

SUPPLEMENT TO PROSPECTUS
DATED AUGUST 14, 2002

Isis Pharmaceuticals, Inc.

The Prospectus, dated August 14, 2002, as supplemented by the Prospectus Supplements dated September 16, 2002, October 21, 2002, February 20, 2003, March 10, 2003 and May 30, 2003, is hereby supplemented as follows to restate, in its entirety, the "Selling Security Holders" section on pages 14-16 of the Prospectus.

SELLING SECURITY HOLDERS

We initially issued the notes to the initial purchasers of the notes who then resold the notes in transactions exempt from the registration requirements of the Securities Act to persons reasonably believed to be "qualified institutional buyers" (as defined in Rule 144A under the Securities Act) and non-U.S. persons outside the U.S. pursuant to Regulation S under the Securities Act. The selling security holders (which term includes their transferees, pledgees, donees or their successors) may from time to time offer and sell pursuant to this prospectus or any applicable prospectus supplement any or all of the notes and common stock issuable upon conversion of the notes.

No offer or sale under this prospectus may be made by a selling security holder unless that holder is listed in the table in this prospectus or until that holder has notified us and a supplement to this prospectus has been filed or an amendment to the registration statement of which this prospectus is a part has become effective. We will supplement or amend this prospectus to include additional selling security holders upon request and upon provision of all required information to us. Information concerning the selling security holders may change from time to time and any changed information will be set forth in supplements to this prospectus if and when necessary.

The following table sets forth information about each selling security holder, including the name, the number and percentage of the notes beneficially owned and being offered by the selling security holder and the number and percentage of common stock beneficially owned and being offered by the selling security holder. The percentages of common stock beneficially owned and being offered are based on the number of shares of our common stock that were outstanding as of December 31, 2003. Unless otherwise indicated below, none of the selling security holders nor any of their affiliates, officers, directors or principal equity holders has held any position or office or has had any material relationship with us within the past three years.

Name	Principal Amount of Notes Beneficially Owned and Offered Hereby (1)	Percentage of Notes Outstanding	Shares of Common Stock Beneficially Owned and Offered Hereby	Percentage of Common Stock Outstanding
Akela Capital Master Fund	3,000,000	2.4%	180,451	*
Alpine Associates	7,950,000	6.4%	478,195	*
Alpine Partners	1,050,000	*	63,157	*
American Investors Life Ins	100,000	*	6,015	*
American Samoa Government	18,000	*	1,082	*
Aristeia International	5,197,000	4.2%	312,601	*
Aristeia Trading LLC	1,553,000	1.2%	93,413	*
Ascend Managed Account Ltd	19,797	*	1,190	*
Ascend Offshore Fund Ltd	129,203	*	7,771	*
Ascend Partners LP	20,720	*	1,246	*
Ascend Partners Sapient LP	30,280	*	1,821	*
ATSF Transamerica Convertible Securities	30,000	*	1,804	*
Baird, Patrick & Co	1,500,000	1.2%	90,225	*
BP Amoco PLC Master Trust	571,000	*	34,345	*
Canyon Capital Arbitrage Master Fund, Ltd.	3,300,00	2.6%	198,496	*
Canyon Mac 18, Ltd. (RMF)	550,000	*	33,082	*
Canyon Value Realization Fund (Cayman) Ltd.	4,950,000	4.0%	297,744	*
CFFX, LLC	3,000,000	2.4%	180,451	*
Cheyne Capital Management Limited	2,000,000	1.6%	120,300	*
Context Convertible Arbitrage Fund	450,000	*	27,067	*
Context Convertible Arbitrage Offshore Fund, Ltd.	275,000	*	16,541	*
Credit Suisse First Boston Corporation	3,200,000	2.6%	192,481	*
Deutsche Bank Securities Inc.	3,500,000	2.8%	210,526	*
DKR Fixed Income Holding Fund Ltd.	1,000,000	*	60,150	*
Dodeca Fund, LP	600,000	*	36,090	*
Estate of James Campbell	146,000	*	8,781	*

Fidelity Financial Trust: Fidelity Convertible Securities Fund	1,500,000	1.2%	90,225	*
First Union Securities Inc.	13,500,000	10.8%	812,030	1.5%
Grace Brothers Management, LLC	750,000	*	45,112	*
Highbridge International LLC	20,000,000	16.0%	1,203,008	2.2%
Hotel Union & Hotel Industry of Hawaii Pension Plan	193,000	*	11,609	*
IDEX Transamerica Convertible Securities Fund	75,000	*	4,511	*
JC Penney Insurance Co Group	500,000	*	30,075	*
Jefferies & Co.	750,000	*	45,112	*
Jefferies & Company Inc.	4,000	*	240	*
K D Convertible Arbitrage Fund LP	1,000,000	*	60,150	*
KBC Financial Products (Cayman Islands) Limited	3,500,000	2.8%	210,526	*
KBC Financial Products USA Inc.	2,650,000	2.1%	159,398	*
Lincoln Nat'l Global Asset Allocation Fund, Inc.	90,000	*	5,413	*
Liongate Capital	2,000,000	1.6%	120,300	*
McMahan Securities Co. Ltd.	1,550,000	1.2%	93,233	*
Morgan Stanley & Co, Incorporated	500,000	*	30,075	*
Pacific Life Insurance Company	500,000	*	30,075	*
Sterling Investment Co.	500,000	*	30,075	*
The James Campbell Corporation	121,000	*	7,278	*
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TQA Master Fund Ltd.	1,000,000	*	60,150	*
Transamerica Life Insurance & Annuity Co.	4,450,000	3.6%	267,669	*
Tribeca Investments LLC	5,000,000	4.0%	300,752	*
UBS Warburg LLC	3,320,000	2.7%	199,699	*
Viacom Inc. Pension Plan	19,000	*	1,142	*
Victory Capital Management as agent for Victory Convertible Fund	450,000	*	27,067	*
Victus Capital LP	1,500,000	1.2%	90,225	*
Wachovia Securities International Ltd	7,500,000	6.0%	451,128	*
WPG Convertible Arbitrage Overseas Master Fund LP	1,500,000	1.2%	90,225	*
Zurich Institutional Benchmarks Master Fund, Ltd.	928,000	*	55,819	*

* Less than one percent

- (1) We prepared this table based on the information supplied to us by the selling security holders named in the table and we have not sought to verify such information. This table only reflects information regarding selling security holders who have provided us with such information. We expect that we will update this table as we receive more information from holders of the notes who have not yet provided us with their information.

The selling security holders listed in the above table may have sold or transferred, in transactions exempt from the registration requirements of the Securities Act, some or all of their notes since the date on which the information in the above table was provided to us. Information about the selling security holders may change over time.

Because the selling security holders may offer all or some of the notes or the shares of common stock issuable upon conversion of the notes from time to time, we cannot estimate the amount of the notes or shares of common stock that will be held by the selling security holders upon the termination of any particular offering by a selling security holder. See "Plan of Distribution."

The date of this Prospectus Supplement is January 5, 2004.

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SELLING SECURITY HOLDERS](#)