

Supplement to Prospectus
Dated March 20, 2007
Isis Pharmaceuticals, Inc.

The Prospectus, dated March 20, 2007 as supplemented by the Prospectus Supplement dated April 6, 2007, is hereby supplemented as follows to restate, in its entirety, the "Selling Security Holders" section on pages 23-25 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). 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 March 12, 2007. 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	Percentage of Notes Outstanding	Shares of Common Stock Beneficially Owned and Offered Hereby	Percentage of Common Stock Outstanding
Absolute Strategies Fund, Forum Funds Trust	400,000	*	27,350	—
ADI Alternative Investments	1,000,000	*	68,376	—
ADI Alternative Investments c/o Casam ADI CB Arbitrage	1,000,000	*	68,376	—
ADI Alternative Investments c/o Kallista Master Fund Ltd.	2,000,000	1.2%	136,752	—
Admiral Flagship Master Fund, Ltd.	500,000	*	34,188	—
Advent Convertible ARB Master	4,628,000	2.8%	316,444	—
Advent Enhanced Phoenix Fund	3,000,000	1.8%	205,128	—
AHFP Context	410,000	*	28,034	—
Alcon Laboratories	377,000	*	25,777	—
Alexander Global Master Fund Ltd.	10,000,000	6.2%	683,761	—
Altma Fund SICAV PLC in respect of the Grafton Sub Fund	1,020,000	*	69,743	—
Argent Classic Convertible Arbitrage Fund L.P.	850,000	*	58,119	—
Argent Classic Convertible Arbitrage Fund Ltd.	5,280,000	3.2%	361,025	—
Argent Classic Convertible Arbitrage Fund II, L.P.	200,000	*	13,675	—
Argentum Multi-Strategy Fund Ltd. — Classic	80,000	*	5,470	—
Arlington County Employees Retirement System	542,000	*	37,059	—
Barclays Capital Securities Ltd.	5,500,000	3.4%	376,068	—
B.C. McCabe Foundation	80,000	*	5,470	—
BNP Paribas Arbitrage(1)**	500,000	*	34,188	—
British Virgin Island Social Security Board	125,000	*	8,547	—
Calamos Market Neutral Income Fund — Calamos Investment Trust	5,000,000	3.1%	341,880	—
CASAM Argent Classic Convertible Arbitrage Fund Limited	160,000	*	10,940	—
CASAM Context Offshore Advantage Fund Limited	380,000	*	25,982	—
CIBC World Markets Corp	1,665,000	1.0%	113,846	—
Citadel Equity Fund, Ltd.(2)**	5,000,000	3.1%	341,880	*
City of Shreveport (LA) Employees Retirement System	80,000	*	5,470	—
City University of New York (CUNY)	108,000	*	7,384	—
ClearBridge Asset Management Inc.(3)**	7,050,000	4.3%	482,051	—
CNH CA Master Account, L.P.(4)	500,000	*	34,188	—

Columbia Convertible Securities Fund	4,000,000	2.5%	273,504	*
Commissioners of the Land Office	850,000	*	58,119	—
Constans Healthcare Convertible Arbitrage Fund	250,000	*	17,094	—
Context Advantage Master Fund, LP	3,820,000	2.4%	261,196	—
Daimler Chrysler Corp Emp #1 Pension Plan, DTD 4/1/89(6)	787,000	*	53,811	—
DBAG London	11,700,000	7.2%	800,000	*
Elite Classic Convertible Arbitrage Ltd.	160,000	*	10,940	—
Family Service Life Insurance Company(15)**	100,000	*	6,837	—
Federated Kaufman Fund, a portfolio of Federated Equity Funds(7)	19,800,000	12.2%	1,353,846	12.7%

Finch Tactical Plus Class B	170,000	*	11,623	—
Florida Power and Light Group Employee Pension Plan(6)	304,000	*	20,786	—
Fore Convertible Master Fund	5,147,000	3.2%	351,931	—
Fore ERISA Fund, Ltd.	493,000	*	33,709	—
Fore Multi Strategy Master Fund, Ltd.	812,000	*	55,521	—
Franklin and Marshall College(6)	19,000	*	1,299	—
Froley Revy Alternative Strategies	600,000	*	41,025	—
GLG Market Neutral Fund(8)	6,000,000	3.7%	410,256	—
GMIMCO Trust	990,000	*	67,692	—
Grady Hospital Foundation	104,000	*	7,111	—
The Guardian Life Insurance Company of America(15)**	5,000,000	3.1%	341,880	—
The Guardian Life Insurance Company of America Pension Trust(15)**	400,000	*	27,350	—
HFRC Opportunity Master Trust	205,000	*	14,017	—
HFRC Select Master Trust Fund	1,300,000	*	88,888	*
Institutional Benchmarks Series (Master Feeder) Ltd.	1,550,000	*	105,982	—
Institutional Benchmarks Series (Master Feeder) Limited in respect of Alcor series	200,000	*	13,675	—
Intl. Truck & Engine Corp Non Contributory Retirement Plan Trust	635,000	*	43,418	—
Intl. Truck & Engine Corp Retirement Plan for Salaried Employee's Trust	280,000	*	19,145	—
KeySpan Foundation	40,000	*	2,735	—
KeySpan Insurance Company	140,000	*	9,572	—
LDG, Limited(9)	259,000	*	17,709	—
Lord Abbett Investment Trust — LA Convertible Fund	3,080,000	1.9%	210,598	—
Lyxor/Context Fund LTD	790,000	*	54,017	—
Lyxor Master Trust Fund	167,000	*	11,418	—
Man Mac 1 Limited	798,000	*	54,564	*
McMahan Securities Co. LP	400,000	*	27,350	—
Mohican VCA Master Fund Ltd	3,100,000	1.9%	211,965	—
National Fuel & Gas Company Retirement Plan	445,000	*	30,427	—
NFS — SCI Funeral and Merchandise Fixed Common Trust	30,000	*	2,051	—
The Northwestern Mutual Life Insurance Company — General Account(10)**	2,250,000	1.4%	153,846	—
The Northwestern Mutual Life Insurance Company — Group Annuity Separate Account(10)**	250,000	*	17,094	—
NYC Teachers' Variable Annuity Fund	1,400,000	*	95,726	—
Occidental Petroleum Corporation	250,000	*	17,094	—
Philadelphia Board of Pensions	550,000	*	37,606	—
Police & Fire Retirement System of the City of Detroit	416,000	*	28,444	—
Polygon Global Opportunities Master Fund(11)	1,000,000	*	68,376	—
ProMutual	685,000	*	46,837	—
Rampart Enhanced Convertible Investors, LLC(6)	140,000	*	9,572	—
San Diego County Employees Retirement Association	2,800,000	1.7%	191,453	*
San Francisco City and County ERS	1,071,000	*	73,230	—
SCI Cemetary Merchandise Common Trust	20,000	*	1,367	—
SCI Pre-Need Common Trust Fund	20,000	*	1,367	—
Stark Master Fund Ltd.(12)**	6,500,000	4.0%	444,444	—
Sterling Invest Co.	1,675,000	1.0%	114,529	—
Total Fina Elf Finance USA, Inc.	245,000	*	16,752	—
TQA Master Fund Ltd.(9)	1,663,000	1.0%	113,709	—
TQA Master Plus Fund, Ltd.(9)(13)	1,020,000	*	69,743	*
Trustmark Insurance Company	267,000	*	18,256	—
Vermont Mutual Insurance Company	140,000	*	9,572	—
Vicis Capital Master Fund	9,000,000	5.5%	615,384	—
Wachovia Securities International Ltd(14)**	3,000,000	1.8%	205,128	—
Worldwide Transactions Limited	210,000	*	14,358	—
Xavex Convertible Arbitrage 10 Fund	270,000	*	18,461	—
Zazove Convertible Arbitrage Fund, L.P.	6,450,000	4.0%	441,025	—
Zazove Hedged Convertible Fund, L.P.	4,000,000	2.5%	273,504	—
Zurich Institutional Benchmarks Master Fund Ltd., c/o TQA Investors, LLC(9)	558,000	*	38,153	*

* Less than 1%

** The selling security holder has represented to us that the notes held by them were purchased in the ordinary course of business and that at the time of purchase of the notes held by them, they did not have any agreements or understandings, directly or indirectly, with any person to distribute the notes held by them or the common stock issuable upon conversion of the notes held by them.

- (1) BNP Paribas Security Corp. is an affiliate of BNP Paribas Arbitrage, a registered broker-dealer.
- (2) Citadel Equity Fund, Ltd. also beneficially owns 630 shares of our common stock, which are not included for sale under this prospectus. The broker-dealers are under common control with Citadel Equity Fund Ltd. and is directly owned by Citadel Equity Fund. The broker dealers are: Aragon Investments Ltd., Palofax Trading LLC, Citadel Trading Group, LLC and Citadel Derivatives Group, LLC. Citadel Limited Partnership ("CLP") is the trading manager of Citadel Equity Fund Ltd. and consequently has investment discretion over securities held by Citadel Equity Fund Ltd. Citadel Investment Group, LLC ("CIG") controls CLP. Kenneth C. Griffin controls CIG and therefore has ultimate investment discretion over securities held by Citadel Equity Fund Ltd. CLP, CIG, and Mr. Griffin each disclaim beneficial ownership of the shares held by Citadel Equity Fund Ltd.
- (3) Selling Security Holder is under common control with Legg Mason Investors Services, LLC ("LMIS"), a limited purpose broker-dealer affiliate. LMIS serves as a principal underwriter for certain mutual funds managed by investment advisory affiliates of Legg Mason Inc.

(4) CNH Partners, LLC is Investment Advisor of the Selling Securityholder and has sole voting and dispositive power over the securities. Investment principals for the Advisor are Robert Krail, Mark Mitchell and Todd Pulvino.

(5) Reserved

(6) Palisade Capital Management, LLC acts as an Investment Advisor.

(7) Federated Kaufman Fund also beneficially owns 9,274,660 shares of our common stock and 1,176,470 shares of our common stock issuable upon exercise of warrants. Neither of these securities are included for sale under this prospectus.

- (8) GLG Market Neutral Fund is a publicly owned company listed on the Irish Stock Exchange. GLG Partners LP, and English limited partnership, acts as the investment manager of the fund and has voting and dispositive power over the securities held by the fund. The general partner of GLG Partners LP is GLG Partners Limited, an English limited company. The shareholders of GLG Partners Limited are Noam Gottesman, Pierre Lagrange, Jonathan Green, Philippe Jabre and Lehman Brothers (Cayman) Limited, a subsidiary of Lehman Brothers Holdings, Inc., a publicly-held entity. The managing directors of GLG Partners Limited are Noam Gottesman, Pierre Lagrange and Emmanuel Roman and, as a result, each has voting and dispositive power over the securities held by the fund. GLG Partners LP, GLG Partners Limited, Noam Gottesman, Pierre Lagrange and Emmanuel Roman disclaim beneficial ownership of the securities held by the Fund, except for their pecuniary interest therein.
- (9) TQA Investors LLC has sole investment power and shared voting power. Its members are: John Idone, Paul Bucci and Darren Langis and Andrew Anderson.
- (10) The following NASD members are affiliated with Northwestern Mutual: Northwestern Mutual Investment Services, LLC, Russell Institutional Services, Russell Implementation Services, Inc., Russell Fund Distributors, Inc., and Todd Securities, LLC
- (11) Polygon Investment Partner LLP and Polygon Investment Partners LP (the "Investment Manager"), Polygon Investments Ltd. (the "Manager"), Alexander E. Jackson, Reade E. Griffith, and Patrick G. G. Dear share voting and dispositive power of the securities held by Polygon Global Opportunities Master Fund. The Investment Mangers, the Manger, Alexander E. Jackson, Reade E. Griffith, and Patrick G. G. Dear disclaim beneficial ownership of the securities held by Polygon Global Opportunities Master Fund.
- (12) Stark Master Fund Ltd. is an affiliate of Reliant Trading, a registered broker-dealer.
- (13) TQA Master Plus Fund, Ltd also beneficially owns 10,000 shares of our common stock, which are not included for sale under this prospectus.
- (14) Wachovia Securities Intl. Ltd and Wachovia Capital Markets LLC are subsidiaries of Wachovia Corporation.
- (15) Park Avenue Securities LLC and Guardian Investor Services LLC are broker dealers which are indirect, wholly owned subsidiaries of The Guardian Life Insurance Company of America.

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.

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 May 15, 2007
