however*, that if the appointment or election (or nomination for election) of any new Board member was approved or recommended by a majority vote of the members of the Incumbent Board then still in office, such new member shall, for purposes of this Plan, be considered as a member of the Incumbent Board).

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

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

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

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

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

(j) "**Continuous Service**" means that the Optionholder's service with the Company or an Affiliate, whether as an Employee, Director or Consultant, is not interrupted or terminated. A change in the capacity in which the Optionholder renders service to the Company or an Affiliate as an Employee, Consultant or Director or a change in the entity for which the Optionholder renders such service, provided that there is no interruption or termination of the Optionholder's service with the

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Company or an Affiliate, shall not terminate an Optionholder's Continuous Service. For example, a change in status from a Non-Employee Director of the Company to a Consultant of an Affiliate or an Employee of the Company shall not constitute an interruption of Continuous Service. The Board or the chief executive officer of the Company, in that party's sole discretion, may determine whether Continuous Service shall be considered interrupted in the case of any leave of absence approved by that party, including sick leave, military leave or any other personal leave.

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

- (i) a sale or other disposition of all or substantially all, as determined by the Board in its discretion, of the consolidated assets of the Company and its Subsidiaries;
- (ii) a sale or other disposition of at least 90% of the outstanding securities of the Company;
- (iii) a merger, consolidation or similar transaction following which the Company is not the surviving corporation; or
- (iv) a merger, consolidation or similar transaction following which the Company is the surviving corporation but the shares of Common Stock outstanding immediately preceding the merger, consolidation or similar transaction are converted or exchanged by virtue of the merger,

consolidation or similar transaction into other property, whether in the form of securities, cash or otherwise.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3. ADMINISTRATION.

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

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

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

(ii)

Agreement, in a manner and to the extent it shall deem necessary or expedient to make the Plan fully effective.

- (iii) To amend the Plan or an Option as provided in Section 12.
- (iv) To terminate or suspend the Plan as provided in Section 13.
- (v) Generally, to exercise such powers and to perform such acts as the Board deems necessary or expedient to promote the best interests of the Company and that are not in conflict with the provisions of the Plan.

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

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

4. SHARES SUBJECT TO THE PLAN.

(a) **Share Reserve.** Subject to the provisions of Section 11(a) relating to Capitalization Adjustments, the Common Stock that may be issued pursuant to Options shall not exceed in the aggregate 600,000 shares of Common Stock.

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

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

5. ELIGIBILITY.

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

6. NON-DISCRETIONARY GRANTS.

(a) **Initial Grants.** Without any further action of the Board, each person who is elected or appointed for the first time after the effective date of this amendment and restatement of the Plan to be a Non-Employee Director automatically shall, upon the date of his or her initial election or appointment to be a Non-Employee Director by the Board or stockholders of the Company, as applicable, be granted an Initial Grant to purchase 20,000 shares of Common Stock on the terms and conditions set forth herein.

(b) **Annual Grants.** Without any further action of the Board, after the effective date of this amendment and restatement of the Plan, a Non-Employee Director shall be granted an Annual Grant as follows: On July 1 of each year, beginning on July 1, 2002, each person who is then a Non-Employee Director automatically shall be granted an Annual Grant to purchase 10,000 shares of Common Stock

on the terms and conditions set forth herein. Should the date of grant set forth above be a legal holiday, then such grant shall be made on the next business day.

7. OPTION PROVISIONS.

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

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

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

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

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

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

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

(i)

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

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

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

(h) **Extension of Termination Date.** An Optionholder's Option Agreement may also provide that if the exercise of the Option following the termination of the Optionholder's Continuous Service (other than upon the Optionholder's death or Disability) would be prohibited at any time solely because the issuance of shares of Common Stock would violate the registration requirements under the Securities Act, then the Option shall terminate on the earlier of (i) the expiration of the term of the Option set

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forth in subsection 7(a) or (ii) the expiration of a period of 3 months after the termination of the Optionholder's Continuous Service during which the exercise of the Option would not be in violation of such registration requirements.

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

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

8. COVENANTS OF THE COMPANY.

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

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

9. USE OF PROCEEDS FROM STOCK.

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

10. MISCELLANEOUS.

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

(b) **Stockholder Rights.** No Optionholder shall be deemed to be the holder of, or to have any of the rights of a holder with respect to, any shares of Common Stock subject to such Option unless

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

(c) **No Service Rights.** Nothing in the Plan or any instrument executed or Option granted pursuant thereto shall confer upon any Optionholder any right to continue to serve the Company as a Non-Employee Director or shall affect the right of the Company or an Affiliate to terminate (i) the employment of an

Employee with or without notice and with or without cause, (ii) the service of a Consultant pursuant to the terms of such Consultant's agreement with the Company or an Affiliate or (iii) the service of a Director pursuant to the Bylaws of the Company or an Affiliate, and any applicable provisions of the corporate law of the state in which the Company or the Affiliate is incorporated, as the case may be.

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

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

11. ADJUSTMENTS UPON CHANGES IN STOCK.

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

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determination shall be final, binding and conclusive. (The conversion of any convertible securities of the Company shall not be treated as a transaction "without receipt of consideration" by the Company.)

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

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

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

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

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triggers the Payment): reduction of cash payments; cancellation of accelerated vesting of Options or other equity-based awards; reduction of employee benefits. In the event that acceleration of vesting of Options or other equity-based compensation is to be reduced, such acceleration of vesting shall be cancelled in the reverse order of the date of grant of the Optionholder's Options or other equity-based awards unless the Optionholder elects in writing a different order for cancellation.

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

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

12. AMENDMENT OF THE PLAN AND OPTIONS.

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

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

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

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

13. TERMINATION OR SUSPENSION OF THE PLAN.

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

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

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14. EFFECTIVE DATE OF PLAN.

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

15. CHOICE OF LAW.

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

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ANNUAL MEETING OF STOCKHOLDERS OF ISIS PHARMACEUTICALS, INC.

May 31, 2002

Co. # _____

Acct. # _____

PROXY VOTING INSTRUCTIONS

TO VOTE BY MAIL

Please date, sign and mail your proxy card in the envelope provided as soon as possible.

TO VOTE BY TELEPHONE (TOUCH-TONE PHONE ONLY)

Please call toll-free 1-800-PROXIES (1-800-776-9437) and follow the instructions. Have your control number and the proxy card available when you call.

TO VOTE BY INTERNET

Please access the web page at "www.voteproxy.com" and follow the on-screen instructions. Have your control number available when you access the web page.

YOUR CONTROL NUMBER IS -->

*/ Please Detach and Mail in the Envelope Provided */

A **Please mark your votes as in this example.**

FOR all nominees listed at right (except as marked to the contrary below).

WITHHOLD AUTHORITY to vote for all nominees listed at right

Proposal 1: To elect two directors to hold office until the 2005 Annual Meeting of Stockholders or until his or her successor is elected and has qualified.

O

O

To withhold authority to vote for any nominee(s), write such nominee(s) name(s) below:

THE BOARD OF DIRECTORS RECOMMENDS A VOTE FOR THE NOMINEES FOR DIRECTOR LISTED BELOW

Nominees: B. Lynne Parshall
Joseph H. Wender

THE BOARD OF DIRECTORS RECOMMENDS A VOTE FOR PROPOSALS 2 AND 3.

| | FOR | AGAINST | ABSTAIN |
|---|----------|----------|----------|
| Proposal 2: Approve the 2002 Non-Employee Directors' Stock Option Plan | O | O | O |
| Proposal 3: To ratify the selection of Ernst & Young LLP as independent auditors of the Company for its fiscal year ending December 31, 2002. | O | O | O |

Please vote, date and promptly return this proxy in the enclosed return envelope which is postage prepaid if mailed in the United States.

| | | | |
|-----------------------------|------------|-----------------|------------|
| SIGNATURE _____ | DATE _____ | SIGNATURE _____ | DATE _____ |
| (SIGNATURE IF HELD JOINTLY) | | | |

NOTE: Please sign exactly as your name appears hereon. If the stock is registered in the names of two or more persons, each should sign. Executors, administrators, trustees, guardians and attorneys-in-fact should add their titles. If signer is a corporation, please give full corporate name and have a duly authorized officer sign, stating title. If signer is a partnership, please sign in partnership name by authorized person.

ISIS PHARMACEUTICALS, INC.

PROXY SOLICITED BY THE BOARD OF DIRECTORS

FOR THE ANNUAL MEETING OF STOCKHOLDERS TO BE HELD ON MAY 31, 2002

The undersigned hereby appoints STANLEY T. CROOKE and B. LYNNE PARSHALL, and each of them, as attorneys and proxies of the undersigned, with full power of substitution, to vote all of the shares of stock of Isis Pharmaceuticals, Inc. (the "Company") which the undersigned may be entitled to vote at the Annual Meeting of Stockholders of the Company to be held at the Company's offices at 2292 Faraday Avenue, Carlsbad, California 92008 on Friday, May 31, 2002 at 2:30 p.m., and at any and all continuations and adjournments thereof, with all powers that the undersigned would possess if personally present, upon and in respect of the following matters and in accordance with the following instructions, with discretionary authority as to any and all other matters that may properly come before the meeting.

UNLESS A CONTRARY DIRECTION IS INDICATED, THIS PROXY WILL BE VOTED FOR PROPOSAL 1 AND FOR PROPOSALS 2 AND 3 AS MORE SPECIFICALLY DESCRIBED IN THE PROXY STATEMENT. IF SPECIFIC INSTRUCTIONS ARE INDICATED, THIS PROXY WILL BE VOTED IN ACCORDANCE THEREWITH.

Please date, sign and mail your proxy card back as soon as possible!

Annual Meeting of Stockholders
ISIS PHARMACEUTICALS, INC.

May 31, 2002

*/ Please Detach and Mail in the Envelope Provided */

A Please mark your votes as in this example.

FOR all nominees listed at right (except as marked to the contrary below).

WITHHOLD AUTHORITY to vote for all nominees listed at right

Proposal 1: To elect two directors to hold office until the 2005 Annual Meeting of Stockholders or until his or her successor is elected and has qualified.

O

O

To withhold authority to vote for any nominee(s), write such nominee(s) name(s) below:

THE BOARD OF DIRECTORS RECOMMENDS A VOTE FOR THE NOMINEES FOR DIRECTOR LISTED BELOW

Nominees: B. Lynne Parshall
Joseph H. Wender

THE BOARD OF DIRECTORS RECOMMENDS A VOTE FOR PROPOSALS 2 AND 3.

FOR

AGAINST

ABSTAIN

Proposal 2: Approve the 2002 Non-Employee Directors' Stock Option Plan

O

O

O

Proposal 3: To ratify the selection of Ernst & Young LLP as independent auditors of the Company for its fiscal year ending December 31, 2002.

O

O

O

Please vote, date and promptly return this proxy in the enclosed return envelope which is postage prepaid if mailed in the United States.

SIGNATURE _____ DATE _____ SIGNATURE _____ DATE _____
(SIGNATURE IF HELD JOINTLY)

NOTE: Please sign exactly as your name appears hereon. If the stock is registered in the names of two or more persons, each should sign. Executors, administrators, trustees, guardians and attorneys-in-fact should add their titles. If signer is a corporation, please give full corporate name and have a duly authorized officer sign, stating title. If signer is a partnership, please sign in partnership name by authorized person.

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- [Exhibit A ISIS PHARMACEUTICALS, INC. 2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN ADOPTED BY THE BOARD OF DIRECTORS SEPTEMBER 11, 2001 APPROVED BY STOCKHOLDERS, 2002 EFFECTIVE DATE: , 2002](#)