

As filed with the Securities and Exchange Commission on April 8, 2003

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# SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

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## SCHEDULE TO

Tender Offer Statement under Section 14(d)(1) or 13(e)(1)  
of the Securities Exchange Act of 1934

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### ISIS PHARMACEUTICALS, INC.

(Name of Subject Company—Issuer and Filing Person—Offeror)

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464330-10-9

(CUSIP Number of Class of Securities)

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B. Lynne Parshall, Esq.  
Executive Vice President  
Isis Pharmaceuticals, Inc.  
2292 Faraday Avenue  
Carlsbad, California 92008  
(760) 931-9200

(Name, address, and telephone number, of person authorized to receive notices and communications on behalf of Filing Person)

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#### CALCULATION OF FILING FEE

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Transaction Valuation	Amount of Filing Fee**
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\$49,323,328

\$3,991

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\* Calculated solely for purposes of determining the filing fee. This amount assumes that options to purchase 6,440,348 shares of Common Stock of Isis Pharmaceuticals, Inc. having an aggregate value of \$49,323,328 will be exchanged pursuant to this offer. The aggregate value of such options was calculated based on the Black-Scholes option pricing model as of March 31, 2003.

\*\* \$80.90 per \$1,000,000 of the aggregate offering amount, pursuant to Rule 0-11 of the Securities Exchange Act of 1934, as amended.

Check the box if any part of the fee is offset as provided by Rule 0-11(a)(2) and identify the filing with which the offsetting fee was previously paid. Identify the previous filing by registration statement number, or the Form or Schedule and the date of its filing.

Amount Previously Paid: Not applicable.

Filing Party: Not applicable.

Form or Registration No.: Not applicable.

Date Filed: Not applicable.

Check the box if the filing relates solely to preliminary communications made before the commencement of a tender offer.

Check the appropriate boxes below to designate any transactions to which the statement relates:

Third-party tender offer subject to Rule 14d-1.

Issuer tender offer subject to Rule 13e-4.

Going-private transaction subject to Rule 13e-3.

Amendment to Schedule 13D under Rule 13d-2.

Check the following box if the filing is a final amendment reporting the results of the tender offer: //

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## SCHEDULE TO

### ITEM 1. SUMMARY TERM SHEET.

The information set forth in the Offer to Exchange under the "Summary of Terms" section is incorporated herein by reference.

### ITEM 2. SUBJECT COMPANY INFORMATION.

(a) Name and Address. The name of the issuer is Isis Pharmaceuticals, Inc., a Delaware corporation (the "Company"), the address of its principal executive office is 2292 Faraday Avenue, Carlsbad, California 92008 and the telephone number of its principal executive office is (760) 931-9200. The information set forth in the Offer to Exchange under Section 16 ("Information About Isis") is incorporated herein by reference.

(b) Securities. This Tender Offer Statement on Schedule TO relates to an offer by the Company to exchange options issued prior to January 5, 2002 with exercise prices equal to or greater than \$5.00 per share currently outstanding under the Company's 2000 Broad-Based Equity Incentive Plan (the "2000 Plan") or the Company's 1989 Stock Option Plan (the "1989 Plan") (collectively, the "Option Plans"), to purchase shares of the Company's Common Stock, par value \$0.001 per share (the "Common Stock") held by optionholders as of April 8, 2003 (the "Eligible Option Grants") for replacement options (the "Replacement Options") to purchase shares of the Company's Common Stock to be granted under the 2000 Plan, upon the terms and subject to the conditions set forth in the Offer to Exchange (the "Offer"). Only employees of Isis as of April 8, 2003, who were not affected by the April 1, 2003 reduction in force and continue to be employed through the Offer expiration date of May 8, 2003, or a later date if the Offer period is extended, are eligible to participate in the Offer (the "Eligible Participants"). The Company's non-employee directors are not eligible to participate in the Offer. If an Eligible Participant accepts this Offer with respect to any Eligible Option, the Eligible Participant does not have to exchange all of his or her Eligible Option Grants. However, the Eligible Participant must tender all shares issuable under each particular Eligible Option it wishes to tender. The Company is conducting the exchange with respect to Eligible Option Grants based on the following exchange ratios dependent upon the exercise price of your stock options:

Option Price	Exchange Ratio (new for old)
Greater than or equal to \$5 but less than \$10	1:1.5
Greater than or equal to \$10 but less than \$15	1:2
Greater than or equal to \$15 but less than \$20	1:2.5
Greater than or equal to \$20	1:3

Thus, the Company will issue a Replacement Option covering an amount of shares equal to the applicable exchange ratio multiplied by the number of shares subject to a tendered Eligible Option. Eligible Participants who are currently on medical, maternity, worker's compensation, military or other statutorily protected leave of absence are eligible to participate in the Offer. However, individuals who would otherwise be Eligible Participants who (1) are on a leave of absence for any other reason and do not return to active status before the Offer termination date of May 8, 2003, or a later date if the Offer period is extended, or (2) whose services or employment are terminated or discontinued at any time before the Offer termination date of May 8, 2003, or a later date if the Offer period is extended, are not eligible to participate in this Offer and shall not be deemed Eligible Participants. The information set forth in the Offer to Exchange under the "Summary of Terms" section, Section 1 ("Number of Options; Expiration Date"), Section 5 ("Acceptance of Options for Exchange and Cancellation and Issuance of Replacement Options") and Section 8 ("Source and Amount of Consideration; Terms of Replacement Options") is incorporated herein by reference.

(c) Trading Market and Price. The information set forth in the Offer to Exchange under Section 7 ("Price Range of Common Stock") is incorporated herein by reference.

### ITEM 3. IDENTITY AND BACKGROUND OF THE FILING PERSON.

(a) Name and Address. The information set forth under Item 2(a) above is incorporated herein by reference.

### ITEM 4. TERMS OF THE TRANSACTION.

(a) Material Terms. The information set forth in the Offer to Exchange under the "Summary of Terms" section, Section 1 ("Number of Options; Expiration Date"), Section 3 ("Procedures"), Section 4 ("Change in Election"), Section 5 ("Acceptance of Options for Exchange and Cancellation and Issuance of Replacement Options"), Section 6 ("Conditions of the Offer"), Section 8 ("Source and Amount of Consideration; Terms of Replacement Options"), Section 10 ("Status of Options Acquired in the Offer; Accounting Consequences of the Offer"), Section 11 ("Legal Matters; Regulatory Approvals"), Section 12 ("Material U.S. Federal Income Tax Consequences"), Section 13 ("Terms of the Offer Specific to Eligible Participants Employed Outside of the United States"), and Section 14 ("Extension of Offer; Termination; Amendment") is incorporated herein by reference.

(b) Purchases. The information set forth in the Offer to Exchange under Section 9 ("Interests of Directors and Officers; Transactions and Arrangements Involving the Options") is incorporated herein by reference.

### ITEM 5. PAST CONTACTS, TRANSACTIONS, NEGOTIATIONS AND AGREEMENTS.

(a) Agreements Involving the Subject Company's Securities. The information set forth in the Offer to Exchange under Section 9 ("Interests of Directors and Officers; Transactions and Arrangements Involving the Options") is incorporated herein by reference.

### ITEM 6. PURPOSES OF THE TRANSACTION AND PLANS OR PROPOSALS.

(a) Purposes. The information set forth in the Offer to Exchange under Section 2 ("Purpose of the Offer") is incorporated herein by reference.

(b) Use of Securities Acquired. The information set forth in the Offer to Exchange under Section 5 ("Acceptance of Options for Exchange and Cancellation and Issuance of Replacement Options") and Section 10 ("Status of Options Acquired in the Offer; Accounting Consequences of the Offer") is incorporated herein by reference.

(c) Plans.

In December 2001, the severance benefits agreements we had with certain key employees expired. As a result, in April 2003, our board of directors approved entering new agreements with certain key employees, including our executive officers, pursuant to which we will agree to provide them severance benefits under certain conditions. In the event that one of the employee's employment is terminated without "cause", as defined in the agreement, by us on or before December 31, 2005 (the "Severance Period"), the employee will be eligible to receive a severance payment equal to a minimum of 9 months of his or her then current base salary, less payroll deductions and withholdings.

In the event that one of these employee's employment is terminated during the Severance Period as a result of a change in control as defined in the agreement, the employee's severance payment will be increased so that he or she will receive a minimum of 13.5 months of his or her then current base salary, less payroll deductions and withholdings.

Although Mr. Miller is currently a member of our Board of Directors, he is not running for re-election at our June Annual Meeting of Stockholders. As a result, he will continue to serve as a director through the date of the Annual Meeting. At that time, we will reduce the number of members on the Board to eight members.

At present, the Board of Directors is composed of nine (9) members. The Company from time to time evaluates strategic acquisitions and will continue to do so in the future. The Company may issue its

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stock or pay cash in connection with such acquisitions. The Company may obtain cash for such acquisitions through a variety of means, including, without limitation, through the issuance of additional stock. The information set forth in the Offer to Exchange under Section 9 ("Interests of Directors and Officers; Transactions and Arrangements Involving the Options") is incorporated herein by reference.

#### **ITEM 7. SOURCE AND AMOUNT OF FUNDS OR OTHER CONSIDERATION.**

(a) Source of Funds. The information set forth in the Offer to Exchange under Section 1 ("Number of Options; Expiration Date"), Section 8 ("Source and Amount of Consideration; Terms of Replacement Options") and Section 15 ("Fees and Expenses") is incorporated herein by reference.

(b) Conditions. The information set forth in the Offer to Exchange under Section 6 ("Conditions of the Offer") is incorporated herein by reference.

(c) Borrowed Funds. Not applicable.

#### **ITEM 8. INTEREST IN THE SECURITIES OF THE SUBJECT COMPANY.**

(a) Securities Ownership. Not applicable.

(b) Securities Transactions. The information set forth in the Offer to Exchange under Section 9 ("Interests of Directors and Officers; Transactions and Arrangements Involving the Options") is incorporated herein by reference.

#### **ITEM 9. PERSONS/ASSETS, RETAINED, EMPLOYED, COMPENSATED OR USED.**

Not applicable.

#### **ITEM 10. FINANCIAL STATEMENTS.**

(a) Financial Information. Item 8 ("Financial Statements and Supplementary Data") of Isis Pharmaceuticals, Inc.'s Annual Report on Form 10-K for the fiscal year ended December 31, 2002, filed on March 31, 2003, including all material incorporated by reference therein, is incorporated herein by reference. The information set forth in the Offer to Exchange under Section 16 ("Information About Isis") and Section 18 ("Additional Information") is incorporated herein by reference.

(b) Pro Forma Financial Information. Not applicable.

#### **ITEM 11. ADDITIONAL INFORMATION.**

Not applicable.

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#### **ITEM 12. EXHIBITS.**

<b>Exhibit Number</b>	<b>Description</b>
99.(a)(1)(A)	Offer to Exchange, dated April 7, 2003.
99.(a)(1)(B)	Form of Electronic Letter of Transmittal—Memorandum to Employees.
99.(a)(1)(C)	Form of Summary of Terms.
99.(a)(1)(D)	Form of Election Form.
99.(a)(1)(E)	Form of Notice of Change in Election from Accept to Reject.

99.(a)(1)(F)	Form of Notice of Change in Election from Reject to Accept.
99.(a)(1)(G)	Powerpoint slide presentation to holders of Eligible Option Grants.
99.(a)(1)(H)	Form of Confirmation of Participation in the Offer to Exchange.
99.(a)(1)(J)	Isis Pharmaceuticals, Inc.'s Annual Report on Form 10-K, for its fiscal year ended December 31, 2002, filed with the Securities and Exchange Commission on March 31, 2003, and incorporated herein by reference.
99.(b)	Not applicable.
99.(d)(1)(A)	Isis Pharmaceuticals, Inc.'s 2000 Broad-Based Equity Incentive Plan and related form of option agreement (incorporated herein by reference to the indicated exhibit in Isis Pharmaceuticals Annual Report on Form 10-K for the year ended December 31, 1999, originally filed March 28, 2000.
99.(d)(1)(B)	Rights Agreement dated as of December 8, 2000 between Isis Pharmaceuticals, Inc. and American Stock Transfer & Trust Company (incorporated herein by reference to Isis Pharmaceuticals, Inc.'s Report on Form 8-K dated December 8, 2000)
99.(g)	Not applicable.

**ITEM 13. INFORMATION REQUIRED BY SCHEDULE 13E-3.**

Not applicable.

[Remainder of this page intentionally left blank.]

**SIGNATURE**

After due inquiry and to the best of my knowledge and belief, I certify that the information set forth in this statement is true, complete and correct.

Dated: April 7, 2003

**ISIS PHARMACEUTICALS, INC.**

By: /s/ B. LYNNE PARSHALL

Name: B. Lynne Parshall

Title: Executive Vice President & CFO

**INDEX OF EXHIBITS**

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99.(b)	Not applicable.
99.(d)(1)(A)	Isis Pharmaceuticals, Inc.'s 2000 Broad-Based Equity Incentive Plan and related form of option agreement (incorporated herein by reference to the indicated exhibit in Isis Pharmaceuticals Annual Report on Form 10-K for the year ended December 31, 1999, originally filed March 28, 2000.
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99.(g)	Not applicable.

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**ISIS PHARMACEUTICALS, INC.  
2292 FARADAY AVENUE  
CARLSBAD, CA 92008  
(760) 931-9200**

**OFFER TO EXCHANGE  
OUTSTANDING OPTIONS  
TO PURCHASE COMMON STOCK  
APRIL 7, 2003**

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**ISIS PHARMACEUTICALS, INC.**

**OFFER TO EXCHANGE OUTSTANDING OPTIONS**

**THE OFFER EXPIRES AT 12:00 A.M., PACIFIC TIME, THURSDAY, MAY 8, 2003,  
UNLESS THE OFFER IS EXTENDED**

Isis Pharmaceuticals, Inc. (the "Company" or "Isis") is offering employees of Isis and its subsidiaries the opportunity to exchange all outstanding stock options with exercise prices equal to or greater than \$5.00 per share granted to them prior to January 5, 2002, under the Isis Pharmaceuticals, Inc. 2000 Broad-Based Equity Incentive Plan or the Isis Pharmaceutical 1989 Stock Option Plan, for a replacement option to purchase shares of our Common Stock (the "Offer"). The Company's non-employee directors are not eligible to participate in the Offer.

We are conducting the exchange of eligible options based on the following exchange ratios dependent upon the exercise price of your stock options:

<b>Option Price</b>	<b>Exchange Ratio (new for old)</b>
Greater than or equal to \$5 but less than \$10	1:1.5
Greater than or equal to \$10 but less than \$15	1:2
Greater than or equal to \$15 but less than \$20	1:2.5
Greater than or equal to \$20	1:3

If you choose to participate in the Offer, we will exchange the eligible options you tender for a replacement option to purchase a smaller number of shares of Common Stock calculated by multiplying the applicable exchange ratio by the number of shares that were subject to your eligible options, provided that you are employed with Isis on Thursday, May 8, 2003 (or later date if we extend the Offer). The terms of your replacement option will be substantially the same as the terms of your eligible options, except that the replacement option will:

- Have an exercise price equal to the greater of \$5.00 or the close price of our Common Stock as reported on the Nasdaq Stock Market on the last trading day before the date of the option exchange;
- Vest as follows: 33.34% will vest on January 1, 2004, then 2.78% will vest monthly thereafter for two years; and
- Expire on December 31, 2008.

As an example, assume that you hold two Eligible Option Grants: one Eligible Option Grant to purchase 6,000 shares of our Common Stock at an exercise price of \$7.00 per share and a second Eligible Option Grant to purchase 3,000 shares of our Common Stock at an exercise price of \$20.00 per share. Assume that the closing price of our Common Stock on the last day of trading before the date of the option exchange is \$4.50. If you choose to participate in the Offer, in exchange for the cancellation of both of your previous Eligible Option Grants, you will receive a replacement option for 5,000 shares (4,000 shares plus 1,000 shares) at an exercise price of \$5.00 per share. This replacement option will vest as follows: 33.34% (1667 shares) will vest on January 1, 2004, then 2.78% (139 shares) will vest monthly thereafter for two years, so that all 5,000 shares will be fully vested on January 1, 2006. The replacement option will expire if you do not exercise it before its expiration date, which is December 31, 2008.

If you wish to participate in the offer, you do not have to exchange all of your eligible options. However, you must exchange all shares issuable under each particular eligible option you wish to exchange. You may tender a partially exercised Eligible Option Grant so long as you tender all unexercised shares subject to such Eligible Option Grant

Only employees of Isis or one of its subsidiaries as of April 8, 2003 who were not affected by the April 1, 2003 reduction in force and continue to be employees through the Offer termination date of May 8, 2003 (or a later date if we extend the Offer period) are eligible to participate in the Offer. If

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you are on active status on the date the Offer expires, you are eligible to participate in the Offer. In addition, if you are currently on medical, maternity, worker's compensation, military or other statutorily-protected leave of absence, you are also eligible to participate in the Offer, whether or not you return to active status before the date the Offer expires. However, if you are on a leave of absence for any other reason, or if your employment with us terminates for any reason at any time before the Offer expires, you are not eligible to participate in the Offer.

We are making the Offer upon the terms and subject to the conditions described in the Offer to Exchange Outstanding Options (the "Offer Document"). This Offer is subject to conditions that we describe in Section 6 of the Offer Document. We are not making the Offer to employees in any jurisdiction in which the Offer or the acceptance of any tender of eligible options would not comply with the laws of such jurisdiction, and we will not accept any tender of eligible options from or on behalf of employees in any such jurisdiction. However, we may, at our discretion, take any actions necessary for us to extend the Offer to eligible employees in any jurisdiction.

**Although our Board of Directors has approved this Offer, neither we nor our Board of Directors makes any recommendations as to whether or not you should choose to participate in the Offer by tendering your eligible options for exchange. You must make your own decision whether to participate in the Offer. You should carefully review the Offer in its entirety before deciding whether to choose to change your eligible options.**

Shares of our Common Stock are quoted on the Nasdaq National Market under the symbol "ISIS." On April 7, 2003, the closing price of our Common Stock as reported on the Nasdaq National Market was \$3.74 per share. We recommend that you obtain current market quotations for our Common Stock before deciding whether to choose to exchange your options.

You should direct questions about this Offer, requests for assistance in completing the related documentation and requests for additional copies of the Offer Document or related documents to Linda Powell via email at [lpowell@isisph.com](mailto:lpowell@isisph.com) or via telephone at (760) 603-2471.

**This transaction has not been approved or disapproved by the Securities and Exchange Commission (the "SEC"), nor has the SEC passed upon the fairness or merits of such transaction or upon the accuracy or adequacy of the information contained in this document. Any representation to the contrary is a criminal offense. In the event of any conflict between this documentation and the terms of our 2000 Broad-Based Equity Incentive Plan or any applicable legislation, the terms or legislation (as the case may be) will take precedence. All references to taxation consequences are for guidance only.**

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## IMPORTANT

To accept this Offer, ***you must complete and sign the Election Form and deliver the Election Form to Linda Powell at Isis before 12:00 a.m., Pacific Time, on Thursday, May 8, 2003*** (or a later expiration date if we extend the Offer period). We ask you to return your Election Form, even if you choose not to participate in the Offer. The Election Form is the only document you need to return to indicate that you are choosing to participate in the Offer. You do not need to return the stock option agreements for your eligible options to effectively choose to accept the Offer; such stock option agreements will be cancelled automatically if Isis accepts your eligible options for exchange. However, you will be required to return such stock option agreements upon Isis' request.

The decision to accept or reject the Offer is an individual one that should be based on a variety of factors, and you should consult your personal advisors if you have questions about your financial or tax situation. The only information the Company is providing about the Offer is contained in this Offer Document and the tender offer statement filed with the SEC on April 8, 2003.

**We have not authorized any person to make any recommendation on the Company's behalf as to whether or not you should choose to participate in this Offer. We have not authorized anyone to give you any information or to make any representation in connection with this Offer other than the information and representations contained in this Offer Document and the tender offer statement filed with the SEC on April 8, 2003. If anyone makes any recommendation or representation to you or gives you any such information, it has not been authorized by the Company and you must not rely upon that recommendation, representation or information as having been authorized by us.**

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## SUMMARY OF TERMS

The following is a summary of terms (the "Summary") about the Offer to Exchange Outstanding Options (the "Offer Document," which, as it may be amended from time to time, constitutes the "Offer") presented in a question and answer format. We urge you to read carefully the remainder of the Offer Document and the accompanying documents because the information in this Summary is not complete. We have included references to the sections of the Offer Document where you can find a more complete description of the topics in this Summary.

### Q1. WHAT SECURITIES ARE WE OFFERING TO EXCHANGE AND WHO CAN PARTICIPATE IN THE OFFER?

We are offering to exchange all stock options granted prior to January 5, 2002, with exercise prices equal to or greater than \$5.00 per share currently outstanding under our 2000 Broad-Based Equity Incentive Plan (the "2000 Plan") or our 1989 Stock Option Plan (the "1989 Plan") (collectively, the "Plans") and held by Eligible Participants (the "Eligible Option Grants"). "Eligible Participants" are our employees, including our executive officers, as of April 8, 2003 who were not affected by the April 1, 2003 reduction in force and continue to be employed by us through the expiration date of the Offer. Our non-employee directors are not eligible to participate in the Offer. Our employees who are on active status on the date the Offer expires are Eligible Participants. In addition, our employees who are currently on medical, maternity, worker's compensation, military or other statutorily-protected leave of absence are also Eligible Participants, even if they do not return to active status before the date the Offer expires. However, an employee who is on a leave of absence for any other reason and does not return to active status before the Offer expires, or an employee whose employment with us terminates for any reason at any time before the Offer expires, is not an Eligible Participant. (See Section 1 of the Offer Document).

### Q2. WHY ARE WE MAKING THE OFFER

Our compensation philosophy is to retain and motivate our employees through appropriate levels of cash and equity compensation. Many of our outstanding options have exercise prices that are significantly higher than the current market price of our Common Stock. For that reason, we believe that it is unlikely that our employees will exercise these options in the near future and that these options do not provide proper incentives for our employees. By making this Offer, we believe we will be able to improve employee morale and provide a proper incentive to our employees by realigning our compensation programs to more closely reflect current market and economic conditions. (See Section 2 of the Offer Document.)

### Q3. ARE THERE CONDITIONS TO THE OFFER?

The Offer is subject to a number of general conditions, including the conditions described in Section 6 of the Offer Document, which may lead us to terminate or amend the Offer. However, if you are an Eligible Participant with Eligible Option Grants, the only conditions specific to your participation (assuming the Offer is not terminated or amended) are that you submit your Election Form before the deadline, and that you cannot exchange a fraction of the shares subject to an Eligible Option Grant. You may tender a partially exercised Eligible Option Grant so long as you tender all unexercised shares subject to such Eligible Option Grant. You should note that the Offer is not conditioned on a minimum of option holders accepting the Offer or a minimum of options being exchanged.

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### Q4. HOW MANY OPTION SHARES WILL I RECEIVE IN EXCHANGE FOR THE OPTION SHARES EXCHANGED?

If you choose to participate in the Offer under the terms described in the Offer Document, we will exchange your Eligible Option Grants for a new option (a "Replacement Option") based on the following exchange ratios depending on the exercise price of the Eligible Option Grants you tender.

Option Price	Exchange Ratio (new for old)
Greater than or equal to \$5 but less than \$10	1:1.5
Greater than or equal to \$10 but less than \$15	1:2
Greater than or equal to \$15 but less than \$20	1:2.5
Greater than or equal to \$20	1:3

As an example, assume that you hold two Eligible Option Grants: one Eligible Option Grant to purchase 6,000 shares of our Common Stock at an exercise price of \$7.00 per share and a second Eligible Option Grant to purchase 3,000 shares of our Common Stock at an exercise price of \$20.00 per share. Assume that the closing price of our Common Stock on the last day of trading before the date of the option exchange is \$4.50. If you choose to participate in the Offer, in exchange for the cancellation of both your Eligible Option Grants, you will receive a replacement option of 5,000 shares (4,000 shares plus 1,000 shares) at an exercise price of \$5.00 per share.

We will issue Replacement Options under the 2000 Broad-Based Equity Incentive Plan. (See Section 8 of the Offer Document.)

### Q5. WHEN WILL I RECEIVE MY REPLACEMENT OPTION?

We will grant Replacement Options on May 8, 2003 (or a later date if we extend the Offer). We expect to distribute your Replacement Option stock option agreement promptly following the date of grant.

### Q6. WHAT WILL BE THE TERMS AND CONDITIONS OF THE REPLACEMENT OPTIONS?

The exercise price, expiration date and vesting schedule of the Replacement Options will be different than the Eligible Option Grants. In all other aspects, the terms and conditions of the Replacement Options will be substantially the same as the Eligible Option Grants that are exchanged. See below for a discussion of the exercise price, expiration date and vesting schedule of the Replacement Options.

**Q7. WHAT WILL BE THE EXERCISE PRICE OF THE REPLACEMENT OPTIONS?**

The Replacement Options will have an exercise price equal to the greater of \$5.00 or the closing price of our Common Stock as reported on the Nasdaq National Market on the last market trading day before the date of grant. In the event that our Common Stock is not reported on the Nasdaq National Market as of such date, the exercise price will be the greater of \$5.00 or the fair market value as determined by our Board of Directors. We cannot guarantee that the exercise price for your Replacement Option will be lower than the exercise price for the Eligible Option Grants that you exchange. We recommend that you obtain current market quotations for our Common Stock before deciding whether to exchange your Eligible Option Grants. (See Section 7 of the Offer Document.)

**Q8. WHEN WILL MY REPLACEMENT OPTION EXPIRE?**

Your Replacement Option will expire at 5:00 p.m. Pacific Time, on December 31, 2008, so long as you remain employed by us.

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**Q9. WHEN WILL THE REPLACEMENT OPTIONS VEST AND WHAT WILL BE THE VESTING SCHEDULE OF THE REPLACEMENT OPTIONS?**

Each Replacement Option will vest as follows: 33.34% will vest on January 1, 2004, then 2.78% will vest monthly thereafter for two years, so that it will be fully vested on January 1, 2006.

In the event of a Change in Control, as further described in Section 8 of the Offer Document) then the vesting and exercisability of the Replacement Options will be accelerated in full; provided, however, that if such potential acceleration of the vesting and exercisability of this stock option would cause a contemplated Change in Control transaction that would otherwise be eligible to be accounted for as a "pooling-of-interests" transaction to become ineligible for such accounting treatment under generally accepted accounting principles as determined by the our independent certified public accountants prior to the Change of Control, such acceleration will not occur. (See Section 8 of the Offer Document).

**Q10. IF I HAVE INCENTIVE STOCK OPTIONS THAT ARE ELIGIBLE OPTIONS, WHAT HAPPENS IF I CHOOSE NOT TO EXCHANGE THEM IN THE OFFER?**

Choosing not to exchange your Eligible Option Grants will not subject you to U.S. Federal Income Tax. We do not believe that this Offer will change any of the terms of your Eligible Option Grants if you do not accept the Offer. However, the IRS may characterize the Offer to you as a "modification" of those Eligible Option Grants that are incentive stock options, even if you decline the Offer. A successful assertion by the IRS that such options have been modified could extend the options' holding period to qualify for favorable tax treatment and could cause a portion of such options to be treated as nonqualified stock options.

If you choose not to exchange your Eligible Option Grants and they include incentive stock options, we recommend that you consult with your tax advisor to determine the tax consequences if you later exercise those options and sell the Common Stock that you receive upon exercise.

**Q11. HOW LONG WILL I HAVE TO WAIT TO PURCHASE COMMON STOCK UNDER MY REPLACEMENT OPTION?**

The shares subject to your Replacement Option will vest according to the vesting schedule described in Question 9, so that they are fully vested on January 1, 2006. You will be able to exercise and sell shares subject to your Replacement Option as they vest. You will not be able to exercise or sell any shares subject to your Replacement Option that have not vested.

**Q12. IF I CHOOSE TO EXCHANGE MY ELIGIBLE OPTIONS, WILL THAT DECISION AFFECT OTHER COMPONENTS OF MY COMPENSATION?**

No. Whether or not you accept or reject the Offer will not affect your compensation in the future. Your acceptance or rejection of the Offer will not result in your becoming more or less likely to receive stock option grants in the future, other than the Replacement Options.

**Q13. IF I CHOOSE TO EXCHANGE ELIGIBLE OPTIONS, DO I HAVE TO EXCHANGE ALL OF MY ELIGIBLE OPTIONS OR CAN I EXCHANGE JUST SOME OF THEM?**

Should you choose to accept this Offer, you are not obligated to tender each Eligible Option Grant and are free to elect to tender as many or as few of the Eligible Option Grants as you wish. However, please note that you must tender all shares issuable under each particular Eligible Option Grant you wish to tender. You may tender a partially exercised Eligible Option Grant so long as you tender all unexercised shares subject to such Eligible Option Grant.

For example, if you hold an Eligible Option Grant to purchase 1,000 shares at an exercise price of \$7.00 and a second Eligible Option Grant to purchase 2,000 shares at \$12.00 per share, and each Eligible Option Grant was issued prior to January 5, 2002, you can choose to exchange just the

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\$12.00 Eligible Option Grant or just the \$7.00 Eligible Option Grant. However, if you choose to exchange just the \$12.00 Eligible Option Grant, you would have to exchange all 2,000 shares subject to that option. Similarly, if you choose to exchange just the \$7.00 Eligible Option Grant, you would have to exchange all 1,000 shares subject to that option.

**Q14. IF I HAVE STOCK OPTIONS WITH EXERCISE PRICES BELOW \$5.00 PER SHARE, WHAT HAPPENS TO THOSE OPTIONS IF I EXCHANGE ELIGIBLE OPTIONS?**

Nothing. Regardless of whether or not you choose to exchange your Eligible Option Grants under this Offer, there will be no change to your current options with exercise prices below \$5.00 per share. Such options will remain subject to the same terms and conditions under the Plan and your applicable stock option agreement as existed before the Offer.

**Q15. WILL I HAVE TO PAY TAXES IF I EXCHANGE MY OPTIONS IN THE OFFER?**

If you accept the Offer, you will not recognize income for U.S. Federal Income Tax purposes at the time of the exchange or at the time we grant a Replacement Option to you. If you are a non-U.S. employee and you accept the Offer, please refer to Appendix A for information about the tax treatment in your country. We recommend that you consult with your tax advisor to determine the tax consequences or potential social insurance contribution consequences (for non-U.S. employees) of accepting the Offer. (See Section 12 to the Offer Document if you are a U.S. employee and Appendix A to this document entitled "Guide to International Tax Issues" if you are a non-U.S. employee).

**Q16. IF MY ELIGIBLE OPTIONS INCLUDE INCENTIVE STOCK OPTIONS, WILL MY REPLACEMENT OPTION ALSO BE AN INCENTIVE STOCK OPTION, OR WILL IT BE A NONQUALIFIED STOCK OPTION?**

All Replacement Options will be nonqualified stock options and thus not subject to the favorable tax treatment applicable to incentive stock options. See Section 12 of the Offer to Exchange for a discussion of incentive and nonqualified stock options.

**Q17. WHEN DOES THE OFFER EXPIRE? CAN THE OFFER BE EXTENDED, AND IF SO, HOW WILL I KNOW IF IT IS EXTENDED?**

The Offer expires on May 8, 2003 at 12:00 a.m., Pacific Time, unless we extend it.

Although we do not currently intend to do so, we may, in our discretion, extend the Offer at any time. If we extend the Offer, we will announce the extension no later than 12:00 a.m., Pacific Time, on May 8, 2003. (See Section 15 of the Offer Document).

**Q18. WHAT DO I NEED TO DO?**

To accept this Offer, you must complete and sign the Election Form and deliver the Election Form to Linda Powell at Isis before 12:00 a.m., Pacific Time, on May 8, 2003 (or a later expiration date if we extend the Offer). Even if you choose not to participate in the Offer, we ask all Eligible Participants to return your Election Form. You may send the Election Form via mail, courier, hand delivery or facsimile. Linda Powell is located at our corporate headquarters at 2292 Faraday Avenue, Carlsbad, CA 92008. Linda Powell's direct facsimile number is (760) 603-4650. Election Forms must be received before 12:00 a.m., Pacific Time, on May 8, 2003 (or a later expiration date if we extend the Offer), *not* just mailed (or otherwise sent) by the expiration time. If Election Forms are sent by facsimile, originals should be sent by mail, courier or hand delivery as soon as possible.

You should direct questions about this Offer, requests for assistance in completing the related documentation and requests for additional copies of the Offer Document or related documents to Linda Powell via e-mail to [lpowell@isisph.com](mailto:lpowell@isisph.com) or via telephone at (760) 603-2471. You should

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review the Offer Document, the Election Form and all of their attachments before making your election.

If we extend the Offer beyond May 8, 2003, then you must sign and deliver the Election Form before the extended expiration date. We may reject any Eligible Option Grant to the extent that we determine the Election Form is not properly completed or to the extent that we determine it would be unlawful to accept the options. Although we may later extend, terminate or amend the Offer, we currently expect to accept all properly exchanged options promptly following the deadline of 12:00 a.m., Pacific Time, on May 8, 2003 (or a later expiration deadline if we extend the Offer). If you do not sign and deliver the Election Form before the Offer expires, it will have the same effect as if you rejected the Offer (See Section 3 of the Offer Document).

**Q19. DURING WHAT PERIOD OF TIME MAY I CHANGE MY PREVIOUS CHOICE TO ACCEPT OR REJECT THE OFFER?**

You may change your previous choice to accept or reject the Offer at any time before 12:00 a.m., Pacific Time, on May 8, 2003. If we extend the Offer beyond that time, you may change your previous choice at any time until the extended expiration deadline. To change your choice, you must deliver a Notice of Change in Election Form to Linda Powell before the Offer expires. If you change your choice from "reject" to "accept" you must also fill out and deliver a new Election Form. You may change your choice as many times as you want (See Section 4 of the Offer Document).

**Q20. WHAT HAPPENS TO MY OPTIONS IF I DO NOT ACCEPT THE OFFER?**

Nothing. If you do not accept the Offer, you will keep all of your current options and you will not receive a Replacement Option. No changes will be made to your current options (See Section 12 of the Offer Document for a discussion of any possible "modification" to your current incentive stock options in the event that you choose not to exchange your Eligible Option Grants).

**Q21. UNDER WHAT CIRCUMSTANCES WOULD ISIS NOT ACCEPT MY OPTIONS?**

We currently expect we will accept all Eligible Option Grants that are properly submitted for exchange and for which the choice has not been validly withdrawn. We may, however, reject any or all Election Forms, Notice of Change in Election Forms or exchanged options if we determine they were not properly executed or delivered, if we determine it is unlawful to accept the exchanged options or if certain conditions exist which in our reasonable judgment make it inadvisable to proceed with the Offer (See Section 3 of the Offer Document).

**Q22. AFTER I AM GRANTED A REPLACEMENT OPTION, WHAT HAPPENS IF THAT REPLACEMENT OPTION ENDS UP UNDERWATER?**

This Offer is a one-time offer. We do not expect to repeat this Offer in the future. Please note that unlike prior stock options granted under the Plans, which generally are valid for up to ten years from the date of initial grant (subject to continued service with Isis), your Replacement Option will expire on December 31, 2008 or approximately 66 months after the date of grant.) WE CAN PROVIDE NO ASSURANCE AS TO THE PRICE OF OUR COMMON STOCK AT ANY TIME IN THE FUTURE, AND NOTHING CONTAINED IN THIS DOCUMENT OR THE OTHER DOCUMENTS YOU RECEIVE RELATING TO THIS OFFER SHOULD BE INTERPRETED IN ANY WAY AS A CLAIM RELATING TO THE FUTURE PROSPECTS OF THE PRICE OF OUR COMMON STOCK, NOR SHOULD YOU DRAW ANY INFERENCE ABOUT SUCH FUTURE PROSPECTS FROM ANYTHING CONTAINED HEREIN OR THEREIN.

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**Q23. IF I AM AN ELIGIBLE PARTICIPANT EMPLOYED OUTSIDE OF THE UNITED STATES, AM I SUBJECT TO THE SAME TERMS AS DESCRIBED IN THE OFFER?**

If you are an Eligible Participant employed outside of the United States who holds Eligible Option Grants, you may participate in the Offer under the same terms as described herein. International employees should also refer to Appendix A to the Offer Document entitled "Guide to International Tax Issues" for a discussion of the tax and other consequences of accepting or rejecting the Offer under the law of the country in which you are employed.

**Q24. WHOM CAN I CONTACT IF I HAVE QUESTIONS ABOUT THE OFFER?**

For additional information or assistance, you should contact Linda Powell via e-mail at [lpowell@isisph.com](mailto:lpowell@isisph.com) or via telephone at (760) 603-2471. In addition, there will be a company-wide meeting to present and discuss information about the Offer.

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**THE OFFER**

**1. NUMBER OF OPTIONS; EXPIRATION DATE.**

We are offering to grant Replacement Options to purchase our Common Stock in exchange for Eligible Option Grants held by Eligible Participants. "Eligible Participants" are our employees as of April 8, 2003 who we continue to employ through the expiration date of the Offer and who were not affected by the April 1, 2003 reduction in force. Our non-employee directors are not eligible to participate. If you are on active status on the date the Offer expires, you are an Eligible Participant under the terms of this Offer. In addition, if you are currently on medical, maternity, worker's compensation, military or other statutorily protected leave of absence, you are also an Eligible Participant under the terms of the Offer, even if you do not return to active status before the date the Offer expires. However, if you are on a leave of absence for any other reason, or your employment with us terminates for any reason at any time before the Offer expires, you are not an Eligible Participant and cannot participate in the Offer.

"Eligible Option Grants" are those options granted prior to January 5, 2002 under our 1989 Stock Option Plan (the "1989 Plan") and/or our 2000 Broad-Based Equity Plan (the "2000 Plan") (collectively, the "Plans") with exercise prices equal to or greater than \$5.00 per share.

We are conducting the exchange with respect to Eligible Option Grants based on the following exchange ratios depending on the exercise price of the Eligible Option Grants you tender.

Option Price	Exchange Ratio (new for old)
Greater than or equal to \$5 but less than \$10	1:1.5
Greater than or equal to \$10 but less than \$15	1:2
Greater than or equal to \$15 but less than \$20	1:2.5
Greater than or equal to \$20	1:3

The exercise price of the Replacement Options will equal the greater of \$5.00 or the closing price of our Common Stock as reported on the Nasdaq Stock Market on the last trading day before the date of the option exchange.

You are not obligated to tender each Eligible Option Grant and are free to elect to tender as many or as few Eligible Option Grants as you wish. However, you must tender all shares issuable under each particular Eligible Option Grant you wish to tender.

If you have stock options with exercise prices below \$5.00 per share, accepting this Offer will not affect the terms and conditions of those stock options.

The Offer is subject to the terms and conditions described in this Offer Document. We will only accept options that are properly submitted for exchange and not validly withdrawn before the expiration date of the Offer, in accordance with Section 5 of this Offer Document.

If you exchange Eligible Option Grants, you will receive in exchange a Replacement Option covering a number of shares equal to the applicable exchange ratio multiplied by the total number of option shares subject to the Eligible Option Grant(s) you exchange.

As an example, assume that you hold two Eligible Option Grants: one Eligible Option Grant to purchase 6,000 shares of our Common Stock at an exercise price of \$7.00 per share and a second Eligible Option Grant to purchase 3,000 shares of our Common Stock at an exercise price of \$20.00 per share. Assume that the closing price of our Common Stock on the last day of trading before the date of the option exchange is \$4.50. If you choose to participate in the Offer, in exchange for the cancellation of both your previous Eligible Option Grants, you will receive a Replacement Option of 5,000 shares (4,000 shares plus 1,000 shares) at an exercise price of \$5.00 per share. This Replacement

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Option will vest as follows: 33.34% (1667 shares) will vest on January 1, 2004, then 2.78% (139 shares) will vest monthly thereafter for two years, so that all 5,000 shares will be fully vested on January 1, 2006. The Replacement Option will expire if you do not exercise it before its expiration date, which is December 31, 2008.

We will grant Replacement Options under the 2000 Broad-Based Equity Incentive Plan.

The term "expiration date" of this Offer means 12:00 a.m., Pacific Time, on May 8, 2003, unless and until we, in our discretion, extend the period of time during which the Offer will remain open. If we extend the period of time during which the Offer will remain open, the term "expiration date" will refer to the latest time and date at which the Offer expires. See Section 15 of this Offer Document for a description of our rights to extend, delay, terminate and/or amend the Offer.

We will publish a notice if we decide to take any of the following actions:

- change the number of shares subject to the Replacement Option that you will receive in exchange for your Eligible Option Grants;
- change the number of Eligible Option Grants that you can exchange in the Offer; or
- extend or terminate the Offer.

If the Offer is scheduled to expire within ten (10) business days from the date we notify you of such an increase or decrease, we also intend to extend the Offer until ten (10) business days after the date the notice is published. A "business day" means any day other than a Saturday, Sunday or federal holiday and consists of the time period from 12:01 a.m. through 12:00 a.m..

## 2. PURPOSE OF THE OFFER.

Isis' compensation philosophy is to motivate our employees through appropriate levels of cash and equity compensation. We granted the Eligible Option Grants for the following purposes:

- to provide our employees an opportunity to acquire or increase a financial interest in Isis, thereby creating a stronger incentive to assist Isis in achieving our corporate goals;
- to motivate, retain and reward our employees by providing competitive compensation packages; and
- to strengthen the alignment of interests between our employees and stockholders.

Since many of our outstanding options have exercise prices that are significantly higher than the current market price of our Common Stock, we believe that it is unlikely that our employees will exercise these options in the near future and that these options do not provide proper incentives for our employees. By making this Offer, we intend to maximize stockholder value by creating better performance incentives for our employees and to improve employee morale by realigning our compensation programs to more closely reflect the current market and economic conditions.

The Board of Directors has approved this Offer. ***We cannot guarantee that the Replacement Option will have a lower exercise price than those of the Eligible Option Grants.*** The decision to accept or reject the Offer is an individual one that should be based on a variety of factors, and you should consult with your personal advisors if you have questions about your financial or tax situation or the advisability of accepting this Offer.

## 3. PROCEDURES.

**Making Your Election.** To accept this Offer, you must complete and sign the Election Form and deliver the Election Form to Linda Powell at Isis before 12:00 a.m., Pacific Time, on May 8, 2003 (or a later expiration date if we extend the Offer). Even if you choose not to participate in the Offer, we ask that

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you return your Election Form. You may send the Election Form via mail, courier, hand delivery or facsimile. Linda Powell is located at our corporate headquarters, located at 2292 Faraday Avenue, Carlsbad, California 92008; her direct facsimile number is (760) 603-2471. Election Forms must be **received** before 12:00 a.m., Pacific Time, on May 8, 2003 (or a later expiration date if we extend the Offer), not just placed in the mail or other delivery system by the expiration time. Election Forms received by facsimile will be valid if received by the expiration time even though the originals are not yet received, but we request that you send originals by mail, courier or hand delivery as soon as possible. You do not need to return your stock option agreements for your Eligible Option Grants to accept the Offer, as they will be automatically cancelled if Isis accepts your Eligible Option Grants for exchange. However, you will be required to return your stock option agreements upon Isis' request.

**Determination of Validity; Rejection of Options; Waiver of Defects; No Obligation to Give Notice of Defects.** We will determine, in our discretion, all questions as to the number of shares subject to Eligible Option Grants and the validity, form, eligibility (including time of receipt) and acceptance of Election Forms and Notice of Change in Election Forms. Our determinations regarding these matters will be final and binding on all parties. We may reject any or all Election Forms, Notice of Change in Election Forms or exchanged options if we determine they were not properly executed or delivered or if we determine it is unlawful to accept the exchanged options. We may waive any or all of the conditions of the Offer for all Eligible Participants. We may waive any defect or irregularity in any Election Form or Notice of Change in Election Form with respect to any particular option or any particular optionholder. No Eligible Option Grants will be accepted for exchange until all defects or irregularities have been cured by the optionholder exchanging the Eligible Option Grants or waived by us. Neither we nor any other person is obligated to notify you of any defects or irregularities involved in the election to exchange any options, and no one will be liable for failing to give you notice of any such defects or irregularities.

**Our Acceptance Constitutes an Agreement.** If you choose to exchange your options according to the procedures described above, you will have accepted the Offer. Our acceptance of Eligible Option Grants that are properly submitted for exchange will form a binding agreement between us and you on the terms and subject to the conditions of this Offer.

Subject to our rights to extend, terminate and/or amend the Offer, we currently expect that promptly after the expiration date of the Offer we will accept all properly and timely made elections to exchange options that have not been validly withdrawn.

#### 4. CHANGE IN ELECTION.

You may only change your choice to accept or reject the Offer by following the procedures described in this Section 4.

You may change your choice to accept or reject the Offer at any time before 12:00 a.m., Pacific Time, on May 8, 2003. If we extend the Offer beyond that time, you may change your choice at any time until the extended expiration of the Offer.

Please note you have been supplied with two different Notice of Change in Election Forms, one of which you should use if you wish to reject the Offer after having accepted it and the other of which you should use if you wish to accept the Offer after having rejected it. If you intend to change your choice, it is important you follow the procedures outlined below.

To change your choice to accept or reject the Offer, you **must deliver** a Notice of Change in Election Form to Linda Powell at Isis before the Offer expires. The Notice of Change in Election Form must be signed by you, have your name on it, and must clearly indicate whether you choose to accept or reject the Offer. Please note that if you previously chose to reject the Offer and wish to change your choice and accept the Offer, you must also fill out and deliver a new Election Form along with the Notice of

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Change in Election. You may send the Notice of Change in Election Form and new Election Form (if applicable) via mail, courier, hand delivery or facsimile. Linda Powell is located at Isis' corporate headquarters, located at 2292 Faraday Avenue, Carlsbad, California 92008; her direct facsimile number is (760) 603-2471. Notice of Change in Election Forms received by facsimile will be valid if received by the expiration date even though the originals are not yet received, but we request that you send the originals by mail, courier or hand delivery as soon as possible.

Neither we nor any other person is obligated to give you notice of any defects or irregularities in any Notice of Change in Election Form, and no one will be liable for failing to give you notice of any defects or irregularities. We will determine, in our discretion, all questions as to the form and validity, including time of receipt, of Notice of Change in Election Forms. Our determinations regarding these matters will be final and binding.

#### 5. ACCEPTANCE OF OPTIONS FOR EXCHANGE AND CANCELLATION AND ISSUANCE OF REPLACEMENT OPTIONS.

On the terms and subject to the conditions of this Offer and as promptly as practicable following the expiration date, we will accept the Eligible Option Grants for exchange and cancel all Eligible Option Grants properly elected for exchange and not validly withdrawn before the expiration date. We will grant the Replacement Option on May 8, 2003 (or a later date if we extend the Offer).

If you are not continuously employed by or in continuous service with Isis through the expiration date of the Offer, you will not be eligible to receive a Replacement Option. We will give you notice of our acceptance for exchange and cancellation of Eligible Option Grants validly elected for exchange and not properly withdrawn as of the expiration date. We will notify you on or before May 8, 2003 (or a later expiration date if we extend the Offer), or as soon as possible thereafter, if we reject your election. If you are not notified of a rejection and you receive notice of our acceptance for exchange and cancellation of your Eligible Option Grants validly elected for exchange and not properly withdrawn, you may assume that your properly executed and delivered Election Form has been accepted. After we accept Eligible Option Grants for exchange and cancellation, we will promptly send each optionholder who accepted the Offer a letter confirming acceptance and the number of shares underlying the Replacement Option that we will grant to the optionholder.

#### 6. CONDITIONS OF THE OFFER.

We will not be required to accept any Eligible Option Grants that you choose to exchange. We may terminate or amend the Offer, or postpone our acceptance and cancellation of any Eligible Option Grants that you choose to exchange, any time before May 8, 2003 (or a later expiration date if we extend the Offer), if we determine that any event has occurred that, in our reasonable judgment, makes it inadvisable for us to proceed with the Offer or to accept and cancel Eligible Option Grants that you choose to exchange. The conditions are as follows:

- if any action or proceeding by any government authority or any other person, domestic or foreign, is threatened or pending that challenges the making of the Offer, the acquisition of some of the Eligible Option Grants, the issuance of Replacement Options, or otherwise relates to the Offer or that, in our reasonable judgment, could adversely affect our business, condition, income, operations or prospects or materially impair the benefits we believe we will receive from the Offer;

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- if any action is threatened, pending or taken, or any approval is withheld, by any authority, which, in our reasonable judgment, might directly or indirectly:
    - (a) make it illegal for us to accept some of the Eligible Option Grants or to issue some of the Replacement Options or otherwise restrict or prohibit completion of the Offer or otherwise relate to the Offer;
    - (b) delay or restrict our ability, or render us unable, to accept the Eligible Option Grants for exchange and cancellation or to issue Replacement Options in exchange for some of the Eligible Option Grants;
    - (c) materially impair our ability to provide employees with compensation by decreasing the value of the Replacement Options or otherwise; or
    - (d) materially and adversely affect our business, condition, income, operations or prospects;

- if there is:
  - (a) any general suspension of trading in, or limitation on prices for, securities on any national securities exchange or in the over-the-counter market; or
  - (b) the declaration of a banking moratorium or any suspension of payments in respect of banks in the United States, whether or not mandatory;
  
- if another person publicly makes or proposes a tender or exchange offer for some or all of our Common Stock, or an offer to merge with or acquire us, or we learn that:
  - (a) any person, entity or "group," within the meaning of Section 13(d)(3) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), has acquired or proposed to acquire beneficial ownership of more than 5% of the outstanding shares of our Common Stock, or any new group shall have been formed that beneficially owns more than 5% of the outstanding shares of our Common Stock, other than any such person, entity or group that has filed a Schedule 13D or Schedule 13G with the SEC before May 8, 2003;
  - (b) any such person, entity or group that has filed a Schedule 13D or Schedule 13G with the SEC before May 8, 2003 has acquired or proposed to acquire beneficial ownership of an additional 2% or more of the outstanding shares of our Common Stock; or
  - (c) any person, entity or group shall have filed a Notification and Report Form under the Hart-Scott-Rodino Antitrust Improvements Act of 1976 disclosing or made a public announcement that it intends to acquire us or any of our assets or securities;
  
- if any change occurs in our business, condition, assets, income, operations, prospects or stock ownership that, in our reasonable judgment, may be material to us, including the following:
  - (a) litigation or other proceedings instituted against us or one of our subsidiaries, or any of our officers or directors in their capacities as such, before or by any Federal, state or local court, commission, regulatory body, administrative agency or other governmental or legislative body, domestic or foreign, in which an unfavorable ruling, decision, action, order, decree or finding resulting from such litigation or proceeding would materially and adversely affect us;
  - (b) a material loss or interference with our business or properties from fire, explosion, earthquake, flood or other casualty, whether or not covered by insurance, or from any labor dispute;

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- (c) a substantial decline or increase in our stock price or significant volatility in the market price of our stock resulting from any number of factors including, but not limited to, fluctuations in our operating results, announcements of technological innovations, new products or clinical trial results, the announcement, commencement, termination or modification of collaborative relationships by us or our competitors or general market conditions;
  - (d) the suspension of trading in our common stock by the SEC or by the Nasdaq Stock Market; or
  - (e) a material change in the prospects for our business in the future resulting from any number of factors, such as announcements of technological innovations, new products, clinical trial results, the announcement, commencement, termination or modification of collaborative relationships by us or our competitors, general market conditions, a material adverse change in the financial or securities markets in the United States or in political, financial or economic conditions in the United States or any outbreak or material escalation of foreign or domestic hostilities or other calamity or crisis; or
- if we are required to extend the expiration date of the Offer beyond May 8, 2003 as a result of action or determination by the SEC or other regulatory authority.

The conditions to the Offer are for our benefit. We may assert the conditions to the Offer in our discretion before the expiration date. We may also waive any condition to the Offer in accordance with applicable law, at any time before the expiration date, whether or not we waive any other condition to the Offer.

Our failure to exercise any of these rights is not a waiver of any of these rights. The waiver of any of these rights with respect to particular facts and circumstances is not a waiver with respect to any other facts and circumstances. Any determination we make concerning the conditions in this Section 6 will be final and binding upon everyone. We currently expect that we will accept all Eligible Option Grants that are properly submitted to be exchanged and have not been validly withdrawn.

## 7. PRICE RANGE OF COMMON STOCK.

There is no established trading market for the Eligible Option Grants. The securities underlying the Eligible Option Grants are shares of our Common Stock. Our Common Stock is quoted on the Nasdaq National Market under the symbol "ISIS." The following table shows, for the periods indicated, the high and low closing sale prices per share of our Common Stock as reported on the Nasdaq National Market.

	HIGH	LOW
<b>Year Ending December 31, 2003</b>		
First Quarter	\$ 7.55	\$ 2.50
<b>Year Ended December 31, 2002</b>		
First Quarter	\$ 22.40	\$ 14.07
Second Quarter	\$ 18.00	\$ 6.76
Third Quarter	\$ 11.86	\$ 6.10
Fourth Quarter	\$ 11.00	\$ 6.00
<b>Year Ended December 31, 2001</b>		
First Quarter	\$ 13.00	\$ 7.97
Second Quarter	\$ 13.17	\$ 7.88
Third Quarter	\$ 18.05	\$ 9.75
Fourth Quarter	\$ 27.15	\$ 16.70

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As of April 4, 2003, the last reported sale price of our Common Stock, as reported on the Nasdaq National Market, was \$3.74 per share.

*We cannot guarantee that your Replacement Option will have a lower exercise price than those of your Eligible Option Grants.* We recommend that you obtain current market quotations for our Common Stock before deciding whether to exchange your options.

## 8. SOURCE AND AMOUNT OF CONSIDERATION; TERMS OF REPLACEMENT OPTIONS.

**Consideration.** We are conducting the exchange with respect to Eligible Option Grants based on the exchange ratios described in Section 1 above.

Thus, for Eligible Participants who choose to participate in the Offer, on May 8, 2003 (or a later date if we extend the Offer), we will grant you a Replacement Option covering a number of shares equal to the applicable exchange ratio multiplied by the number of shares subject to your Eligible Option Grant(s) that are exchanged (so long as your employment with Isis continues through that date).

If we receive and accept exchange of all outstanding Eligible Option Grants as of April 8, 2003, we expect that we will grant Replacement Options in exchange for such Eligible Option Grants to purchase an aggregate total of 6,440,348 shares of our Common Stock. The Common Stock issuable upon exercise of all such Replacement Options would equal approximately 11.63% of the total shares of our Common Stock outstanding as of April 4, 2003.

**Terms of Replacement Options.** Replacement Options will be granted under the 2000 Plan. Replacement Option stock option agreements will be executed between each optionholder who accepts the Offer and Isis. The Replacement Option stock option agreements will not permit the optionholders to exercise any Replacement Options before the time such options vest. The issuance of Replacement Options under this Offer will not create any contractual or other right of the recipients to continued employment, to receive any future grants of stock options or benefits in lieu of stock options.

The following description of the 2000 Plan and the Replacement Option stock option agreements is a summary, and is not complete. Replacement Options will be subject to the terms and conditions of the 2000 Plan and the applicable stock option agreement. Additional information about the 2000 Plan may be found in the Form S-8 Registration Statement on file with the SEC and the related Prospectus prepared in connection with the 2000 Plan. The 2000 Plan is available at [www.sec.gov](http://www.sec.gov) as well as on the Isis intranet, under Legal Department Main Page (click on "stock options & ESPP"), or you can contact Linda Powell to request a copy of this document and the current form of your stock option agreement. Copies will be provided promptly and at our expense. The form of stock option agreement may be changed with the approval of our Board of Directors or the Compensation Committee thereof before the date the Replacement Options are granted. Any information that is included on or linked to our intranet site is not part of this Offering.

**General.** The **2000 Broad-Based Equity Incentive Plan** was adopted in January 2000. As of April 7, 2003, there were 740,726 shares of our Common Stock reserved for issuance pursuant to the 2000 Plan of which options to purchase 4,996,693 shares of our Common Stock were issued and outstanding. The 2000 Plan permits us to grant only nonqualified options, which are not intended to qualify as incentive stock options under the Internal Revenue Code. Replacement Options will be granted under this 2000 Plan in exchange for Eligible Option Grants originally issued under this 2000 Plan or our 1989 Stock Option Plan.

**Administration.** The Board of Directors administers the 2000 Plan and has delegated administration of the 2000 Plan to the Compensation Committee of the Board of Directors, and the Compensation Committee has delegated administration of the 2000 Plan to the Non-Management Stock Option Committee with respect to certain option grants to employees who are not our executive officers. The Board of Directors has the authority to construe, interpret and amend the 2000 Plan.

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**Term.** The term of each option granted under the 2000 Plan is fixed by the 2000 Plan administrator at the time of grant and generally is a term of 10 years. However, the Replacement Options we plan to grant under the 2000 Plan will have a term that expires at 5:00 p.m., Pacific Time, on December 31, 2008.

**Time of Exercise.** Generally, you may exercise the vested portion of a Replacement Option at any time before the expiration of the option. Under the terms of your stock option agreement, if your employment with the Company terminates for any reason other than your death or permanent disability, you will generally have three (3) months after your termination date (provided that the Replacement Option has not expired) in which to exercise your Replacement Option. If your employment with us terminates as a result of your permanent disability, you will generally have twelve (12) months after your termination date in which to exercise your Replacement Option. If your employment with us terminates as a result of your death, generally your estate or beneficiaries must exercise the vested portion of your Replacement Option within eighteen (18) months following your termination date. Replacement Options to be granted under the 2000 Plan will have a term that expires at 5:00 p.m., Pacific Time, on December 31, 2008.

**Exercise Price.** The Replacement Options will have an exercise price equal to the greater of \$5.00 or the closing price of our Common Stock as reported on the Nasdaq National Market on the last market trading day before the date of grant. In the event that our Common Stock is not reported on the Nasdaq National Market as of such date, the exercise price shall be the greater of \$5.00 or the fair market value of our Common Stock as determined by our Board of Directors. **We cannot guarantee that the Replacement Option will have a lower exercise price than those of the Eligible Option Grants.** We recommend that you obtain current market quotations for our Common Stock before deciding whether to exchange your options. If any change is made in our Common Stock subject to the Replacement Options without the receipt of consideration by us (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by us), the number of shares subject to and the exercise price of the Replacement Options will be appropriately adjusted.

**Vesting.** Each Replacement Option will vest as follows: 33.34% will vest on January 1, 2004, then 2.78% will vest monthly thereafter for two years, so that it will be fully vested on January 1, 2006.

In the event of a Change in Control (as defined below) then the vesting and exercisability of the Replacement Options will be accelerated in full; provided, however, that if such potential acceleration of the vesting and exercisability of this stock option would cause a contemplated Change in Control transaction that would otherwise be eligible to be accounted for as a "pooling-of-interests" transaction to become ineligible for such accounting treatment under generally accepted accounting principles as determined by the our independent certified public accountants prior to the Change of Control, such acceleration will not occur.

For purposes of this acceleration clause in the Replacement Options only, Change in Control means: (i) a sale of all or substantially all of our assets; (ii) a merger or consolidation in which we are not the surviving corporation and in which beneficial ownership of our securities representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of directors has changed; (iii) a reverse merger in which we are the surviving corporation but the shares of Common Stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise, and in which beneficial ownership of our securities representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of directors has changed; or (iv) an acquisition by any person, entity or group within the meaning of Section 13(d) or 14(d) of the Exchange Act, or any comparable successor provisions (excluding any employee benefit plan, or related trust, sponsored or maintained by us or one of our

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subsidiaries or other entity controlled by us) of the beneficial ownership (within the meaning of Rule 13d-3 promulgated under the Exchange Act, or comparable successor rule) of our securities representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of directors.

**Tax Consequences.** If you are a U.S. employee, you should refer to Section 12 of the Offer for a discussion of the U.S. Federal Income Tax consequences of accepting or rejecting the Replacement Options under this Offer Document. If you are an international employee, please refer to Appendix A to this document entitled "Guide to International Tax Issues."

**Registration of Option Shares.** All shares of Common Stock issuable upon exercise of options under the 2000 Plan, including the shares that will be issuable upon exercise of all Replacement Options, have been registered or will be registered under the Securities Act of 1933, as amended (the "Securities Act"), on a Registration Statement on Form S-8 filed with the SEC. Unless you are considered a control person or other "affiliate" (as defined by the SEC) of Isis, you will be able to sell your Replacement Option shares free of any transfer restrictions under applicable securities laws.

## 9. INTERESTS OF DIRECTORS AND OFFICERS; TRANSACTIONS AND ARRANGEMENTS INVOLVING THE OPTIONS.

The directors and executive officers of Isis and their positions and offices as of April 7, 2003, are set forth in the following table:

Name	Age	Position(s) Held With The Company
Stanley T. Crooke, M.D., Ph.D.	58	Chairman, Chief Executive Officer
Spencer R. Berthelsen, M.D.	51	Director
Christopher F. O. Gabrieli	43	Director
William R. Miller	74	Director
Frederick T. Muto, J.D.	49	Director
B. Lynne Parshall, J.D.	48	Director, Executive Vice President, Secretary, CFO
John C. Reed, M.D.	44	Director
Mark B. Skaletsky	54	Director
Joseph H. Wender	58	Director
C. Frank Bennett, Ph.D.	46	Vice President, Antisense Research
Richard K. Brown, Ph.D.	50	Vice President, Corporate Development
Douglas L. Cole, Ph.D.	55	Vice President, Technical Development
David J. Ecker, Ph.D.	48	President, Ibis Therapeutics
Arthur A. Levin, Ph.D.	49	Vice President, Development
Patricia Lowenstam	56	Vice President, Human Resources, Operations, Health/Safety/Environment
Karen S. Lundstedt	38	Vice President, Corporate Communications
John A. McNeil	38	Vice President, Infomatics
Aron F. Stein, Ph.D.	44	Vice President, Regulatory Affairs & Quality

The address of each director and executive officer is c/o Isis Pharmaceuticals, Inc., 2292 Faraday Avenue, Carlsbad, CA 92008, and the telephone number is (760) 931-9200.

The biographies for our executive officers, including those officers who also serve on our board of directors are included in our Annual Report on Form 10-K for the fiscal year ended December 31,

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2002, filed with the SEC on March 31, 2003, and incorporated by reference herein, and the biographies for our non-employee directors are as follows:

**Christopher F.O. Gabrieli**, has served as a director of Isis since May 1994. Mr. Gabrieli served as a director from January 1989 to May 1992. He is the Chairman of Massachusetts 2020, a non-profit public policy organization. He is also a member of the general partners of Bessemer Venture Partners III L.P., Bessemer Venture Partners IV L.P. and related venture capital partnerships, where he worked from 1986 to 2000. He is also Chairman of the Board of EPIX Medical, Inc., a developer of magnetic resonance imaging contrast agents.

**Frederick T. Muto**, 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.

**William R. Miller**, 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.

**Spencer R. Berthelsen, M.D.**, was elected to the Isis Board of Directors in May of 2002. Since 1980, he has practiced Internal Medicine with the Kelsey Seybold Clinic, a 280 physician medical group based in the Texas Medical Center in Houston. Dr. Berthelsen has served in various senior leadership positions at Kelsey Seybold including Chairman of the Department of Internal Medicine, Medical Director, and Chairman of the Board of Directors since October 2001. He is a Clinical Professor of Medicine at the University of Texas Health Science Center at Houston and a Clinical Associate Professor of Medicine at Baylor College of Medicine. Dr. Berthelsen has served on the Board of the Texas Academy of Internal Medicine and the Caremark National Pharmacy and Therapeutics Committee since 1999.

**Joseph H. Wender**, 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 Affinity Financial, an internet financial institution.

**John C. Reed, M.D., Ph.D.**, 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**, 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,

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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 ImmunoGen, Inc., a biopharmaceutical company, 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.

As of March 31, 2003, our executive officers and non-employee directors (eight (8) people) as a group held options outstanding under the 1989 Stock Option Plan, 2000 Broad-Based Equity Incentive Plan and 2002 Non-Employee Directors' Plan to purchase a total of 2,896,588 shares of our Common Stock. This represented approximately 29.2% of the shares subject to all options outstanding under these plans and awards made outside of these plans as of that date. Executive officers as a group hold 2,556,088 Eligible Option Grants. The non-employee members of our Board of Directors are not eligible to participate in the Offer.

The following are, to the best of our knowledge, the only transactions that we, our directors, our executive officers or the affiliates of any of our directors or executive officers have engaged in that involved options to purchase shares of our Common Stock or involved a purchase of our Common Stock during the sixty (60) days prior to this Offer:

- On February 21, 2003, B. Lynne Parshall transferred 10,000 options each to both of her daughters.

There is no agreement, arrangement or understanding between us (or, to the best of our knowledge, any of our directors or executive officers) and any other person for the purchase or acquisition from us of any of its securities, except for the following:

- outstanding options to purchase an aggregate of 4,879,743 shares of our Common Stock (as of Monday, March 31, 2003) pursuant to our 2000 Broad-Based Equity Incentive Plan;
- outstanding options to purchase an aggregate of 4,731,228 shares of our Common Stock (as of Monday, March 31, 2003) pursuant to our 1989 Stock Option Plan;
- outstanding options to purchase an aggregate of 293,000 shares of our Common Stock (as of Monday, March 31, 2003) pursuant to our 2002 Non-Employee Director Stock Option Plan;

- an aggregate of up to 1,300,000 shares of our Common Stock reserved for issuance to our employees under our 2000 Employee Stock Purchase Plan (the "ESPP"), of which an aggregate of 953,819 shares have been issued and an aggregate of 346,099 shares remain available for issuance;
- Warrants to purchase 236,185 shares of common stock held by Elan Corporation.
- Warrants to purchase 800,000 shares of common stock, issued in conjunction with a private debt financing
- Shares of our Series B Convertible Preferred Stock;
- Shares of our Series C Junior Participating Preferred Stock;
- A convertible promissory note held by Elan Corporation; and
- \$125,000,000 in 5<sup>1</sup>/<sub>2</sub>% convertible subordinated notes due may 2009.

Each of these agreement, arrangement or understanding are more fully described in our Annual Report on Form 10-K for the fiscal year ended December 31, 2002, filed with the SEC on March 31, 2003, and incorporated by reference herein.

## **10. STATUS OF OPTIONS ACQUIRED IN THE OFFER; ACCOUNTING CONSEQUENCES OF THE OFFER.**

Eligible Option Grants that have been granted under the Plans and exchanged for Replacement Options under the Offer will be cancelled and the shares of Common Stock that may be purchased under those options will be returned to the pool of shares available for grants of new awards or options under the Plans without further stockholder action, except as required by applicable law or the rules of the Nasdaq National Market or any other securities quotation system or any stock exchange on which our Common Stock is then quoted or listed.

We may have to record future compensation expenses as a result of the Offer because:

- we will grant new options within six months and a day of the date we accept and cancel Eligible Option Grants returned to us;
- the exercise price of the Replacement Options will be less than the exercise price of the Eligible Option Grants returned to us on the date we grant the new options; and
- making the Offer will cause any Eligible Option Grants to be treated for financial reporting purposes as a variable award from the start date of the Offer.

As a result of our decision to extend this Offer to our employees, all Replacement Options, as well as any Eligible Option Grants that are not returned under this Offer, will be treated for financial reporting purposes as variable awards. This means that we will be required to record a non-cash accounting charge reflecting increases and decreases (down to but not below the exercise price) in the price of our Common Stock in compensation expense in connection with the Replacement Options and any Eligible Option Grants that are not exchanged and cancelled. We will have to continue to reflect decreases and increases in the price of our common stock in our statement of operations with respect to these options until they are exercised, forfeited or terminated. The higher the market value of our Common Stock, the greater the compensation expense.

## **11. LEGAL MATTERS; REGULATORY APPROVALS.**

We are not aware of any license or regulatory permit that appears to be material to our business that might be adversely affected by the Offer, or of any approval or other action by any government or regulatory authority or agency that is required for the acquisition or ownership of the options as described in the Offer. If any other approval or action should be required, we presently intend to seek the approval or take the action. This could require us to delay the acceptance of your Eligible Option Grants for exchange. We cannot assure you that we would be able to obtain any required approval or take any other required action. Our failure to obtain any required approval or take any required action might result in harm to our business. Our obligation under the Offer to accept exchanged Eligible Option Grants and to issue Replacement Options is subject to conditions, including the conditions described in Section 6 of the Offer Document.

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

The following is a general summary of the material U.S. Federal Income Tax consequences of the exchange of options under the Offer. (If you are a non-U.S. employee, we recommend that you consult with your tax advisor to determine the tax consequences and/or social insurance contribution consequences of the Offer. Non-U.S. employees may also refer to Appendix A to this document entitled "Guide to International Tax Issues" for a general summary of the tax consequences of the exchange of options under the Offer in their country.) This discussion is based on the Internal Revenue Code, its legislative history, Treasury Regulations and administrative and judicial interpretations as of the date of the Offer, all of which may change, possibly on a retroactive basis. This summary does not

discuss all of the tax consequences that may be relevant to you in light of your particular circumstances, nor is it intended to apply in all respects to all categories of optionholders.

We believe that the exchange of Eligible Option Grants for Replacement Options will be treated as a non-taxable exchange. In other words, you will not be required to recognize income for federal income tax purposes at the time of your exchange as Eligible Option Grants.

At the date of grant of the Replacement Option, you will not be required to recognize income for federal income tax purposes. In other words, the grant of options is not recognized as taxable income.

Replacement Options will be nonqualified stock options. We recommend that you consult your tax advisor with respect to the federal, state, local and foreign tax consequences of participating in the Offer.

*Certain Federal Income Tax Consequences of Incentive Stock Options.* You will not be subject to any current income tax if you choose to exchange your incentive stock options for Replacement Options.

We do not believe that our Offer to you will change any of the terms of your Eligible Option Grants if you do not accept the Offer. However, if you choose not to accept this Offer, it is possible that the IRS would assert that your right to exchange your incentive stock options under this Offer is a "modification" of your incentive stock options, even if you do not exchange the options. A successful assertion by the IRS that the options are modified could extend the options' holding period to qualify for favorable tax treatment and could cause a portion of your incentive stock options to be treated as nonqualified stock options.

Under current law, you generally will not realize taxable income when you exercise an incentive stock option. However, your alternative minimum taxable income will be increased by the amount that the aggregate fair market value of the shares you may purchase under the option (generally determined as of the date you exercise the option) exceeds the aggregate exercise price of the option. (The balance of this discussion assumes that you will not be subject to the alternative minimum tax for a year in which you exercise an incentive stock option.) Except in certain circumstances that are described in the Plans and in your stock option agreement, such as your death or disability, if an option is exercised more than three (3) months after your employment is terminated, the option will not be treated as an incentive stock option and is subject to taxation under the rules applicable to nonqualified stock options that are discussed below.

If you sell Common Stock that you acquired by exercising an incentive stock option, the tax consequences of the sale depend on whether the disposition is "qualifying" or "disqualifying." (The balance of this discussion, including the discussion regarding nonqualified stock options below, assumes that you exercise your option by paying the exercise price in cash. Please contact your tax advisor if you are considering exercising an option using Company Common Stock or other consideration.) The disposition of the Common Stock is qualifying if it is made after the later of: (a) more than two (2) years from the date the incentive stock option was granted and (b) more than one (1) year after the date the incentive stock option was exercised.

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If the disposition of the Common Stock you received when you exercised incentive stock options is qualifying, any excess of the sale price over the exercise price of the option will be treated as long-term capital gain taxable to you at the time of the sale. If the disposition is not qualifying, which we refer to as a "disqualifying disposition," the excess of the fair market value of the Common Stock on the date the option was exercised over the exercise price will be taxable ordinary income to you at the time of the sale. However, if the difference between the sale price and the option exercise price is less than the amount in the preceding sentence and the sale is a disposition in which a loss, if realized, would have been recognized, this lesser amount is ordinary income to you. Any amount in excess of the ordinary income amount will be long term capital gain or short term capital gain, depending on whether or not the Common Stock was sold more than one year after the option was exercised.

If you sell Common Stock you received when you exercised an incentive stock option in a qualifying disposition, the Company will not be entitled to a deduction equal to the gain you realize when you completed that sale. However, if you sell, in a disqualifying disposition, Common Stock you received when you exercised an incentive stock option, the Company will be entitled to a deduction equal to the amount of ordinary income taxable to you.

*Certain Federal Income Tax Consequences of Nonqualified Stock Options.* Under current law, you will not realize taxable income upon the grant of a nonqualified stock option. However, when you exercise the option, the difference between the exercise price of the option and the fair market value of the shares subject to the option on the date of exercise will be treated as ordinary income to you, and you will be subject to withholding of income and employment taxes at that time. The Company will be entitled to a deduction equal to the amount of ordinary income taxable to you if we comply with applicable withholding and reporting requirements.

The subsequent sale of the shares acquired pursuant to the exercise of a nonqualified stock option generally will give rise to capital gain or loss equal to the difference between the sale price and the sum of the exercise price paid for the shares plus the ordinary income recognized with respect to the shares, and this capital gain or loss will be treated as long term capital gain or loss if you held the shares for more than one year following exercise of the option.

*Consult Your Tax Advisor.* We recommend that you consult your tax advisor with respect to the federal, state, local and foreign tax consequences of participating in the Offer and with respect to certain federal income tax consequences not discussed in this Section 12, such as the exercise of an option using consideration other than cash and the application of the alternative minimum tax.

### **13. TERMS OF THE OFFER SPECIFIC TO ELIGIBLE PARTICIPANTS EMPLOYED OUTSIDE THE UNITED STATES.**

If you are an Eligible Participant employed outside the United States who holds Eligible Option Grants, you are subject to the terms of this Offer as described herein. International Employees should refer to Appendix A to this document entitled "Guide to International Tax Issues" for a discussion of the tax and other consequences of accepting or rejecting the Offer under the law of the country in which you are employed.

BEFORE ACCEPTING THIS OFFER, WE RECOMMEND THAT YOU CONSULT WITH YOUR TAX ADVISOR TO DETERMINE THE TAX AND SOCIAL CONTRIBUTION CONSEQUENCES OF THE OFFER, INCLUDING BUT NOT LIMITED TO A DETERMINATION OF WHETHER TAXES IN ADDITION TO THE AMOUNTS WITHHELD FROM THE CONSIDERATION, IF ANY, WILL BE DUE AS A RESULT OF CHOOSING TO PARTICIPATE IN THE OFFER.

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### **14. EXTENSION OF OFFER; TERMINATION; AMENDMENT.**

We may at any time, and from time to time, extend the period of time during which the Offer is open and delay accepting any options surrendered or exchanged by announcing the extension and giving oral or written notice of the extension to the optionholders.

If any of the conditions specified in Section 6 of the Offer Document occur before the expiration date, we may postpone accepting for cancellation any Eligible Option Grants in order to terminate or amend the Offer. To postpone the accepting for cancellation of any Eligible Option Grants, we must announce the postponement and give oral or written notice of the postponement to the Eligible Participants. Our right to delay accepting and canceling Eligible Option Grants may be limited by Rule 13e-4(f)(5) under the Exchange Act, which requires that we pay the consideration offered or return the surrendered options promptly after we terminate or withdraw the Offer.

As long as we comply with any applicable laws, we may amend the Offer in any way, including decreasing or increasing the consideration offered in the Offer to optionholders or decreasing or increasing the number of Eligible Option Grants to be exchanged or surrendered in the Offer.

We may amend the Offer at any time by announcing the amendment. If we extend the length of time during which the Offer is open, we will issue the amendment no later than 11:59 p.m., Pacific Time, on the extended expiration date. Any announcement relating to the Offer will be sent promptly to optionholders in a manner reasonably designed to inform optionholders of the change.

If we materially change the terms of the Offer or the information about the Offer, or if we waive a material condition of the Offer, we may extend the Offer to the extent required by Rules 13e-4(d)(2) and 13e-4(e)(3) under the Exchange Act. Under these rules, the minimum period an Offer must remain open following material changes in the terms of the Offer or information about the Offer, other than a change in price or a change in percentage of securities sought, will depend on the facts and circumstances. We will publish a notice if we decide to take any of the following actions:

- change the number of shares subject to the Replacement Option that you will receive in exchange for your Eligible Option Grants;
- change the number of Eligible Option Grants that you can exchange in the Offer; or
- extend or terminate the Offer.

If the Offer is scheduled to expire within ten (10) business days from the date we notify you of such an increase or decrease, we will extend the Offer until ten (10) business days after the date the notice is published.

## 15. FEES AND EXPENSES.

We will not pay any fees or commissions to any broker, dealer or other person asking holders of Eligible Option Grants to exchange such options pursuant to this Offer.

## 16. INFORMATION ABOUT ISIS.

Our principal executive offices are located at 2292 Faraday Avenue, Carlsbad, California 92008, and our telephone number is (760) 931-9200. Information regarding our directors and executive officers is contained in Section 9 herein. Our web site address is [www.isispharm.com](http://www.isispharm.com). The information included on or linked to our web site is not a part of this Offer.

We are exploiting our expertise in RNA to discover and develop novel human therapeutic drugs. We have commercialized our first product, Vitravene® (fomivirsen), to treat CMV-induced retinitis in AIDS patients. In addition, Isis has 13 antisense products in its development pipeline with two in late-stage development and six in Phase II human clinical trials. Affinitak, an inhibitor of PKC-alpha, is

in a Phase III trial for non-small cell lung cancer, and alicaforsen (ISIS 2302), an ICAM-1 inhibitor, is in a Phase III trial in Crohn's disease. Isis has a broad patent estate as the owner or exclusive licensee of nearly 1,200 issued patents worldwide. Isis' GeneTrove™ division uses antisense to assist pharmaceutical industry partners in validating and prioritizing potential gene targets through customized services. Ibis Therapeutics™ is a division focused on the discovery of small molecule drugs that bind to RNA.

Information concerning our business, including our background, strategy, products, manufacturing, product development, competition, intellectual property and employees, as well as the financial information included in our Annual Report on Form 10-K for the fiscal year ended December 31, 2002, are incorporated by reference herein and may be inspected at, and copies may be obtained from, the same places and in the same manner as set forth under Section 18 ("Additional Information").

*Financial.* Set forth below is a selected summary of our financial data. The selected financial data are derived from our audited consolidated financial statements, as filed with the SEC. The selected financial data should be read in conjunction with the consolidated financial statements and notes thereto and "Management's Discussion and Analysis of Financial Condition and Results of Operations" included in our Annual Report on Form 10-K for the year ended December 31, 2002, filed with the SEC on March 31, 2003. All amounts are in thousands, except per share data.

	Years Ended December 31,	
	2002	2001
<b>Statement of Operations Data:</b>		
Revenues (includes amounts for R&D, licensing and royalties)	\$ 80,179	\$ 53,273
Research and development expenses	\$ 124,074	\$ 83,741
Net loss applicable to common stock	\$ (73,302)	\$ (75,131)
Basic and diluted net loss per share	\$ (1.35)	\$ (1.70)
Shares used in computing basic and diluted net loss per share	54,480	44,109
	2002	2001
<b>Balance Sheet Data:</b>		
Cash, cash equivalents and short-term investments	\$ 289,353	\$ 312,018
Working capital	\$ 244,230	\$ 280,569

Total assets	\$	438,683	\$	417,061
Long-term debt and capital lease obligations, less current portion	\$	192,893	\$	125,710
Accumulated deficit	\$	(459,893)	\$	(386,591)
Stockholders' equity (deficit)	\$	155,477	\$	223,099
Book value per share (1)	\$	2.82		

(1) Book value per share is completed by dividing total stockholders' equity by the number of shares of common stock outstanding at December 31, 2002.

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**RATIO OF EARNINGS TO FIXED CHARGES**  
(in thousands, except ratio of earnings to fixed charges)

The following table sets forth our ratio of earnings to fixed charges for the years ended December 31, 2001 and 2002. As earnings were inadequate to cover the combined fixed charges, we have provided the average deficiency amounts. For purposes of this computation, earnings are defined as net loss excluding the preferred stock dividend requirement on our Series A and Series B preferred stock. Fixed charges are the sum of (i) interest costs including the amortization of deferred financing costs; and (ii) the portion of operating lease rental expense that is representative of the interest factor of 15%.

	Years Ended December 31,	
	2002	2001
Ratio of earnings to fixed charges		
Coverage deficiency	(72,242)	(73,832)

The financial information included in our Annual Report on Form 10-K for the year ended December 31 2002, is incorporated by reference herein and may be inspected at, and copies may be obtained from, the places and in the manner described in Section 19 ("Additional Information").

**17. RISK FACTORS.**

Information concerning risk factors included in our Annual Report on Form 10-K for the fiscal year ended December 31, 2002, is incorporated by reference herein. Additional risks and uncertainties not presently known to us or that we currently deem immaterial also may impair our business operations. If any of the risks actually occur, our business could be harmed. In that event, the trading price of our Common Stock could decline.

Our Common Stock is listed for quotation on the Nasdaq National Market System.

**18. ADDITIONAL INFORMATION.**

We have filed with the SEC a Tender Offer Statement on Schedule TO, of which this Offer Document is a part, with respect to the Offer. This Offer does not contain all of the information contained in the Schedule TO and the exhibits to the Schedule TO. We recommend that you review the Schedule TO, including its exhibits, and the following additional materials that we have filed with the SEC before making a decision on whether to accept the Offer:

- our Annual Report on Form 10-K for the year ended December 31, 2002;
- our Definitive Proxy Statement for our 2002 Annual Meeting of Shareholders, filed with the SEC on April 5, 2002; and
- the description of our common stock in our Registration Statement on Form 8-A filed with the SEC on April 12, 1991, as updated by our Certificate of Amendment of our Restated Certificate of Incorporation filed with our Quarterly Report on Form 10-Q for the period ended June 30, 2001.

The SEC file number for these filings is 0-19125. These filings and our other SEC filings may be examined, and copies may be obtained, at the following SEC public reference rooms:

450 Fifth Street, N.W.  
Room 1024  
Washington, D.C. 20549

500 West Madison Street  
Suite 1400  
Chicago, Illinois 60661

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You may obtain information on the operation of the public reference rooms by calling the SEC at 1-800-SEC-0330.

Our SEC filings are also available to the public on the SEC's Internet site at <http://www.sec.gov>. Our Common Stock is quoted on the Nasdaq National Market under the symbol "ISIS."

You can obtain a copy of any or all of the documents to which we have referred you, except the Form 8-A, on our web site at [www.isispharm.com](http://www.isispharm.com). The information included on or linked to on our web site is not a part of this Offer. We will also provide without charge to each person to whom we deliver a copy of this Offer Document, upon his or her written or oral request, a copy of any or all of the documents to which we have referred you, other than exhibits to these documents (unless the exhibits are specifically incorporated by reference into the documents). Requests should be directed to:

or by telephoning us at (760) 931-9200 between the hours of 9:00 a.m. and 5:00 p.m., Pacific Time. As you read the documents listed in this Section 18, you may find some inconsistencies in information from one document to another. Should you find inconsistencies between the documents, or between a document and this Offer Document, you should rely on the statements made in the most recent document.

The information contained in this Offer Document about Isis should be read together with the information contained in the documents to which we have referred you.

#### **19. FORWARD-LOOKING STATEMENTS; MISCELLANEOUS.**

This Offer Document and our SEC reports referred to above include forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act. However, the safe harbors of Section 27A of the Securities Act and 21E of the Exchange Act do not apply to statements made in connection with this Offer. These forward-looking statements involve risks and uncertainties that include, among others, those set forth in Section 18 of this document. More information about factors that potentially could affect our financial results is included in our filings with the SEC, including our Annual Report on Form 10-K for the year ended December 31, 2002.

If at any time we become aware of any jurisdiction where the making of this Offer violates the law, we will make a good faith effort to comply with the law. If we cannot comply with the law, the Offer will not be made to, nor will exchanges be accepted from or on behalf of, the optionholders residing in that jurisdiction.

Your decision to accept or reject this Offer is an individual one that should be based on a variety of factors. You should consult your personal advisors if you have questions about your financial or tax situation. The information about this Offer from Isis is limited to this document.

Isis Pharmaceuticals, Inc.

April 7, 2003

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## **APPENDIX A GUIDE TO INTERNATIONAL TAX ISSUES**

### **ISIS PHARMACEUTICALS, INC. STOCK OPTION EXCHANGE: A GUIDE TO TAX ISSUES IN THE UNITED KINGDOM**

#### **Tax Information**

The following is a general summary of the material tax consequences of the exchange of your Eligible Option Grants and the grant of a Replacement Option under the Offer for persons subject to income and/or employment taxes in the United Kingdom. This discussion is based on United Kingdom tax law as of the date of the Offer, which is subject to change, possibly on a retroactive basis. The information may be out of date at the time you exercise your Replacement Option or sell the shares you acquire upon exercise. This summary is general in nature and does not discuss all of the tax consequences that may be relevant to you in light of your particular circumstances, nor is it intended to be applicable in all respects to all categories of option holders. We advise all option holders considering replacing their Eligible Option Grants to meet with their own tax advisors. If you are a citizen or resident of another country, the information contained in this summary may not be applicable to you. You are advised to seek appropriate professional advice as to how the tax or other laws in your country apply to your specific situation.

#### **Option Replacement**

We do not believe that there will be a tax liability in connection with the tender of your Eligible Option Grants in exchange for your Replacement Option.

#### **Grant**

You will not be subject to tax when the Replacement Option is granted to you.

#### **Exercise**

You may be granted all or a portion of your Replacement Option under an option plan approved by the U.K. Inland Revenue. However, no assurances can be given to this effect. Options can be granted under an approved plan only with a market value at the date of grant of up to £30,000. Although, options granted under an approved plan may entitle an optionholder to preferential income tax treatment, the Replacement Option do not have a long enough term to allow you to receive such preferential income tax treatment. To the extent that you exercise the Replacement Option, you will be subject to income tax on the exercise of the Replacement Option. Whether or not the exercise is after the statutory time period for preferential income tax treatment, grants made under an approved plan exempt you from paying National Insurance Contributions (NICs) in connection with the exercise of your options. If you are granted options with a market value exceeding £30,000 at the date of grant, you will be granted the excess options under an unapproved plan and favorable tax and NICs treatment will not be available to these options.

#### **Sale of Shares**

When you sell your shares acquired upon exercise of the Replacement Option, you will be subject to capital gains tax. The tax is due on any increase in the value of the shares between the date on which you exercise your Replacement Option and the date on which you sell the shares acquired upon exercise of such options. Any capital gains tax you may owe is subject to an annual personal exemption and to tapering relief calculated with reference to the period of time during which you held the shares following the exercise of your Replacement Option and period in which you are employed by us or a related company.

## **Withholding and Reporting**

We are required to arrange for the payment of income tax on the spread at exercise or to withhold funds on account of income tax on the spread at exercise from the payroll, the proceeds of exercise and sale, or otherwise, and to remit such amounts to the U.K. Inland Revenue on your behalf. We will also report the details of any option grant and exercise on its annual U.K. Inland Revenue tax return.

We are not responsible for withholding funds with respect to the sale of the shares you receive upon the exercise of your Replacement Option. You must report details of any liabilities arising from the exercise of your Replacement Option and from the sale or disposal of shares on your personal U.K. Inland Revenue tax return.

As you know, tax calculations are complex and specific to your individual situation. We withhold based on an estimation of the applicable tax you will owe. If your actual tax liability differs from the amount withheld, you are responsible for paying the additional taxes.

### **U.K. Notice**

You should consider the tax consequences of voluntarily canceling your existing options. Your existing options may have been granted as part of an option plan approved by U.K. Inland Revenue. Briefly, if the holding period and other requirements for options granted under an approved plan have been (or will be) met, your options have favorable income tax treatment and you will be exempt from paying NICs in connection with the exercise of such options. However, if you decide to exchange your existing options for the Replacement Option, you will forfeit such preferential tax and social insurance treatment of your existing options.

## QuickLinks

[Exhibit 99.\(a\)\(1\)\(A\)](#)

[OFFER TO EXCHANGE OUTSTANDING OPTIONS TO PURCHASE COMMON STOCK APRIL 7, 2003](#)  
[RATIO OF EARNINGS TO FIXED CHARGES \(in thousands, except ratio of earnings to fixed charges\)](#)

MEMO

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To: «M\_1st\_name» «Last\_Name»  
From: B. Lynne Parshall  
Date: APRIL 9, 2003  
Subject: Stock Option Exchange Program

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Isis is pleased to announce that its Board of Directors has approved management's proposal to allow eligible employees the opportunity to exchange outstanding stock options granted prior to January 5, 2002, under Isis' 1989 Stock Option Plan and 2000 Broad-Based Equity Incentive Plan for replacement options to purchase shares of Isis' Common Stock. This is a one-time opportunity designed to improve performance incentives for our employees and thereby maximize stockholder value. The key features of this offer are summarized below.

Please also read the distributed Offer to Exchange and Summary of Terms of Option Exchange in their entirety, because the information in this memorandum is not complete and does not contain all of the information relevant to your decision whether or not to participate in this offer. You can obtain a copy of Offer to Exchange and Summary of Terms of Option Exchange on the Isis Intranet under the heading "Stock Option Exchange Program." In addition, if you contact Linda Powell at (760) 603-2471 she will provide you a copy of these documents.

Isis is offering its employees the opportunity to exchange eligible options as follows:

Option Price	Exchange Ratio (new for old)
Greater than or equal to \$5 but less than \$10	1:1.5
Greater than or equal to \$10 but less than \$15	1:2
Greater than or equal to \$15 but less than \$20	1:2.5
Greater than or equal to \$20	1:3

Thus, for those employees who elect to participate in the offer, on May 8, 2003 (or a later date if the offer is extended), Isis will grant you a replacement option covering the number of shares of common stock at the ratio described above.

There are certain other conditions to exchanging your options that are set forth in detail in the Offer to Exchange and accompanying documents. In particular, if you elect to exchange any eligible option, the entire option must be exchanged. In addition, you must be continuously employed by Isis through the date of grant of the replacement options in order to receive any replacement grant.

Your replacement options will be granted on May 8, 2003 (or a later date if the offer is extended) with an exercise price equal to the greater of \$5.00 or the last reported closing price of Isis' common stock before the date the Exchange Offering ends, 12:00 a.m. on May 8, 2003 (or a later date if the offer is extended). Your replacement options will all be nonqualified stock options and will vest as follows: 33.34% vest on January 1, 2004, then 2.78% vest monthly thereafter for two years. The replacement options will expire on December 31, 2008.

Program participation is entirely voluntary, and although our Board of Directors has approved this offer, Isis makes no recommendation as to whether or not you should tender your options for exchange. You must make your own decision whether to tender your options. Participation involves certain risks that are discussed in the documents to be distributed to you. Isis is making this offer upon the terms and subject to the conditions described in the offer to exchange and accompanying documents. You should carefully read the distributed materials and understand all aspects of the

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exchange offer before deciding whether to participate. In addition, we recommend that you consult with your tax and financial advisors before you make your decision regarding participation.

If you decide to participate in this offer, please follow the procedures outlined in the distributed documents. You currently have stock options that have been granted to you at your time of hire and during your tenure with the Company as detailed in the attachment. These grants ("Existing Options") were issued to you under the 1989 Stock Option Plan and/or the 2000 Broad-Based Equity Incentive Plan.

The Exchanged Options will have terms consistent with the 2000 Broad-Based Equity Plan and will be evidenced by an agreement between you and Isis. Once you agree to the cancellation of the Existing Options, you no longer have any rights under the Existing Options.

Please note that you are not required to cancel Existing Options in exchange for Exchanged Options. You may retain your Existing Options and all rights connected with these options. You may also cancel one or more eligible grants of your Existing Options and keep others.

**You must indicate by 12:00 a.m. on May 8, 2003 whether or not you wish to participate in this program. Even if you do not wish to participate, we ask that you complete the form below and return it to Linda Powell by 12:00 a.m. on May 8, 2003. All employees must complete and return this form.**

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## QuickLinks

[Exhibit 99.\(a\)\(1\)\(B\)](#)

## SUMMARY OF TERMS

The following is a summary of terms (the "Summary") about the Offer to Exchange Outstanding Options (the "Offer Document," which, as it may be amended from time to time, constitutes the "Offer") presented in a question and answer format. We urge you to read carefully the remainder of the Offer Document and the accompanying documents because the information in this Summary is not complete. We have included references to the sections of the Offer Document where you can find a more complete description of the topics in this Summary.

### Q1. WHAT SECURITIES ARE WE OFFERING TO EXCHANGE AND WHO CAN PARTICIPATE IN THE OFFER?

We are offering to exchange all stock options granted prior to January 5, 2002, with exercise prices equal to or greater than \$5.00 per share currently outstanding under our 2000 Broad-Based Equity Incentive Plan (the "2000 Plan") or our 1989 Stock Option Plan (the "1989 Plan") (collectively, the "Plans") and held by Eligible Participants (the "Eligible Option Grants"). "Eligible Participants" are our employees, including our executive officers, as of April 8, 2003 who were not affected by the April 1, 2003 reduction in force and continue to be employed by us through the expiration date of the Offer. Our non-employee directors are not eligible to participate in the Offer. Our employees who are on active status on the date the Offer expires are Eligible Participants. In addition, our employees who are currently on medical, maternity, worker's compensation, military or other statutorily-protected leave of absence are also Eligible Participants, even if they do not return to active status before the date the Offer expires. However, an employee who is on a leave of absence for any other reason and does not return to active status before the Offer expires, or an employee whose employment with us terminates for any reason at any time before the Offer expires, is not an Eligible Participant. (See Section 1 of the Offer Document).

### Q2. WHY ARE WE MAKING THE OFFER

Our compensation philosophy is to retain and motivate our employees through appropriate levels of cash and equity compensation. Many of our outstanding options have exercise prices that are significantly higher than the current market price of our Common Stock. For that reason, we believe that it is unlikely that our employees will exercise these options in the near future and that these options do not provide proper incentives for our employees. By making this Offer, we believe we will be able to improve employee morale and provide a proper incentive to our employees by realigning our compensation programs to more closely reflect current market and economic conditions. (See Section 2 of the Offer Document.)

### Q3. ARE THERE CONDITIONS TO THE OFFER?

The Offer is subject to a number of general conditions, including the conditions described in Section 6 of the Offer Document, which may lead us to terminate or amend the Offer. However, if you are an Eligible Participant with Eligible Option Grants, the only conditions specific to your participation (assuming the Offer is not terminated or amended) are that you submit your Election Form before the deadline, and that you cannot exchange a fraction of the shares subject to an Eligible Option Grant. You may tender a partially exercised Eligible Option Grant so long as you tender all unexercised shares subject to such Eligible Option Grant. You should note that the Offer is not conditioned on a minimum of option holders accepting the Offer or a minimum of options being exchanged.

### Q4. HOW MANY OPTION SHARES WILL I RECEIVE IN EXCHANGE FOR THE OPTION SHARES EXCHANGED?

If you choose to participate in the Offer under the terms described in the Offer Document, we will exchange your Eligible Option Grants for a new option (a "Replacement Option") based on the

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following exchange ratios depending on the exercise price of the Eligible Option Grants you tender.

Option Price	Exchange Ratio (new for old)
Greater than or equal to \$5 but less than \$10	1:1.5
Greater than or equal to \$10 but less than \$15	1:2
Greater than or equal to \$15 but less than \$20	1:2.5
Greater than or equal to \$20	1:3

As an example, assume that you hold two Eligible Option Grants: one Eligible Option Grant to purchase 6,000 shares of our Common Stock at an exercise price of \$7.00 per share and a second Eligible Option Grant to purchase 3,000 shares of our Common Stock at an exercise price of \$20.00 per share. Assume that the closing price of our Common Stock on the last day of trading before the date of the option exchange is \$4.50. If you choose to participate in the Offer, in exchange for the cancellation of both your Eligible Option Grants, you will receive a replacement option of 5,000 shares (4,000 shares plus 1,000 shares) at an exercise price of \$5.00 per share.

We will issue Replacement Options under the 2000 Broad-Based Equity Incentive Plan. (See Section 8 of the Offer Document.)

### Q5. WHEN WILL I RECEIVE MY REPLACEMENT OPTION?

We will grant Replacement Options on May 8, 2003 (or a later date if we extend the Offer). We expect to distribute your Replacement Option stock option agreement promptly following the date of grant.

### Q6. WHAT WILL BE THE TERMS AND CONDITIONS OF THE REPLACEMENT OPTIONS?

The exercise price, expiration date and vesting schedule of the Replacement Options will be different than the Eligible Option Grants. In all other aspects, the terms and conditions of the Replacement Options will be substantially the same as the Eligible Option Grants that are exchanged. See below for a

discussion of the exercise price, expiration date and vesting schedule of the Replacement Options.

**Q7. WHAT WILL BE THE EXERCISE PRICE OF THE REPLACEMENT OPTIONS?**

The Replacement Options will have an exercise price equal to the greater of \$5.00 or the closing price of our Common Stock as reported on the Nasdaq National Market on the last market trading day before the date of grant. In the event that our Common Stock is not reported on the Nasdaq National Market as of such date, the exercise price will be the greater of \$5.00 or the fair market value as determined by our Board of Directors. We cannot guarantee that the exercise price for your Replacement Option will be lower than the exercise price for the Eligible Option Grants that you exchange. We recommend that you obtain current market quotations for our Common Stock before deciding whether to exchange your Eligible Option Grants. (See Section 7 of the Offer Document.)

**Q8. WHEN WILL MY REPLACEMENT OPTION EXPIRE?**

Your Replacement Option will expire at 5:00 p.m. Pacific Time, on December 31, 2008, so long as you remain employed by us.

**Q9. WHEN WILL THE REPLACEMENT OPTIONS VEST AND WHAT WILL BE THE VESTING SCHEDULE OF THE REPLACEMENT OPTIONS?**

Each Replacement Option will vest as follows: 33.34% will vest on January 1, 2004, then 2.78% will vest monthly thereafter for two years, so that it will be fully vested on January 1, 2006.

In the event of a Change in Control, as further described in Section 8 of the Offer Document) then the vesting and exercisability of the Replacement Options will be accelerated in full; provided, however, that if such potential acceleration of the vesting and exercisability of this stock option

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would cause a contemplated Change in Control transaction that would otherwise be eligible to be accounted for as a "pooling-of-interests" transaction to become ineligible for such accounting treatment under generally accepted accounting principles as determined by the our independent certified public accountants prior to the Change of Control, such acceleration will not occur. (See Section 8 of the Offer Document).

**Q10. IF I HAVE INCENTIVE STOCK OPTIONS THAT ARE ELIGIBLE OPTIONS, WHAT HAPPENS IF I CHOOSE NOT TO EXCHANGE THEM IN THE OFFER?**

Choosing not to exchange your Eligible Option Grants will not subject you to U.S. Federal Income Tax. We do not believe that this Offer will change any of the terms of your Eligible Option Grants if you do not accept the Offer. However, the IRS may characterize the Offer to you as a "modification" of those Eligible Option Grants that are incentive stock options, even if you decline the Offer. A successful assertion by the IRS that such options have been modified could extend the options' holding period to qualify for favorable tax treatment and could cause a portion of such options to be treated as nonqualified stock options.

If you choose not to exchange your Eligible Option Grants and they include incentive stock options, we recommend that you consult with your tax advisor to determine the tax consequences if you later exercise those options and sell the Common Stock that you receive upon exercise.

**Q11. HOW LONG WILL I HAVE TO WAIT TO PURCHASE COMMON STOCK UNDER MY REPLACEMENT OPTION?**

The shares subject to your Replacement Option will vest according to the vesting schedule described in Question 9, so that they are fully vested on January 1, 2006. You will be able to exercise and sell shares subject to your Replacement Option as they vest. You will not be able to exercise or sell any shares subject to your Replacement Option that have not vested.

**Q12. IF I CHOOSE TO EXCHANGE MY ELIGIBLE OPTIONS, WILL THAT DECISION AFFECT OTHER COMPONENTS OF MY COMPENSATION?**

No. Whether or not you accept or reject the Offer will not affect your compensation in the future. Your acceptance or rejection of the Offer will not result in your becoming more or less likely to receive stock option grants in the future, other than the Replacement Options.

**Q13. IF I CHOOSE TO EXCHANGE ELIGIBLE OPTIONS, DO I HAVE TO EXCHANGE ALL OF MY ELIGIBLE OPTIONS OR CAN I EXCHANGE JUST SOME OF THEM?**

Should you choose to accept this Offer, you are not obligated to tender each Eligible Option Grant and are free to elect to tender as many or as few of the Eligible Option Grants as you wish. However, please note that you must tender all shares issuable under each particular Eligible Option Grant you wish to tender. You may tender a partially exercised Eligible Option Grant so long as you tender all unexercised shares subject to such Eligible Option Grant.

For example, if you hold an Eligible Option Grant to purchase 1,000 shares at an exercise price of \$7.00 and a second Eligible Option Grant to purchase 2,000 shares at \$12.00 per share, and each Eligible Option Grant was issued prior to January 5, 2002, you can choose to exchange just the \$12.00 Eligible Option Grant or just the \$7.00 Eligible Option Grant. However, if you choose to exchange just the \$12.00 Eligible Option Grant, you would have to exchange all 2,000 shares subject to that option. Similarly, if you choose to exchange just the \$7.00 Eligible Option Grant, you would have to exchange all 1,000 shares subject to that option.

**Q14. IF I HAVE STOCK OPTIONS WITH EXERCISE PRICES BELOW \$5.00 PER SHARE, WHAT HAPPENS TO THOSE OPTIONS IF I EXCHANGE ELIGIBLE OPTIONS?**

Nothing. Regardless of whether or not you choose to exchange your Eligible Option Grants under this Offer, there will be no change to your current options with exercise prices below \$5.00 per share. Such options will remain subject to the same terms and conditions under the Plan and your applicable stock option agreement as existed before the Offer.

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**Q15. WILL I HAVE TO PAY TAXES IF I EXCHANGE MY OPTIONS IN THE OFFER?**

If you accept the Offer, you will not recognize income for U.S. Federal Income Tax purposes at the time of the exchange or at the time we grant a Replacement Option to you. If you are a non-U.S. employee and you accept the Offer, please refer to Appendix A for information about the tax treatment in your country. We recommend that you consult with your tax advisor to determine the tax consequences or potential social insurance contribution consequences (for non-U.S. employees) of accepting the Offer. (See Section 12 to the Offer Document if you are a U.S. employee and Appendix A to this document entitled "Guide to International Tax Issues" if you are a non-U.S. employee).

**Q16. IF MY ELIGIBLE OPTIONS INCLUDE INCENTIVE STOCK OPTIONS, WILL MY REPLACEMENT OPTION ALSO BE AN INCENTIVE STOCK OPTION, OR WILL IT BE A NONQUALIFIED STOCK OPTION?**

All Replacement Options will be nonqualified stock options and thus not subject to the favorable tax treatment applicable to incentive stock options. See Section 12 of the Offer to Exchange for a discussion of incentive and nonqualified stock options.

**Q17. WHEN DOES THE OFFER EXPIRE? CAN THE OFFER BE EXTENDED, AND IF SO, HOW WILL I KNOW IF IT IS EXTENDED?**

The Offer expires on May 8, 2003 at 12:00 a.m., Pacific Time, unless we extend it.

Although we do not currently intend to do so, we may, in our discretion, extend the Offer at any time. If we extend the Offer, we will announce the extension no later than 12:00 a.m., Pacific Time, on May 8, 2003. (See Section 15 of the Offer Document).

**Q18. WHAT DO I NEED TO DO?**

To accept this Offer, you must complete and sign the Election Form and deliver the Election Form to Linda Powell at Isis before 12:00 a.m., Pacific Time, on May 8, 2003 (or a later expiration date if we extend the Offer). Even if you choose not to participate in the Offer, we ask all Eligible Participants to return your Election Form. You may send the Election Form via mail, courier, hand delivery or facsimile. Linda Powell is located at our corporate headquarters at 2292 Faraday Avenue, Carlsbad, CA 92008. Linda Powell's direct facsimile number is (760) 603-4650. Election Forms must be received before 12:00 a.m., Pacific Time, on May 8, 2003 (or a later expiration date if we extend the Offer), *not* just mailed (or otherwise sent) by the expiration time. If Election Forms are sent by facsimile, originals should be sent by mail, courier or hand delivery as soon as possible.

You should direct questions about this Offer, requests for assistance in completing the related documentation and requests for additional copies of the Offer Document or related documents to Linda Powell via e-mail to [lpowell@isisph.com](mailto:lpowell@isisph.com) or via telephone at (760) 603-2471. You should review the Offer Document, the Election Form and all of their attachments before making your election.

If we extend the Offer beyond May 8, 2003, then you must sign and deliver the Election Form before the extended expiration date. We may reject any Eligible Option Grant to the extent that we determine the Election Form is not properly completed or to the extent that we determine it would be unlawful to accept the options. Although we may later extend, terminate or amend the Offer, we currently expect to accept all properly exchanged options promptly following the deadline of 12:00 a.m., Pacific Time, on May 8, 2003 (or a later expiration deadline if we extend the Offer). If you do not sign and deliver the Election Form before the Offer expires, it will have the same effect as if you rejected the Offer (See Section 3 of the Offer Document).

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**Q19. DURING WHAT PERIOD OF TIME MAY I CHANGE MY PREVIOUS CHOICE TO ACCEPT OR REJECT THE OFFER?**

You may change your previous choice to accept or reject the Offer at any time before 12:00 a.m., Pacific Time, on May 8, 2003. If we extend the Offer beyond that time, you may change your previous choice at any time until the extended expiration deadline. To change your choice, you must deliver a Notice of Change in Election Form to Linda Powell before the Offer expires. If you change your choice from "reject" to "accept" you must also fill out and deliver a new Election Form. You may change your choice as many times as you want (See Section 4 of the Offer Document).

**Q20. WHAT HAPPENS TO MY OPTIONS IF I DO NOT ACCEPT THE OFFER?**

Nothing. If you do not accept the Offer, you will keep all of your current options and you will not receive a Replacement Option. No changes will be made to your current options (See Section 12 of the Offer Document for a discussion of any possible "modification" to your current incentive stock options in the event that you choose not to exchange your Eligible Option Grants).

**Q21. UNDER WHAT CIRCUMSTANCES WOULD ISIS NOT ACCEPT MY OPTIONS?**

We currently expect we will accept all Eligible Option Grants that are properly submitted for exchange and for which the choice has not been validly withdrawn. We may, however, reject any or all Election Forms, Notice of Change in Election Forms or exchanged options if we determine they were not properly executed or delivered, if we determine it is unlawful to accept the exchanged options or if certain conditions exist which in our reasonable judgment make it inadvisable to proceed with the Offer (See Section 3 of the Offer Document).

**Q22. AFTER I AM GRANTED A REPLACEMENT OPTION, WHAT HAPPENS IF THAT REPLACEMENT OPTION ENDS UP UNDERWATER?**

This Offer is a one-time offer. We do not expect to repeat this Offer in the future. Please note that unlike prior stock options granted under the Plans, which generally are valid for up to ten years from the date of initial grant (subject to continued service with Isis), your Replacement Option will expire on December 31, 2008 or approximately 66 months after the date of grant.) WE CAN PROVIDE NO ASSURANCE AS TO THE PRICE OF OUR COMMON STOCK AT ANY TIME IN THE FUTURE, AND NOTHING CONTAINED IN THIS DOCUMENT OR THE OTHER DOCUMENTS YOU RECEIVE RELATING TO THIS OFFER SHOULD BE INTERPRETED IN ANY WAY AS A CLAIM RELATING TO THE FUTURE PROSPECTS OF THE PRICE OF OUR COMMON STOCK, NOR SHOULD YOU DRAW ANY INFERENCE ABOUT SUCH FUTURE PROSPECTS FROM ANYTHING CONTAINED HEREIN OR THEREIN.

**Q23. IF I AM AN ELIGIBLE PARTICIPANT EMPLOYED OUTSIDE OF THE UNITED STATES, AM I SUBJECT TO THE SAME TERMS AS DESCRIBED IN THE OFFER?**

If you are an Eligible Participant employed outside of the United States who holds Eligible Option Grants, you may participate in the Offer under the same terms as described herein. International employees should also refer to Appendix A to the Offer Document entitled "Guide to International Tax Issues" for a discussion of the tax and other consequences of accepting or rejecting the Offer under the law of the country in which you are employed.

**Q24. WHOM CAN I CONTACT IF I HAVE QUESTIONS ABOUT THE OFFER?**

For additional information or assistance, you should contact Linda Powell via e-mail at [lpowell@isisph.com](mailto:lpowell@isisph.com) or via telephone at (760) 603-2471. In addition, there will be a company-wide meeting to present and discuss information about the Offer.

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QuickLinks

[Exhibit 99.\(a\)\(1\)\(C\)](#)

[SUMMARY OF TERMS](#)



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By

Date

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Title

**Return this form, *along with the original grant form* of any grants to be Exchanged, to Linda Powell no later than 12:00 a.m. on May 8, 2003**

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QuickLinks

[Exhibit 99.\(a\)\(1\)\(D\)](#)

[Election Form](#)

**NOTICE OF CHANGE IN ELECTION FROM ACCEPT TO REJECT**

If you previously elected to accept Isis Pharmaceuticals, Inc. ("Isis") Offer to Exchange, and you would like to change your election and reject the Offer, you must sign this Notice and return it to Linda Powell at Isis before 12:00 a.m., Pacific Daylight Time, on Thursday, May 8, 2003, unless the Offer is extended. This Notice of Change in Election may be sent via mail or courier to the attention of Linda Powell at Isis' corporate offices, located at 2292 Faraday Avenue, Carlsbad, CA 92008. Notices will also be accepted via facsimile. Linda Powell's direct facsimile number is (760) 603-2471. If you do elect to return this Notice via facsimile, please provide us with an original executed copy as soon as possible. If you have questions regarding the process for returning this Notice, please contact Linda Powell via email at [lpowell@isisph.com](mailto:lpowell@isisph.com) or via telephone at (760) 603-2471.

To Isis:

I previously received a copy of the Offer to Exchange (dated April 7, 2003), the cover letter, the Summary of Terms and an Election Form. I signed and returned the Election Form, in which I elected to accept Isis' Offer to Exchange. **I now wish to change that election, and reject Isis' Offer to Exchange.** I understand that by signing this Notice and delivering it pursuant to the instructions above, I will be able to withdraw my acceptance of the Offer, and reject the Offer to Exchange instead.

I understand that in order to reject the Offer, I must sign and deliver this Notice to Linda Powell at Isis' corporate offices, located at 2292 Faraday Avenue, Carlsbad, CA 92008 before 12:00 a.m., Pacific Daylight Time, on Thursday, May 8, 2003, or if Isis extends the deadline to exchange options, before the extended expiration of the Offer.

By rejecting the Offer to Exchange, I understand that I will not receive any Replacement Options, and I will keep my Eligible Option Grants that otherwise would have been required to be exchanged if I were participating in the Offer. These options will continue to be governed by the stock option plan under which these options were granted and the existing stock option agreements between Isis and me.

I have completed and signed the following exactly as my name appears on my original Election Form. By executing this form, I hereby bind my successors, assigns and legal representatives.

I **do not** accept the offer to exchange options.

\_\_\_\_\_  
Optionee Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name (Please print)

**Isis hereby agrees and accepts this Notice of Change in Election from Accept to Reject, and such acceptance will be binding on Isis' successors, assigns and legal representatives:**

**ISIS PHARMACEUTICALS, INC.**

\_\_\_\_\_  
By

\_\_\_\_\_  
Date

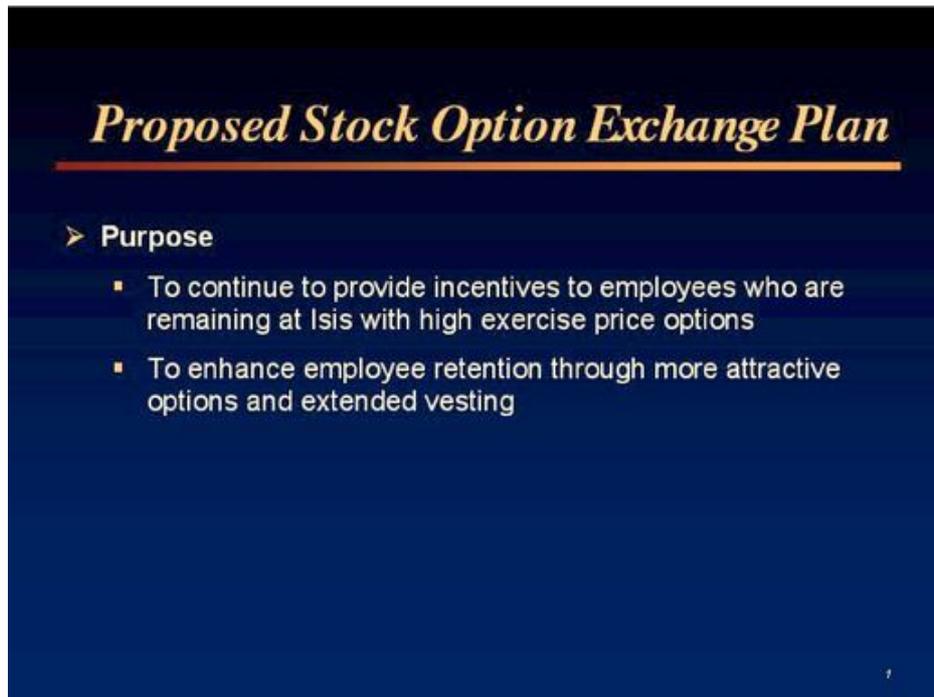
\_\_\_\_\_  
Title

QuickLinks

[Exhibit 99.\(a\)\(1\)\(E\)](#)

[NOTICE OF CHANGE IN ELECTION FROM ACCEPT TO REJECT](#)





***Proposed Stock Option Exchange Plan***

➤ **Purpose**

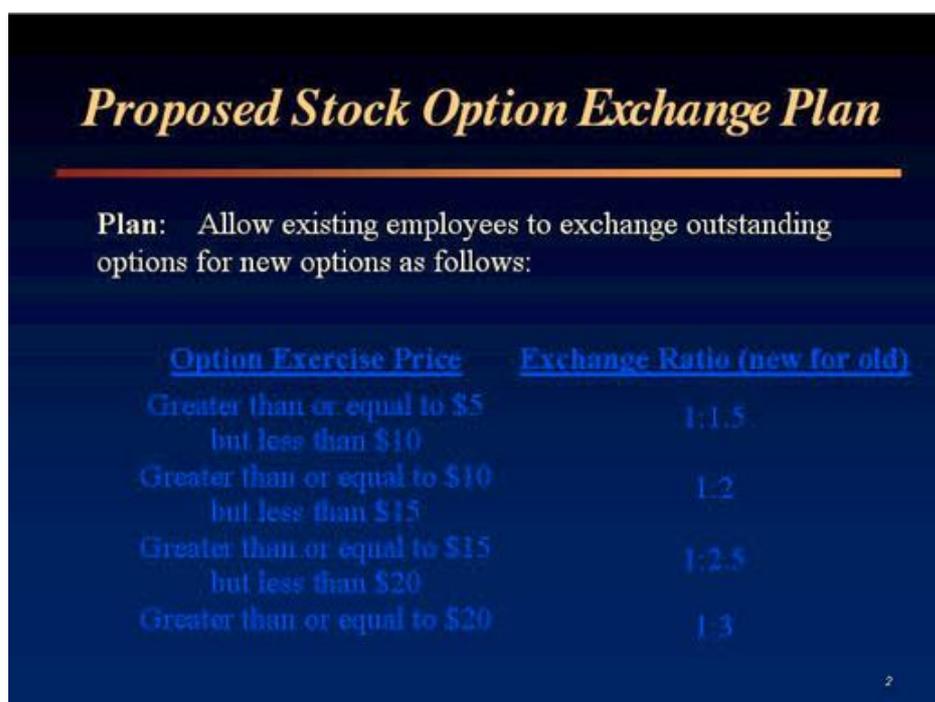
- To continue to provide incentives to employees who are remaining at Isis with high exercise price options
- To enhance employee retention through more attractive options and extended vesting

1

**Proposed Stock Option Exchange Plan**

• **Purpose**

- To continue to provide incentives to employees who are remaining at Isis with high exercise price options
- To enhance employee retention through more attractive options and extended vesting



***Proposed Stock Option Exchange Plan***

**Plan:** Allow existing employees to exchange outstanding options for new options as follows:

<u>Option Exercise Price</u>	<u>Exchange Ratio (new for old)</u>
Greater than or equal to \$5 but less than \$10	1:1.5
Greater than or equal to \$10 but less than \$15	1:2
Greater than or equal to \$15 but less than \$20	1:2.5
Greater than or equal to \$20	1:3

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**Proposed Stock Option Exchange Plan**

**Plan:** Allow existing employees to exchange outstanding options for new options as follows:

Option Exercise Price

Exchange Ratio (new for old)

Greater than or equal to \$5 but less than \$10	1:1.5
Greater than or equal to \$10 but less than \$15	1:2
Greater than or equal to \$15 but less than \$20	1:2.5
Greater than or equal to \$20	1:3

***Proposed Stock Option Exchange Plan***

- New option will have following characteristics
  - Approximately a 5-year term (expire December 31, 2008)
  - New vesting over 3 years (33.34% vest on January 1, 2004, then 2.78% vest monthly thereafter for 2 years)
  - Vesting accelerates in an acquisition
  - Exercise price is the greater of:
    - \$5.00; or
    - The Fair Market Value on the last day of the offering
  - Available for all options granted prior to January 5, 2002
  - New options will be non-qualified stock options not ISOs
- Board of Director members are not eligible to participate

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**Proposed Stock Option Exchange Plan**

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- Board of Director members are not eligible to participate

# Proposed Stock Option Exchange Plan

## Effects of Option Exchange

- |  |   |
|--|---|
| <p>➤ <b>Old Option</b></p> <ul style="list-style-type: none"> <li>▪ 3,000 shares</li> <li>▪ \$7 exercise price</li> <li>▪ Fully vested</li> <li>▪ 6-year term remaining</li> </ul> | <p>➤ <b>New Option</b></p> <ul style="list-style-type: none"> <li>▪ 2,000 shares</li> <li>▪ \$5.00 exercise price</li> <li>▪ New 3-year vesting</li> <li>▪ 5-year term remaining</li> </ul> |
|--|---|

Isis stock price 12/31/2006	Value old option	Value new option
\$8	\$3,000	\$6,000
\$10	\$9,000	\$10,000
\$15	\$24,000	\$20,000
\$20	\$39,000	\$30,000
\$30	\$69,000	\$50,000
\$50	\$129,000	\$90,000

It is important to carefully consider these calculations in making your decision to hold or exchange your options

### Proposed Stock Option Exchange Plan

#### Effects of Option Exchange

• **Old Option**

- 3,000 shares
- \$7 exercise price
- Fully vested
- 6-year term remaining

• **New Option**

- 2,000 shares
- \$5.00 exercise price
- New 3-year vesting
- 5-year term remaining

Isis stock price 12/31/2006	Value old option	Value new option
\$ 8	\$ 3,000	\$ 6,000
\$ 10	\$ 9,000	\$ 10,000
\$ 15	\$ 24,000	\$ 20,000
\$ 20	\$ 39,000	\$ 30,000
\$ 30	\$ 69,000	\$ 50,000
\$ 50	\$ 129,000	\$ 90,000

It is important to carefully consider these calculations in making your decision to hold or exchange your options

# Proposed Stock Option Exchange Plan

## Effects of Option Exchange

### ➤ Old Option

- 3,000 shares
- \$12 exercise price
- Fully vested
- 4-year term remaining

### ➤ New Option

- 1,500 shares
- \$5.00 exercise price
- New 3-year vesting
- 5-year term remaining

Isis stock price 12/31/2006	Value old option	Value new option
\$8	-0-	\$4,500
\$10	-0-	\$7,500
\$15	\$9,000	\$15,000
\$20	\$24,000	\$22,500
\$30	\$54,000	\$37,500
\$50	\$114,000	\$67,500

It is important to carefully consider these calculations in making your decision to hold or exchange your options

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### Proposed Stock Option Exchange Plan

#### Effects of Option Exchange

#### • Old Option

- 3,000 shares
- \$12 exercise price
- Fully vested
- 4-year term remaining

#### • New Option

- 1,500 shares
- \$5.00 exercise price
- New 3-year vesting
- 5-year term remaining

Isis stock price 12/31/2006	Value old option	Value new option
\$ 8	-0-	\$ 4,500
\$ 10	-0-	\$ 7,500
\$ 15	\$ 9,000	\$ 15,000
\$ 20	\$ 24,000	\$ 22,500
\$ 30	\$ 54,000	\$ 37,500
\$ 50	\$ 114,000	\$ 67,500

It is important to carefully consider these calculations in making your decision to hold or exchange your options

# Proposed Stock Option Exchange Plan

## Effects of Option Exchange

### > Old Option

- 3,000 shares
- \$16 exercise price
- 3/4 vested
- 7-year term remaining

### > New Option

- 1,200 shares
- \$5.00 exercise price
- New 3-year vesting
- 5-year term remaining

Isis stock price 12/31/2006	Value old option	Value new option
\$8	-0-	\$3,600
\$10	-0-	\$6,000
\$15	-0-	\$12,000
\$20	\$12,000	\$18,000
\$30	\$42,000	\$30,000
\$50	\$102,000	\$34,000

It is important to carefully consider these calculations in making your decision to hold or exchange your options

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### Proposed Stock Option Exchange Plan

#### Effects of Option Exchange

#### Old Option

- 3,000 shares
- \$16 exercise price
- 3/4 vested
- 7-year term remaining

#### New Option

- 1,200 shares
- \$5.00 exercise price
- New 3-year vesting
- 5-year term remaining

Isis stock price 12/31/2006	Value old option	Value new option
\$ 8	-0-	\$ 3,600
\$ 10	-0-	\$ 6,000
\$ 15	-0-	\$ 12,000
\$ 20	\$ 12,000	\$ 18,000
\$ 30	\$ 42,000	\$ 30,000
\$ 50	\$ 102,000	\$ 34,000

It is important to carefully consider these calculations in making your decision to hold or exchange your options

# Proposed Stock Option Exchange Plan

## Effects of Option Exchange

### ➤ Old Option

- 3,000 shares
- \$20 exercise price
- 1/2 vested
- 8-year term remaining

### ➤ New Option

- 1,000 shares
- \$5.00 exercise price
- New 3-year vesting
- 5-year term remaining

Isis stock price 12/31/2006	Value old option	Value new option
\$8	-0-	\$3,000
\$10	-0-	\$5,000
\$15	-0-	\$10,000
\$20	-0-	\$15,000
\$30	\$30,000	\$25,000
\$50	\$90,000	\$45,000

It is important to carefully consider these calculations in making your decision to hold or exchange your options

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### Proposed Stock Option Exchange Plan

#### Effects of Option Exchange

#### • Old Option

- 3,000 shares
- \$20 exercise price
- 1/2 vested
- 8-year term remaining

#### • New Option

- 1,000 shares
- \$5.00 exercise price
- New 3-year vesting
- 5-year term remaining

Isis stock price 12/31/2006	Value old option	Value new option
\$ 8	-0-	\$ 3,000
\$ 10	-0-	\$ 5,000
\$ 15	-0-	\$ 10,000
\$ 20	-0-	\$ 15,000
\$ 30	\$ 30,000	\$ 25,000
\$ 50	\$ 90,000	\$ 45,000

It is important to carefully consider these calculations in making your decision to hold or exchange your options

## *Proposed Stock Option Exchange Plan*

### *Process for Option Exchange*

- Each eligible employee will receive a package April 8, 2003 regarding the option exchange plan
- **You must make your decision to participate no later than 12:00 a.m. May 8, 2003, or you will no longer be eligible to participate**
- **You may withdraw your decision to participate at any time prior to 12:00 a.m. May 8, 2003.**
- Forms must be returned to Linda Powell by 12:00 a.m. May 8, 2003, whether or not you intend to participate
- If you intend to participate, you need to return the original copy of any option grant forms you are exchanging
- New option grant forms for exchanged options will be distributed in May

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#### **Proposed Stock Option Exchange Plan**

##### **Process for Option Exchange**

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## *Proposed Stock Option Exchange Plan*

- PLEASE ALSO READ THE DISTRIBUTED OFFER TO EXCHANGE AND SUMMARY OF TERMS OF OPTION EXCHANGE IN THEIR ENTIRETY, BECAUSE THE INFORMATION IN THIS PRESENTAION IS NOT COMPLETE AND DOES NOT CONTAIN ALL OF THE INFORMATION RELEVANT TO YOUR DECISION WHETHER OR NOT TO PARTICIPATE IN THIS OFFER. YOU CAN OBTAIN A COPY OF OFFER TO EXCHANGE AND SUMMARY OF TERMS OF OPTION EXCHANGE ON THE ISIS INTRANET UNDER THE HEADING "STOCK OPTION EXCHANGE PROGRAM." IN ADDITION, IF YOU CONTACT LINDA POWELL AT (760) 603-2471 SHE WILL PROVIDE YOU A COPY OF THESE DOCUMENTS.

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#### **Proposed Stock Option Exchange Plan**

- PLEASE ALSO READ THE DISTRIBUTED OFFER TO EXCHANGE AND SUMMARY OF TERMS OF OPTION EXCHANGE IN THEIR ENTIRETY, BECAUSE THE INFORMATION IN THIS PRESENTAION IS NOT COMPLETE AND DOES NOT CONTAIN ALL OF THE INFORMATION RELEVANT TO YOUR DECISION WHETHER OR NOT TO PARTICIPATE IN THIS OFFER. YOU CAN OBTAIN A COPY OF OFFER TO EXCHANGE AND SUMMARY OF TERMS OF OPTION EXCHANGE ON THE ISIS INTRANET UNDER THE HEADING "STOCK

## QuickLinks

[Exhibit 99.\(a\)\(1\)\(G\)](#)

[Proposed Stock Option Exchange Plan  
Process for Option Exchange](#)

