

As filed with the Securities and Exchange Commission on May 19, 2003

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# SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

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## Amendment No. 1

to

## 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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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 INTRODUCTORY STATEMENT

This Amendment No. 1 to Schedule TO amends and supplements the Tender Offer Statement on Schedule TO, initially filed with the Securities and Exchange Commission on April 8, 2003, in connection with Isis Pharmaceuticals, Inc.'s (the "Company" or "Isis") offer to exchange outstanding stock options with exercise prices equal to or greater than \$5.00 per share granted 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 replacement options to purchase shares of the Company's Common Stock to be granted under the 2000 Broad-Based Equity Incentive Plan, upon the terms and subject to the conditions set forth in the Offer to Exchange. This Amendment's sole purpose is to report the results of the tender offer.

#### ITEM 4. TERMS OF THE TRANSACTION.

Item 4 of the Schedule TO, is hereby amended and supplemented to add the following:

The Offer expired at midnight, Pacific Time, on Thursday May 8, 2003. Pursuant to the Offer, Isis accepted for cancellation an aggregate of approximately 2,236,206 shares of Common Stock underlying Eligible Options. This number represents approximately 35% of the total shares of Common Stock underlying Eligible Options outstanding as of May 8, 2003. Approximately 225 Eligible Participants, which represents approximately 71% of the Eligible Participants as of



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.

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\* Previously filed as an exhibit to the Schedule TO filed with the Securities and Exchange Commission on April 8, 2003.

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## QuickLinks

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[SIGNATURE](#)

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