UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-K/A

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF
THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2005
Commission file number 0-19125

Isis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

Delaware	**33-0336973**
(State or other jurisdiction of incorporation or organization)	(IRS Employer Identification No.)

1896 Rutherford Road, Carlsbad, CA 92008
(Address of principal executive offices, including zip code)
760-931-9200
(Registrant's telephone number, including area code)
Securities registered pursuant to Section 12(b) of the Act: **None**
Securities registered pursuant to Section 12(g) of the Act:
Common Stock, $.001 Par Value

Indicate by check mark whether the Registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes o No x

Indicate by check mark whether the Registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes o No x

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes x No o

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. o

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, or a non-accelerated filer. See definition of "accelerated filer and large accelerated filer" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer o Accelerated filer x Non-accelerated filer o

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes o No x

The approximate aggregate market value of the voting common stock held by non-affiliates of the registrant, based upon the last sale price of the common stock reported on the National Association of Securities Dealers Automated Quotation National Market System was $174,075,233 as of June 30, 2005.*

The number of shares of voting common stock outstanding as of March 1, 2006 was 72,479,785.

DOCUMENTS INCORPORATED BY REFERENCE
(To the extent indicated herein)

Portions of the registrant's definitive Proxy Statement to be filed on or about March 22, 2006 with the Securities and Exchange Commission in connection with Registrant's annual meeting of stockholders to ber held on May 3, 2006 are incorporated by reference into Part III of this Report. The Exhibit Index (Item No. 15) located on pages 72 to 77 incorporates several documents by reference as indicated therein.

* Excludes 13,007,479 shares of common stock held by directors and officers and by stockholders whose beneficial ownership is known by the Registrant to exceed 10% of the common stock outstanding at June 30, 2005. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the Registrant, or that such person is controlled by or under common control with the Registrant.

EXPLANATORY NOTE

Isis Pharmaceuticals, Inc. (the "Company") is filing this Amendment to its Annual Report on Form 10-K for the year ended December 31, 2005, filed with the Securities Exchange Commission on March 16, 2006 ("Original Filing"), to modify Part II, Item 8, *Consolidated Financial Statements ("F Pages")*, to reclassify cash equivalents that were inadvertently classified as short term investments in the Company's Consolidated Balance Sheet at December 31, 2005. The Company's working capital and total of cash, cash equivalents and short-term investments were accurately stated in all items of the Original Filing. Although we are including in this Amendment the complete text of the F Pages, the only changes to the F Pages from those previously filed with the Original Filing are as follows:

- *Consolidated Balance Sheets*, (page F-3 of the Original Filing) was amended to reclassify certain cash equivalents from Short-term investments to Cash and cash equivalents.

- *Consolidated Statements of Cash Flows* (page F-6 of the Original Filing) was amended to reflect the change in the Consolidated Balance Sheet at

December 31, 2005 as described above.

- *Footnote 2 — Investments* (page F-16 of the Original Filing) was amended to reflect the revised amount of Short-term investments on the amended Consolidated Balance Sheet at December 31, 2005.

Item 15. of Part IV, *Exhibits*, of this Amendment has been revised to contain a currently-dated consent of our independent registered public accounting firm. Additionally, Item 15. of Part IV, *Exhibits*, of this Amendment has been revised to contain currently-dated certifications from our Chief Executive Officer and Chief Financial Officer, as required by Sections 302 and 906 of the Sarbanes-Oxley Act of 2002. The certifications of our Chief Executive Officer and Chief Financial Officer are attached to this Form 10-K/A as Exhibits 31.1, 31.2 and 32.1, respectively.

As this Amendment only relates to the F Pages, the previously issued Management's Discussion and Analysis in the Original Filing is unchanged. This Amendment does not reflect events occurring after the filing of our Annual Report on Form 10-K or include, or otherwise modify or update, the disclosure contained therein in any way except as expressly indicated above. Accordingly, this Amendment should be read in conjunction with the Original Filing and the Company's filings made with the Securities and Exchange Commission subsequent to the Original Filing.

FORWARD-LOOKING STATEMENTS

This report on Form 10-K/A and the information incorporated herein by reference contain forward-looking statements regarding our business, our financial position and the therapeutic and commercial potential of our technologies and products in development. Any statement describing our goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as our goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, in developing and commercializing systems to identify infectious organisms that are effective and commercially attractive, and in the endeavor of building a business around such products. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in our report on Form 10-K for the year ended December 31, 2005 filed with the Securities Exchange Commission on March 16, 2006, including those identified in Item 1A entitled "Risk Factors". Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements.

TRADEMARKS

Affinitak™ is a trademark of Eli Lilly and Company.
Macugen® is a registered trademark of Eyetech Pharmaceuticals, Inc.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a)(1) Index to Financial Statements

We submitted the consolidated financial statements required by this item in a separate section beginning on page F-1 of this Report.

(a)(2) Index to Financial Statement Schedules

We omitted these schedules because they are not required, or are not applicable, or the required information is shown in the consolidated financial statements or notes thereto.

(a)(3) Index to Exhibits

See Index to Exhibits on pages 6.

(b) Exhibits

We listed the exhibits required by this Item under Item 15(a)(3).

(c) Financial Statement Schedules

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report on Form 10-K/A to be signed on its behalf by the undersigned, thereunto duly authorized on the 9th day of August, 2006.

ISIS PHARMACEUTICALS, INC.

By: /s/ STANELY T. CROOKE

Stanley T. Crooke, M.D., Ph.D.
Chairman of the Board, President and Chief Executive Officer (Principal executive officer)

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

Signatures	Title	Date
/s/ STANLEY T. CROOKE Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	August 9, 2006
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	August 9, 2006
/s/ SPENCER R. BERTHELSEN* Spencer R. Berthelsen, M.D.	Director	August 9, 2006
/s/ RICHARD D. DIMARCHI* Richard D. DiMarchi	Director	August 9, 2006
Christopher F. O. Gabrieli	Director	
/s/ JOSEPH KLEIN* Joseph Klein, III.	Director	August 9, 2006
/s/ FREDERICK T. MUTO* Frederick T. Muto	Director	August 9, 2006
/s/ JOHN C. REED, M.D. PH.D.* John C. Reed, M.D., Ph.D.	Director	August 9, 2006
/s/ JOSEPH H. WENDER* Joseph H. Wender	Director	August 9, 2006

*By : /s/ B. LYNNE PARSHALL

B. Lynne Parshall, J.D.
Attorney-in-Fact

INDEX TO EXHIBITS

Exhibit Number	Description of Document
3.1	Amended and Restated Certificate of Incorporation filed June 19, 1991.(1)
3.2	Certificate of Amendment to Restated Certificate of Incorporation filed April 9, 2001.(19)
3.3	Bylaws.(19)
4.3	Certificate of Designation of the Series C Junior Participating Preferred Stock.(17)
4.4	Specimen Common Stock Certificate.(1)
4.5	Form of Right Certificate.(17)
4.6	Subscription, Joint Development and Operating Agreement dated January 14, 2000 among the Registrant, Elan Corporation, plc, Elan International Services, Ltd. and HepaSense, Ltd. (with certain confidential information deleted), together with the related Securities Purchase Agreement, Convertible Promissory Note, Warrant to Purchase Shares of Common Stock, Registration Rights Agreement and License Agreements.(14)
4.7	Registration Rights and Standstill Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(20)
4.8	Loan Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(20)
4.9	Registration Rights Agreement, dated May 1, 2002, among the Registrant, UBS Warburg LLC, Robertson Stephens, Inc., Needham &

		Company, Inc., and Roth Capital Partners, LLC.(16)
4.10		Indenture, dated as of May 1, 2002, between the Registrant and Wells Fargo Bank Minnesota, National Association, as Trustee, with respect to the $125,000,000 51/2% Convertible Subordinated Notes due 2009.(16)
4.11		Form of 51/2% Convertible Subordinated Note due 2009.(16)
4.12		Securities Purchase Agreement, dated August 19, 2005, by and among the Registrant and the purchasers listed on Exhibit A thereto.(37)
4.13		Form of Warrant expiring August 23, 2005.(37)
10.1		Form of Indemnification Agreement entered into between the Registrant and its Directors and Officers with related schedule.(1)
10.2	*	Registrants 1989 Stock Option Plan, as amended.(2)
10.3	*	Registrants 1992 Non-Employee Directors Stock Option Plan, as amended.(4)
10.4	*	Registrants Employee Stock Purchase Plan.(10)
10.5		Form of Employee Assignment of Patent Rights.(1)
10.6	*	Registrants 2000 Broad-Based Equity Incentive Stock Option Plan and related form of option agreement.(10)
10.11		Asset Purchase Agreement between the Registrant and Gen-Probe Incorporated dated December 19, 1997 (with certain confidential information deleted).(6)
10.13		Patent Rights Purchase Agreement between the Registrant and Gilead Sciences, Inc., dated December 18, 1998 (with certain confidential information deleted).(9)
10.14		Rights Agreement dated as of December 8, 2000 between the Registrant and American Stock Transfer & Trust Company.(17)
10.15		Master Agreement between the Registrant and Hybridon, Inc., dated May 24, 2001 (with certain confidential information deleted).(19)

10.17		Subcontract Agreement, dated October 25, 2001 between the Registrant and Science Applications International Corporation.(21)
10.18		Master Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited.(24)
10.19		Collaboration and License Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited (with certain confidential information deleted).(24)
10.20		Clinical Supply Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited (with certain confidential information deleted).(24)
10.21		Stock Purchase Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited.(24)
10.22		Collaboration and Co-development Agreement, dated November 16, 2001 between the Registrant and OncoGenex Technologies Inc. (22)
10.23		Oligonucleotide Manufacturing and Supply Agreement dated December 4, 2001 between the Registrant and Integrated DNA Technologies, Inc. (with certain confidential information deleted).(24)
10.24		Amended and Restated IDT-Isis Licensing Agreement dated December 4, 2001 between the Registrant and Integrated DNA Technologies, Inc. (with certain confidential information deleted).(24)
10.26		License Agreement dated December 31, 2001 between the Registrant and Eyetech Pharmaceuticals, Inc. (with certain confidential information deleted).(25)
10.31		Amended and Restated License Agreement among the Registrant, Orasense Ltd. and Elan Corporation Plc. dated October 24, 2002 (with certain confidential information deleted).(30)
10.32		Amended and Restated License Agreement among the Registrant, Orasense Ltd. and Elan Corporation Plc. dated October 24, 2002 (with certain confidential information deleted).(30)
10.35		Registrant’s Restated Isis Pharmaceuticals, Inc. 10b5-1 Trading Plan dated September 30, 2005.(38)
10.36		Registrant’s 2002 Non-Employee Directors’ Stock Option Plan.(31)
10.37		Registrant’s Form of 2002 Non-Employee Directors’ Stock Option Agreement.(31)
10.41	*	Form of Severance Agreement dated April 2003 entered into between the Registrant Stanley T. Crooke and B. Lynne Parshall.(32)

10.42		Grant letter dated September 29, 2003 from the Centers for Disease Control and Prevention (with certain confidential information deleted).(33)
10.43	*	Amendment No. 1 to Isis Pharmaceuticals, Inc. 2000 Employee Stock Purchase Plan.(33)
10.44		Loan and Security Agreement dated December 15, 2003 between the Registrant and Silicon Valley Bank, including the related negative pledge agreement.(12)
10.47		Subcontract No. 44076514 dated February 26, 2004 between the Registrant and Science Applications International Corporation (with certain confidential information deleted).(13)
10.48		Strategic Collaboration and License Agreement dated March 11, 2004 between the Registrant and Alnylam Pharmaceuticals, Inc. (with certain confidential information deleted).(18)
10.49		Investor Rights Agreement dated March 11, 2004 between the Registrant and Alnylam Pharmaceuticals, Inc.(23)
10.50		Securities Purchase Agreement dated June 4, 2004 between the Registrant and Elan Pharmaceutical Investments II, Ltd.(26)

10.51		Development Agreement dated September 30, 2004 between the Registrant and the National Institute of Allergy and Infectious Diseases (with certain confidential information deleted).(34)
10.52		Amendment No. 1 to License Agreement between the Registrant and Eyetech.(39)
10.53		Sale and Assignment Agreement between the Registrant and Drug Royalty USA, Inc., dated December 21, 2004 (with certain confidential information deleted).(39)
10.54		Security Agreement between the Registrant and Drug Royalty USA, Inc, dated December 21, 2004 (with certain confidential information deleted).(39)
10.55	*	Form of Option Agreement for Options Granted after March 8, 2005 under the 1989 Stock Option Plan.(39)
10.56	*	Form of Option Agreement for Options Granted after March 8, 2005 under the 2000 Broad-Based Equity Incentive Plan.(39)
10.57	*	Form of Option Agreement for Options Granted after March 8, 2005 under the 2002 Non-Employee Director's Stock Option Plan.(39)
10.58		Collaboration and License Agreement between the Registrant and Sarissa, Inc., dated Feb 10, 2005.(39)
10.59		Amendment No.1 to Rights Agreement dated April 7, 2005.(35)
10.60		Collaborative Research Agreement dated May 24, 2005 between the Registrant and Pfizer Inc (with certain confidential information deleted).(36)
10.61		Lease Agreement dated September 6, 2005 between the Registrant and BMR-2282 Faraday Avenue LLC.(38)
10.62		Second Amended and Restated Collaboration Agreement dated August 5, 2005 between the Registrant and Eli Lilly and Company (with certain confidential information deleted).(38)
10.63		Notice of Grant Award issued August 1, 2005 by the Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Disease (with certain confidential information deleted).(38)
10.64		Form of Subcontract Agreement between the Registrant and Science Applications International Corporation.(38)
10.65	*	Letter dated February 27, 2005 extending Dr. Crooke's severance benefit agreement.(39)
10.66	*	Letter dated February 27, 2005 extending Ms. Parshall's severance benefit agreement.(39)
14.1		Registrant's Code of Ethics and Business Conduct.(12)
21.1		List of Subsidiaries for the Registrant. (41)
23.1		Consent of Independent Registered Public Accounting Firm.
24.1		Power of Attorney. (42)
31.1		Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2		Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1		Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.

99.2	Form of Confidentiality Agreement.(11)

(1) Filed as an exhibit to the Registrant's Registration Statement on Form S-1 (No. 33-39640) or amendments thereto and incorporated herein by reference.

(2) Filed as an exhibit to Registrant's Notice of Annual Meeting and Proxy Statement for the 2004 Annual Meeting of Stockholders, filed with the SEC on April 12, 2004, and incorporated herein by reference.

(3) Not used.

(4) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 1996 and incorporated herein by reference.

(5) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 1997 and incorporated herein by reference.

(6) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1997 and incorporated herein by reference.

(7) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 1998 and incorporated herein by reference.

(8) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 1998 and incorporated herein by reference.

(9) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1998 and incorporated herein by reference.

(10) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1999 and incorporated herein by reference.

(11) Filed as an exhibit to the Registrant's Registration Statement on Form S-3 (No. 333-71911) or amendments thereto and incorporated herein by reference.

(12) Filed as an exhibit to the Registrant's Annual Report Form 10-K for the year ended Dec 31, 2003 and incorporated herein by reference.

(13) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2004 and incorporated herein by reference.

(14) Filed as an exhibit to the Registrant's Report on Form 8-K dated January 28, 2000, as amended on October 5, 2001, and incorporated herein by reference.

(15) Filed as an exhibit to the Registrant's Report on Form 10-Q for the quarter ended June 30, 2000 and incorporated herein by reference.

(16) Filed as an exhibit to the Registrant's Registration Statement on Form S-3 (No. 333-89066), originally filed on May 24, 2002, or amendment thereto and incorporated by reference.

(17) Filed as an exhibit to Registrant's Report on Form 8-K dated December 8, 2000 and incorporated herein by reference.

(18) Filed as Exhibit 10.24 to Alnylam Pharmaceutical Inc.'s Registration Statement on Form S-1, File No. 333-113162, and incorporated herein by reference.

(19) Filed as an exhibit to the Registrant's report on Form 10-Q/A for the quarter ended June 30, 2001 and incorporated herein by reference.

(20) Filed as an exhibit to the Registrant's Report on Form 8-K dated August 29, 2001 and incorporated herein by reference.

(21) Filed as an exhibit to the Registrant's Report on Form 8-K filed October 29, 2001 and incorporated herein by reference.

(22) Filed as an exhibit to the Registrant's Report on Form 8-K filed December 12, 2001 and incorporated herein by reference.

(23) Filed as Exhibit 10.25 to Alnylam Pharmaceutical Inc.'s Registration Statement on Form S-1, File No. 333-113162, and incorporated herein by reference.

(24) Filed as an exhibit to the Registrant's Report on Form 8-K filed January 4, 2002 and incorporated herein by reference.

(25) Filed as an exhibit to the Registrant's Report on Form 8-K dated January 7, 2002 and incorporated herein by reference.

(26) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2004 and incorporated herein by reference.

(27) Filed as an exhibit to the Registrant's Report on Form 10-Q for the quarter ended June 30, 2002 and incorporated herein by reference.

(28) Filed as an exhibit to the Registrant's Report on Form 8-K dated September 16, 2002 and incorporated herein by reference.

(29) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2002 and incorporated herein by reference.

(30) Filed as an exhibit to the Registrant's Report on Form 8-K dated November 6, 2002 and incorporated herein by reference.

(31) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2001 and incorporated herein by reference.

(32) Filed as an exhibit to the Registrant's Report on Form 10-Q for the quarter ended June 30, 2003 and incorporated herein by reference.

(33) Filed as an exhibit to the Registrant's Report on Form 10-Q for the quarter ended September 30, 2003 and incorporated herein by reference.

(34) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2004 and incorporated herein by reference.

(35) Filed as an exhibit to Registrant's Current Report on Form 8-K dated April 7, 2005 and incorporated herein by reference.

(36) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2005 and incorporated herein by reference.

(37) Filed as an exhibit to Registrant's Current Report on Form 8-K dated August 22, 2005 and incorporated herein by reference.

(38) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2005 and incorporated herein by reference.

(39) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2004 and incorporated herein by reference.

(40) Filed as an exhibit to Registrant's Current Report on Form 8-K dated February 27, 2006 and incorporated herein by reference.

(41) Previously filed as an exhibit to the initial filing of this Report on Form 10-K.

(42) Filed as part of of the Registrant's Annual Report on Form 10-K for the year ended December 31, 2005, reference is made to page 71.

* Indicates management compensatory plans and arrangements as required to be filed as exhibits to this Report pursuant to Item 14(c).

ISIS PHARMACEUTICALS, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders of Isis Pharmaceuticals, Inc.

We have audited the accompanying consolidated balance sheets of Isis Pharmaceuticals, Inc. and subsidiaries as of December 31, 2005 and 2004, and the related consolidated statements of operations, stockholders' equity (deficit), and cash flows for each of the three years in the period ended December 31, 2005. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of Isis Pharmaceuticals, Inc. and subsidiaries at December 31, 2005 and 2004, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2005, in conformity with U.S. generally accepted accounting principles.

We have also audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the effectiveness of Isis Pharmaceuticals, Inc.'s and subsidiaries' internal control over financial reporting as of December 31, 2005, based on the criteria established in *Internal Control—Integrated Framework* issued by the Committee of Sponsoring Organizations of the Treadway Commission and our report dated March 7, 2006 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
March 7, 2006
except for Note 2, as to which the date is
August 4, 2006

ISIS PHARMACEUTICALS, INC.
CONSOLIDATED BALANCE SHEETS
(In thousands, except share data)

	December 31, 2005 (As amended)	December 31, 2004
ASSETS		
Current assets:		

Cash and cash equivalents	$ 50,885	$ 27,250
Short-term investments	43,504	76,633
Contracts receivable	3,918	10,048
Inventory	951	2,722
Other current assets	6,600	8,956
Total current assets	105,858	125,609
Property, plant and equipment, net	9,130	28,454
Licenses, net	23,770	26,104
Patents, net	18,773	19,097
Deposits and other assets	3,201	3,854
Investments in corporate securities	5,641	5,307
Total assets	$ 166,373	$ 208,425
LIABILITIES AND STOCKHOLDERS' EQUITY (DEFICIT)		
Current liabilities:		
Accounts payable	$ 2,095	$ 6,967
Accrued compensation	3,706	3,475
Accrued liabilities	8,643	8,238
Current portion of long-term obligations	7,835	10,546
Current portion of deferred contract revenue	1,514	14,190
Total current liabilities	23,793	43,416
5 1/2% convertible subordinated notes	125,000	125,000
Long-term obligations, less current portion	14,915	111,611
Long-term deferred contract revenue, less current portion	—	531
Stockholders' equity (deficit):		
Common stock, $0.001 par value; 100,000,000 shares authorized, 72,201,505 and 57,447,333 shares issued and outstanding at December 31, 2005 and 2004, respectively	72	57
Additional paid-in capital	770,263	623,706
Deferred compensation	—	(72)
Accumulated other comprehensive income	3,178	2,623
Accumulated deficit	(770,848)	(698,447)
Total stockholders' equity (deficit)	2,665	(72,133)
Total liabilities and stockholders' equity (deficit)	$ 166,373	$ 208,425

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS
(In thousands, except for per share amounts)

	Years Ended December 31,		
	2005	2004	2003
Revenue:			
Research and development revenue under collaborative agreements	$ 28,610	$ 32,617	$ 49,467
Licensing and royalty revenue	11,523	10,007	523
Total revenue	40,133	42,624	49,990
Expenses:			
Research and development not including compensation (benefit) related to stock options of ($436), ($8), and $673 in 2005, 2004 and 2003, respectively	82,467	118,474	116,963
General and administrative not including compensation (benefit) related to stock options of ($108), $2, and $240 in 2005, 2004, and 2003, respectively	8,432	9,582	9,289
Compensation (benefit) related to stock options	(544)	(6)	913
Restructuring activities	6,960	32,427	1,803
Total operating expenses	97,315	160,477	128,968
Loss from operations:	(57,182)	(117,853)	(78,978)
Investment income	5,094	2,999	5,100
Interest expense	(20,313)	(22,592)	(18,680)
Loss on investment	—	(5,057)	(2,438)
Net loss	(72,401)	(142,503)	(94,996)
Accretion of dividends on preferred stock	—	(361)	(694)
Net loss applicable to common stock	$ (72,401)	$ (142,864)	$ (95,690)
Basic and diluted net loss per share	$ (1.15)	$ (2.52)	$ (1.73)
Shares used in computing basic and diluted net loss per share	62,877	56,642	55,463

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY (DEFICIT)
Years Ended December 31, 2005, 2004 and 2003
(In thousands)

Description	Preferred stock Shares	Preferred stock Amount	Preferred stock Dividend Accretion	Common stock Shares	Common stock Amount	Additional paid in capital	Deferred compensation	Accumulated other comprehensive income/(loss)	Accumulated deficit	Total stockholders' equity (deficit)
Balance at December 31, 2002	12	$ 12,015	$ 1,866	55,216	$ 55	$ 602,101	$ (59)	$ (608)	$ (459,893)	$ 155,477
Comprehensive Loss										
Net loss applicable to common stock	—	—	—	—	—	—	—	—	(95,690)	(95,690)
Change in unrealized gains and (losses)	—	—	—	—	—	—	—	4,084	—	4,084
Comprehensive loss	—	—	—	—	—	—	—	—	—	(91,606)
Dividends accrued on preferred stock	—	—	694	—	—	—	—	—	—	694
Deferred compensation	—	—	—	—	—	1,148	(1,148)	—	—	—
Options exercised and employee stock purchase plan	—	—	—	341	1	1,699	—	—	—	1,700
Compensation benefit relating to the granting of options							913			913
Balance at December 31, 2003	12	$ 12,015	$ 2,560	55,557	$ 56	$ 604,948	$ (294)	$ 3,476	$ (555,583)	$ 67,178
Comprehensive Loss										
Net loss applicable to common stock	—	—	—	—	—	—	—	—	(142,864)	(142,864)
Change in unrealized gains and (losses)	—	—	—	—	—	—	—	(853)	—	(853)
Comprehensive loss	—	—	—	—	—	—	—	—	—	(143,717)
Dividends accrued on preferred stock	—	—	361	—	—	—	—	—	—	361
Deferred compensation	—	—	—	—	—	(228)	228	—	—	—
Options exercised and employee stock purchase plan	—	—	—	834	—	4,051	—	—	—	4,051
Compensation benefit relating to the granting of options	—	—	—	—	—	—	(6)	—	—	(6)
Conversion of preferred stock into common stock	(12)	(12,015)	(2,921)	1,056	1	14,935	—	—	—	—
Balance at December 31, 2004	—	$ —	$ —	57,447	$ 57	$ 623,706	$ (72)	$ 2,623	$ (698,447)	$ (72,133)
Comprehensive Loss										
Net loss applicable to common stock	—	—	—	—	—	—	—	—	(72,401)	(72,401)
Change in unrealized gains and (losses)	—	—	—	—	—	—	—	555	—	555
Comprehensive loss	—	—	—	—	—	—	—	—	—	(71,846)
Deferred compensation	—	—	—	—	—	61	16	—	—	77
Options exercised and employee stock purchase plan	—	—	—	254	1	989	—	—	—	990
Compensation benefit relating to the granting of options	—	—	—	—	—	(678)	56	—	—	(622)
Conversion of Lilly debt	—	—	—	2,500	2	99,998	—	—	—	100,000
Private Placement Offering	—	—	—	12,000	12	46,187	—	—	—	46,199
Balance at December 31, 2005	—	$ —	$ —	72,201	$ 72	$ 770,263	$ —	$ 3,178	$ (770,848)	$ 2,665

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	Years Ended December 31, 2005 (As amended)	2004	2003
Operating activities:			
Net loss	$ (72,401)	$ (142,503)	$ (94,996)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	5,817	8,401	8,551
Amortization of patents	1,545	1,442	1,217
Amortization of licenses	2,326	2,327	2,485
Amortization of premium on investments, net	697	—	—
Compensation (benefit) related to stock options	(544)	(6)	913
Deferred interest on long-term debt	10,795	13,049	5,369
Loss on investments	—	5,057	2,438
Non-cash restructuring activities	—	32,427	—
Non-cash losses related to patents and fixed assets	3,087	2,275	2,813
Income from variable accounting of stock warrants	(1,980)	—	—

Gain on disposal of property, plant and equipment	(1,455)	—	—
Changes in operating assets and liabilities:			
Contracts receivable	5,380	(7,391)	12,249
Inventory	1,771	(9,699)	(2,905)
Other current and long-term assets	(7)	1,373	962
Accounts payable	(4,872)	3,247	(1,804)
Accrued compensation	231	(674)	819
Accrued liabilities	406	1,711	(267)
Deferred contract revenues	(11,840)	(12,787)	(33,318)
Net cash used in operating activities	(61,044)	(101,751)	(95,474)
Investing activities:			
Purchase of short-term investments	(18,381)	(72,479)	(152,910)
Proceeds from the sale of short-term investments	51,029	176,147	156,943
Purchases of property, plant and equipment	(422)	(3,526)	(7,554)
Proceeds from the sale of property, plant and equipment	14,020	—	—
Licenses and other assets	(2,451)	(6,411)	(6,404)
Strategic investments in corporate securities	—	(10,000)	—
Proceeds from the sale of strategic investments	3,283	—	—
Investments in affiliates	—	—	(5,193)
Net cash provided by (used in) investing activities	47,078	83,731	(15,118)
Financing activities:			
Net proceeds from issuance of equity	49,168	4,051	1,700
Proceeds from long-term borrowing	4,603	24,470	67,049
Principal payments on debt and capital lease obligations	(16,170)	(16,368)	(26,896)
Net cash provided by financing activities	37,601	12,153	41,853
Net decrease in cash and cash equivalents	23,635	(5,867)	(68,739)
Cash and cash equivalents at beginning of year	27,250	33,117	101,856
Cash and cash equivalents at end of year	$ 50,885	$ 27,250	$ 33,117
Supplemental disclosures of cash flow information:			
Interest paid	$ 8,877	$ 8,990	$ 12,778
Supplemental disclosures of non-cash investing and financing activities:			
Conversion of contract receivable into long-term investment	$ 750	$ —	$ —
Additions to long-term investments for acquired corporate securities	$ —	$ —	$ 750
Conversion of debt into common stock	$ 100,000	$ —	$ —
Conversion of preferred stock into common stock	$ —	$ 14,934	$ —
Decrease in inventory and deferred revenue	$ —	$ —	$ 8,750
Decrease in property, plant and equipment and notes payable	$ —	$ —	$ 21,200

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS
December 31, 2005

1. Organization and Significant Accounting Policies

Basis of Presentation

The condensed consolidated financial statements include the accounts of Isis Pharmaceuticals, Inc. (“the Company”) and its wholly-owned subsidiaries, Isis Pharmaceuticals Singapore Pte Ltd., Isis USA Limited, Hepasense, Ltd., and Orasense, Ltd. On July 25, 2005, Isis dissolved the Hepasense, Ltd. subsidiary. As more fully described in *Note 8—Restructuring Activities*, the Company closed its Singapore operations in early 2005.

Organization and business activity

Isis Pharmaceuticals was incorporated in California on January 10, 1989. In conjunction with its initial public offering, Isis Pharmaceuticals was reorganized as a Delaware corporation, as Isis Pharmaceuticals, Inc. (“Isis” or the “Company”), in April 1991. Isis was organized principally to develop human therapeutic drugs using antisense and combinatorial technology.

Basic net loss per share

Isis follows the provisions of Statement of Financial Accounting Standards (SFAS) No. 128 *Earnings per Share*. Isis computes basic loss per share by dividing the net loss applicable to common stock by the weighted average number of common shares outstanding during the period (“Basic EPS method”). Isis computes diluted earnings (loss) per common share using the weighted-average number of common and dilutive common equivalent shares outstanding during the period (“Diluted EPS method”). Diluted common equivalent shares of 13.0 million at December 31, 2005 consisted of shares issuable upon

exercise of stock options and convertible debt. As Isis incurred a loss in the years ended December 31, 2005, 2004 and 2003, Isis did not include diluted common equivalent shares in the computation of diluted net loss per share because the effect would be anti-dilutive.

Contract revenue and expenses

Contract revenue consists of non-refundable research and development funding and Isis records contract revenue as earned based on the performance requirements of Isis' collaborative research and development contracts. Isis recognizes contract fees for which no further performance obligations exist when Isis receives the payments or when Isis is reasonably certain it can collect the receivable. Isis records payments received in excess of amounts earned as deferred contract revenue. The Company expenses research and development costs as incurred. For the years ended December 31, 2005, 2004 and 2003, research and development costs of approximately $30.4 million, $36.3 million, and $30.2 million, respectively, were related to collaborative research and development arrangements.

Revenue recognition

Isis recognizes revenue when all of its contractual obligations are satisfied and collection of the underlying receivable is reasonably assured.

Research and development revenue under collaborative agreements

Isis recognizes research and development revenue under collaborative agreements as it incurs the related expenses, up to contractual limits. Isis defers payments received under these agreements that relate to future performance and records revenue as Isis earns it over the specified future performance period. Isis recognizes revenue that relates to nonrefundable, upfront fees over the period of the contractual arrangements as Isis satisfies

its performance obligations. Isis recognizes revenue that relates to milestones, under existing arrangements, upon completion of the milestone's performance requirement. Isis recognizes revenue from arrangements entered into subsequent to June 30, 2003 in accordance with Emerging Issues Task Force Issue No. 00-21 ("EITF 00-21") *Accounting for Revenue Arrangements with Multiple Deliverables*. This issue addresses the timing and method of revenue recognition for revenue arrangements that include the delivery of more than one product or service. Isis sometimes enters into revenue arrangements that contain multiple deliverables. In these cases, Isis recognizes revenue from each element of the arrangement as long as Isis can determine a separate value for each element, Isis has completed its obligation to deliver or perform on that element, and Isis is reasonably assured of collecting the resulting receivable. Isis recognizes revenue from federal contracts and grants in the period in which it pays for the related expenditures. Isis recognizes revenue from product sales as it ships the products. Isis has implemented the provisions of Staff Accounting Bulletin No. 104 ("SAB 104"), which was issued in December 2003. SAB 104 updates portions of the interpretive guidance included in Topic 13 of the codification of Staff Accounting Bulletin No. 101 in order to make this interpretive guidance consistent with current authoritative accounting guidance and SEC rules and regulations. SAB 104 provides interpretation on selected revenue recognition issues and when revenue is properly recognizable. Revenue should not be recognized until it is realized or realizable and earned. It must meet the following criteria: 1) persuasive evidence of an arrangement exists, 2) delivery occurred or services were rendered, 3) the seller's price to the buyer is fixed or determinable and 4) collectibility is reasonably assured.

As part of Isis' alliance with Eli Lilly and Company ("Lilly") in August 2001, Lilly provided Isis a $100.0 million interest free loan to fund the research collaboration. In August 2005, Isis converted the loan into 2.5 million shares of its common stock. During the four years prior to conversion Isis made quarterly draw downs on the loan, which Isis discounted to their net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time Isis entered into the loan. Isis accreted the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan represented value Lilly gave to Isis to help fund the research collaboration. Isis accounted for this value as deferred revenue and recognized it as revenue over the period of performance. This is more fully described in *Note 4—Long-Term Obligations and Commitments and Note 6—Collaborative Arrangements and Licensing Agreements*.

Licensing and royalty revenue

Isis recognizes licensing and royalty revenue immediately, if collectibility is reasonably assured, and if Isis is not required to provide services in the future.

Concentration of credit risk

Financial instruments that potentially subject Isis to concentrations of credit risk consist primarily of cash equivalents, short-term investments and receivables. Isis places its cash equivalents and certain of its short-term investments with high credit-quality financial institutions. Isis invests its excess cash primarily in auction and money market instruments, and municipal and floating rate bonds. Isis and its audit committee establish guidelines relative to credit ratings, diversification and maturities that seek to maintain safety and liquidity.

Cash, cash equivalents and short-term investments

Isis considers all liquid investments with maturities of ninety days or less when purchased to be cash equivalents. Isis' short-term investments have initial maturities of greater than ninety days from date of purchase. Isis classifies its securities as "available-for-sale" in accordance with SFAS 115, *Accounting for Certain Investments in Debt and Equity Securities.* Isis carries these investments at fair market value with any unrealized

gains and losses recorded as a separate component of stockholders' equity. Fair value is based upon market prices quoted on the last day of the fiscal period. Isis uses the specific identification method to determine the cost of debt securities sold. Isis includes gross realized gains and losses in investment income. During 2005, Isis sold a portion of its investment in Alnylam Pharmaceuticals, Inc. resulting in a realized gain of $951,000. Further, Isis determined that there were no other-than-temporary declines in value of investments during the year. During the third quarter of 2004, Isis recorded a non-cash loss on investments of $5.1 million, principally related to the impairment of the Company's equity investment in Alnylam. This loss on investments reflected a decrease in the market value of Alnylam's stock in 2004, which Isis believes was primarily a result of financial market conditions related to biotechnology companies. In the fourth quarter of 2004, Isis recorded a net unrealized gain of $1.4 million related to its equity investment in Alnylam as a separate component of stockholders'

equity. This reflected the increase in the market value of the investment since the impairment in the third quarter of 2004. Additionally, Isis recorded a net unrealized gain of $2.8 million in 2005 reflecting the further increase in market value of its investment in Alnylam.

Inventory valuation

Isis includes in inventory material costs and related manufacturing costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. Isis expenses these costs when it delivers its drugs to partners, or as it provides these drugs for its own clinical trials. Isis reflects its inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. Isis reviews inventory periodically and reduces the carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. Isis considers several factors in estimating the net realizable value; including shelf life of raw materials, alternative uses for its drugs and clinical trial materials and historical write-offs. In 2004, Isis reduced the carrying value of its inventory by $21.0 million related to its restructuring activities. (Note 8—Restructuring Activities).

Inventory includes the following categories as of December 31, 2005 and 2004 (net realizable value, in thousands):

	December 31,	
Raw materials	$ 951	$ 1,329
Finished goods	—	1,393
	$ 951	$ 2,722

Property, plant and equipment

Property, plant and equipment are stated at cost and consist of the following (in thousands):

	December 31,	
	2005	2004
Land	$ —	$ 1,163
Buildings and improvements	10,752	30,305
Equipment and computer software	21,895	27,234
Furniture and fixtures	1,533	1,959
	34,180	60,661
Less accumulated depreciation	(25,050)	(32,207)
	$ 9,130	$ 28,454

Depreciation of property, plant and equipment is provided on the straight-line method over estimated useful lives as follows:

Building	31.5 years
Building improvements	15 years
Manufacturing facilities	10 years
Equipment	5 years
Computer software	3 years
Furniture and fixtures	5 years

Leasehold improvements are depreciated using the shorter of the estimated useful life or remaining lease term.

Licenses

Isis obtains licenses from third parties and capitalizes the costs related to exclusive licenses. Isis' license from Hybridon comprises the majority of the license balance as of December 31, 2005, 2004 and 2003. Isis amortizes capitalized licenses over their estimated useful life or term of the agreement, which for current licenses is between 8 years and 15 years. Accumulated amortization related to licenses was $12.2 million and $9.8 million at December 31, 2005 and 2004, respectively. Based on existing licenses, estimated amortization expense related to licenses is $2.3 million for each of the years ending December 31, 2006, 2007, 2008, 2009 and 2010.

Patents

Isis capitalizes costs consisting principally of outside legal costs and filing fees related to obtaining patents. Isis reviews its capitalized patent costs regularly to determine that they include costs for patent applications Isis is pursuing. Isis evaluates costs related to patents that the Company is not actively pursuing for impairment and writes off any of these costs, if appropriate. Isis amortizes patent costs over their estimated useful lives of 10 years, beginning with the date the patents are issued. The weighted average remaining life of issued patents was 5.2 years and 6.1 years at December 31, 2005 and 2004, respectively. In 2005 and 2004, Isis recorded a non-cash charge of $1.7 million and $6.1 million, respectively, related to the write-down of its patent costs to their estimated net realizable values (*Note 8—Restructuring Activities).*

Accumulated amortization related to patents was $7.0 million and $5.4 million at December 31, 2005 and 2004, respectively. Based on existing patents, estimated amortization expense related to patents is as follows (in millions):

Years Ending December 31,	Amortization (in millions)
2006	$ 1.5
2007	$ 1.4
2008	$ 1.3
2009	$ 1.2
2010	$ 1.0

Investment in affiliates

In April 1999 and January 2000, Isis and Elan formed Orasense, Ltd. and Hepasense, Ltd., respectively, both Bermuda limited companies. Each joint venture was owned 80.1% by Isis and 19.9% by Elan. In 2002, Elan concluded its participation in both the Orasense and HepaSense collaborations. In June 2004, Isis acquired Elan's minority interest in Orasense and HepaSense. As a result, Isis owned 100% of Orasense and HepaSense at December 31, 2004. Isis dissolved the Hepasense subsidiary in July 2005. At December 31, 2005, Isis owned 100% of Orasense.

Fair value of financial instruments

Isis has determined the estimated fair value of its financial instruments. The amounts reported for cash, accounts receivable, accounts payable and accrued expenses approximate the fair value because of their short maturities. Isis reports its investment securities at their estimated fair value based on quoted market prices of comparable instruments.

Long-lived assets

Isis periodically evaluates carrying values of long-lived assets including property, plant and equipment and intangible assets, when events and circumstances indicate that these assets may have been impaired. Isis has adopted SFAS 144, *Accounting for the Impairment of Long-Lived Assets*. In 2005 and 2004, Isis recorded a charge of $15.6 million and $11.5 million, respectively, related to the write-down of equipment and intangible assets to their estimated net realizable values. (*Note 8—Restructuring Activities).*

Use of estimates

The preparation of consolidated financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. Actual results could differ from those estimates.

Consolidation of variable interest entities

Isis has implemented the provisions of Financial Accounting Standards Board Interpretation ("FIN") No. 46, *Consolidation of Variable Interest Entities, an Interpretation of ARB No. 51*, which addresses consolidation by business enterprises of variable interest entities either: (1) that do not have sufficient equity investment at risk to permit the entity to finance its activities without additional subordinated financial support, or (2) in which the equity investors lack an essential characteristic of a controlling financial interest. As of December 31, 2005, Isis had collaborative arrangements with three entities that it considers to be Variable Interest Entities ("VIE") under FIN 46.

As part of the collaboration between Isis and Ercole Biotech, Inc., during 2003 and early 2004, Isis paid Ercole $750,000 in exchange for a convertible note. Isis expensed the payments when made. The note will convert into securities that Ercole issues in a financing. Isis is not required to consolidate Ercole's results of operations under FIN No. 46 as Isis is not the primary beneficiary.

As part of the collaboration between Isis and Sarissa Inc., during February 2005, Isis licensed an anti-cancer antisense drug to Sarissa in exchange for a $1.0 million convertible note. The note will convert into securities that Sarissa issues in a financing. Isis has recognized a valuation allowance of $1.0 million to offset the note, as realization of this asset is uncertain. Isis is not required to consolidate Sarissa's results of operations under FIN No. 46 as Isis is not the primary beneficiary.

As part of the collaboration between Isis and iCo Therapeutics, Inc., during August 2005, Isis licensed iCO 007, an antisense drug to iCo in exchange for a $500,000 upfront fee consisting of a $250,000 cash payment and a $250,000 convertible note. The note will convert into securities that iCo issues in a financing. Isis has recognized a valuation allowance of $250,000 to offset the note, as realization of this asset is uncertain. In December 2005, the Company entered into a manufacturing and supply agreement with iCo. Under the agreement, iCo will purchase drug manufactured by Isis for $700,000. iCo made a $525,000 prepayment to Isis consisting of $175,000 in cash and a $350,000 convertible note, which will convert into iCo stock upon iCo's completion of a

financing. The remaining $175,000 will be paid upon shipment of the drug. Isis has recognized a valuation allowance of $350,000 to offset the note, as realization of this asset is uncertain. Isis is not required to consolidate iCo's results of operations under FIN No. 46 as Isis is not the primary beneficiary.

Stock-based compensation

In January 2000, Isis offered non-officer employees an opportunity to exchange certain of their existing out-of-the-money stock options for new options with exercise prices at the then-current market value. These options are required to be accounted for as variable stock options in accordance with Financial Accounting Standards Board Interpretation No. 44 ("FIN 44"), *Accounting for Certain Transactions Involving Stock Compensation—an Interpretation of APB Opinion No. 25*. Isis reported the resulting compensation expense in its statements of operations. As of December 31, 2002, option holders had exchanged all of these options, or the options had expired. As of December 31, 2005 all of the exchanged, unexpired options were fully vested.

In April 2003, Isis implemented an employee stock option exchange program ("2003 option exchange program"). The 2003 option exchange program allowed employees during the offering period, which began on April 8, 2003 and ended on May 8, 2003, to surrender options granted prior to January 5, 2002, which had higher exercise prices, in exchange for a lesser number of options, which had lower exercise prices. Employees exchanged 2.2 million options having a weighted-average exercise price of $14.89 for 1.0 million options having an exercise price of $5.15. The new options vest over three years beginning on January 1, 2003 and expire on December 31, 2008. Isis accounts for the affected options, until all these options have been exercised or cancelled,

using variable accounting consistent with the provisions of APB 25 and FIN 44. As a result, Isis recorded non-cash compensation benefit of $544,000 and $6,000 in 2005 and 2004, respectively, and will continue to account for the affected options using variable accounting. These amounts are included in Compensation benefit related to stock options on the Consolidated Statements of Operations and include compensation expense related to non-employee options of $13,000 and $2,000 for 2005 and 2004, respectively.

Isis has adopted the disclosure-only provision of SFAS 123, *Accounting for Stock-Based Compensation* ("SFAS 123"). Accordingly, Isis has not recognized compensation expense, except for compensation expense primarily related to the affected options from the 2000 and 2003 option exchange programs, for the Isis stock option plans and the employee stock purchase plan ("ESPP").

Had Isis determined compensation expense consistent with SFAS 123, Isis would have reported the following pro forma amounts for net loss and basic and diluted net loss per share (in thousands, except per share amounts):

	2005	2004	2003
Net loss applicable to common stock—as reported	$ (72,401)	$ (142,864)	$ (95,690)
Net loss applicable to common stock—pro forma	$ (76,660)	$ (148,994)	$ (98,971)
Basic and diluted net loss per share—as reported	$ (1.15)	$ (2.52)	$ (1.73)
Basic and diluted net loss per share—pro forma	$ (1.22)	$ (2.63)	$ (1.79)

For purposes of pro forma disclosures, Isis estimated the fair value of each option grant and ESPP purchase rights on the date of grant using the Black-Scholes option pricing model with the following weighted-average assumptions:

	Stock Options			ESPP		
	2005	2004	2003	2005	2004	2003
Risk free interest rate	4.2%	3.0%	2.5%	3.8%	4.2%	4.3%
Dividend yield	0%	0%	0%	0%	0%	0%
Volatility	57.4%	60.5%	58.0%	53.4%	57.2%	49.5%
Expected Life	4.8 years	4.8 years	4.5 years	6 months	6 months	6 months

The weighted average fair value of options granted was $5.51 for 2005, $6.58 for 2004, and $5.70 for 2003. The weighted average fair value of the ESPP purchase rights was $4.59, $4.67, and $4.46 for 2005, 2004, and 2003, respectively.

Comprehensive loss

SFAS 130, *Reporting Comprehensive Income* ("SFAS 130") requires Isis to display comprehensive loss and its components as part of Isis' full set of consolidated financial statements. The measurement and presentation of net loss did not change. Comprehensive loss is comprised of net loss and certain changes in equity that are excluded from net loss. Specifically, SFAS 130 requires unrealized holding gains and losses on Isis' available-for-sale securities, which Isis reports separately in stockholders' equity, to be included in accumulated other comprehensive loss. Comprehensive loss for the years ended December 31, 2005, 2004 and 2003 has been reflected in the Consolidated Statements of Stockholders' Equity.

Segment Information

Isis operates in two separate segments; Drug Discovery and Development and its Ibis division. In accordance with SFAS 131, *Disclosure about Segments of an Enterprise and Related Information*, Isis provides segment financial information and results for Drug Discovery and Development and its Ibis division based on the segregation of revenues and expenses used for management's assessment of operating performance and operating decisions. Expenses shared by the segments require the use of judgments and estimates in determining the allocation of expenses to the two segments. Different assumptions or allocation methods could result in materially different results by segment. Isis does not include asset or liability information by reportable segment since Isis does not currently segregate this information by segment and it is not used for purposes of making decisions about allocating resources to the segments and assessing their performance.

Impact of recently issued accounting standards

In November 2005, the Financial Accounting Standards Board issued FASB Staff Position FAS 115-1, "*The Meaning of Other-Than-Temporary Impairment and Its Application to Certain Investments*", which provides guidance on determining when investments in certain debt and equity securities are considered impaired, whether that impairment is other-than-temporary, and on measuring such impairment loss. FSP 115-1 codifies the guidance set forth in EITF 03-1, *The Meaning of Other-Than-Temporary Impairment and Its Application to Certain Investments*, issued in March 2004. FSP 115-1 also includes accounting considerations subsequent to the recognition of other-than-temporary impairment and requires certain disclosure about unrealized losses that have not been recognized as other-than-temporary impairments. FSP 115-1 is effective for reporting periods beginning after December 15, 2005 and Isis will adopt FSP 115-1 on January 1, 2006. Isis does not believe the adoption of FSP 115-1 will have a material impact on its financial statements.

In May 2005, the FASB released Statement of Financial Accounting Standard ("SFAS") No. 154, "*Accounting Changes and Error Corrections-a replacement of APB Opinion No. 20 and FASB Statement No. 3*". FAS 154 requires retrospective application to prior periods' financial statements for any changes in accounting principle, unless it is impracticable to determine either the period-specific effects or the cumulative effect of the change. The statement defines retrospective application as the application of a different accounting principle to prior accounting periods as if that principle had always been used or as the adjustment of previously issued financial statements to reflect a change in the reporting entity. The statement also requires that a change in depreciation, amortization, or depletion method for long-lived, non-financial assets be accounted for as a change in accounting estimate affected by a change in accounting principle. The statement carries forward, without change, the guidance contained in Opinion 20 for reporting the correction of an error in previously issued financial statements and a change in accounting estimate. In accordance with the new rule requirements, Isis will adopt FAS 154 for any accounting changes or corrections of errors on January 1, 2006. Isis does not expect the adoption of FAS 154 to have a material impact on its consolidated financial position, results of operations, or cash flows.

On December 16, 2004, the FASB issued SFAS 123(R), *"Share-Based Payment"* which requires companies to expense the estimated fair value of employee stock options and similar awards. On April 14, 2005, the U.S. Securities and Exchange Commission adopted a new rule amending the compliance dates for FAS 123(R). In accordance with the new rule, the accounting provisions of FAS 123(R) will be effective for Isis on January 1, 2006.

Isis will adopt the provisions of FAS 123(R) using a modified prospective application. The modified prospective application will apply to new awards and to awards that are outstanding on the effective date and are subsequently modified or cancelled. Compensation expense for outstanding awards for which the requisite service had not been rendered as of the effective date will be recognized over the remaining service period using the compensation cost calculated for pro forma disclosure purposes under FAS 123.

As permitted by FAS 123, Isis currently accounts for share-based payments to employees using Opinion 25's intrinsic value method and, as such, generally recognizes no compensation cost for employee stock options. Accordingly, the adoption of FAS 123(R)'s fair value method may have a significant impact on its results of operations, although it will have no impact on its overall financial position. Isis cannot predict at this time the impact of adoption of FAS 123(R) because it will depend on levels of share-based payments granted in the future. However, had Isis adopted FAS 123(R) in prior periods, the impact of that standard would have approximated the impact of FAS 123 as described in the disclosure of pro forma net income and earnings per share in Note 1 to the consolidated financial statements. FAS 123(R) also requires the benefits of tax deductions in excess of recognized compensation cost to be reported as a financing cash flow, rather than as an operating cash flow as required under current literature. This requirement will reduce net operating cash flows and increase net financing cash flows in periods after adoption. While Isis cannot estimate what those amounts will be in the future, as a result of its accumulated losses to date, Isis has not recognized a benefit of tax deductions in excess of recognized compensation cost in operating cash flows.

In November 2004, the FASB issued SFAS No. 151, *"Inventory Costs"*, an amendment of ARB No. 43, Chapter 4. This statement amends the guidance in ARB No. 43 Chapter 4, *Inventory Pricing*, to clarify the accounting for abnormal amounts of idle facility expense, freight, handling costs, and wasted material (spoilage). Paragraph 5 of ARB No. 43, Chapter 4, previously stated that " . . . under some circumstances, items such as idle facility expense, excessive spoilage, double freight, and rehandling costs may be so abnormal to require treatment as current period charges . . ." This statement requires that those items be recognized as current-period charges regardless of whether they meet the criterion of "so abnormal." In addition, this statement requires that allocation of fixed production overheads to the costs of conversion be based on the normal capacity of the production

facilities. The provisions of this statement will be effective for inventory costs during the fiscal years beginning after June 15, 2005. Isis does not believe that the adoption of this statement will have a material impact on its financial condition or results of operations.

2. Investments

Isis invests its excess cash in United States Government securities and debt instruments of financial institutions and corporations with strong credit ratings. Isis has established guidelines relative to diversification and maturities that maintain safety and liquidity. These guidelines are periodically reviewed and modified to maximize trends in yields and interest rates without compromising safety and liquidity.

The following table summarizes the contract maturity of debt securities held by Isis as of December 31, 2005:

Less than 1 year	92%
1 - 3 years	8%
Total	100%

Isis has an ownership interest of less than 20% each in two public and two private companies it conducts business with, and accounts for them under the cost method of accounting according to APB 18. The companies are Alnylam and ATL, which are publicly-traded, and Santaris Pharma A/S ("Santaris") and OncoGenex, which are privately-held. In determining if and when decreases in market value of Isis' equity positions below their cost are other-than-temporary, Isis examines historical trends in stock prices, the financial condition and near term prospects of the issuers, and Isis' current need for cash. When Isis determines that a decline in value is other-than-temporary, Isis recognizes an impairment loss in the current period operating results to the extent of the decline. See *Note 1—Organization and Significant Accounting Policies* for a discussion of impairment losses incurred in 2005 and 2004.

The following is a summary of Isis' investments accounted for as available-for-sale securities (in thousands):

December 31, 2005 (as amended)	Maturity in Years	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value
U.S. corporate debt securities	1 or less	$ 15,549	$ 1	$ (28)	$ 15,522
U.S. Treasury securities and obligations of U.S. government agencies	1 or less	20,578	—	(146)	20,432
Total short-term investments		36,127	1	(174)	35,954
U.S. corporate debt securities	1 to 2	185	—	(3)	182
U.S. Treasury securities and obligations of U.S. government agencies	1 to 3	7,552	—	(184)	7,368
Total long-term investments		7,737	—	(187)	7,550
Subtotal		43,864	1	(361)	$ 43,504
Equity securities					
Short-term portion		3,026	1,835	(167)	4,694
Long-term portion		3,806	1,835	—	5,641
Subtotal		$ 6,832	$ 3,670	$ (167)	$ 10,335
		$ 50,696	$ 3,671	$ (528)	$ 53,839

December 31, 2004	Maturity in Years	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value

U.S. corporate debt securities	1 or less	$ 27,564	$ —	$ (121)	$ 27,443
U.S. Treasury securities and obligations of U.S. government agencies	1 or less	14,715	—	(98)	14,617
Total short-term investments		42,279	—	(219)	42,060
U.S. corporate debt securities	1 to 2	6,715	—	(47)	6,668
U.S. Treasury securities and obligations of U.S. government agencies	1 to 3	28,169	—	(264)	27,905
Total long-term investments		34,884	—	(311)	34,573
Subtotal		77,163	—	(530)	76,633
Equity securities					
Short-term portion		3,629	2,713	(129)	6,213
Long-term portion		4,738	569	—	5,307
Subtotal		8,367	3,282	(129)	11,520
		$ 85,530	$ 3,282	$ (659)	$ 88,153

Investments considered to be temporarily impaired at December 31, 2005 are as follows (in thousands):

		Less than 12 months of temporary impairment		Greater than 12 months of temporary impairment		Total temporary impairment	
	Number of Investments	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses
U.S. corporate debt securities	9	$ 8,549	$ 23	$ 1,177	$ 8	$ 9,726	$ 31
U.S. Treasury securities and obligations of U.S. government agencies	22	5,993	19	21,807	311	27,800	330
Total Debt Securities	31	14,542	42	22,984	319	37,526	361
Equity securities	1	1,178	167	—	—	1,178	167
Total temporarily impaired securities	32	$ 15,720	$ 209	$ 22,984	$ 319	$ 38,704	$ 528

Isis believes that the decline in value of these securities is temporary and primarily related to the change in market interest rates since purchase. Isis anticipates full recovery of amortized cost with respect to these securities at maturity.

The Company has amended certain disclosures in *Note 2—Investments* to reflect the reclassification of cash equivalents that were inadvertently classified as short-term investments in the initial balance sheet filed as of December 31, 2005. The reclassification did not impact working capital, total assets or the results of operations.

3. Long-Term Obligations and Commitments

Long-term obligations consisted of the following (in thousands):

	December 31, 2005	December 31, 2004
Lilly $100 million loan	$ —	$ 95,000
Standard operating debt	20,158	32,181
$5^1/_2$% convertible subordinated notes	125,000	125,000
Capital leases and other obligations	2,592	6,741
Total	$ 147,750	$ 258,922
Less: current portion	(7,835)	(10,546)
Less: Lilly debt classified as deferred revenue	—	(11,765)
Total Long-Term Obligations	$ 139,915	$ 236,611

Convertible Partner Debt

Lilly

In August 2001, Lilly made available to Isis a $100 million loan to fund the research collaboration. The loan was interest-free and payable, at Isis' option, in cash or its common stock at $40 per share in August 2005. The loan provided for quarterly draw-downs by Isis. As of December 31, 2004, Isis had drawn down $95.0 million. During the first quarter of 2005, Isis drew the remaining $5.0 million available on the loan facility. In August 2005, Isis converted this loan into 2.5 million shares of its common stock. Isis accounted for this loan using an imputed interest rate of 20%, consistent with market conditions in place at the time the loan agreement was entered into. Isis carried the net present value of the draw-downs as a long-term obligation and recorded interest expense over the term of the loan. The difference between the cash received and the present value of the loan represented value Lilly gave Isis to help fund the research collaboration. Isis accounted for this difference as deferred revenue and recognized it as research and development revenue under collaborative agreements over the period of performance. At December 31, 2004, the balance in long-term obligations related to this loan was $83.2 million, and the balance in deferred revenue was $11.8 million. As a result of the conversion, at December 31, 2005, there was no balance in long-term obligations or deferred revenue related to this loan.

Standard Operating Debt

In December 2003, Isis obtained a $32.0 million term loan from Silicon Valley Bank. The term loan is secured by substantially all of Isis' operating assets, excluding intellectual property, real estate, and certain equity investments. The term loan bears interest at the prime rate less applicable discounts (7.0% at December 31, 2005), is payable in equal monthly payments of principal and interest, matures in December 2008, and is convertible at the election of Isis to a fixed rate at the then-applicable prime rate plus 1.25%. The term loan is subject to certain liquidity and other covenants, including a requirement that Isis maintain a minimum balance in an account at the lending bank at all times equal to the outstanding balance of the loan. Isis was in compliance with these

covenants as of December 31, 2005 and 2004. Isis used the proceeds of the loan to pay partner debt in 2004. The carrying value of this loan at December 31, 2005 and 2004 was $20.2 million and $26.1 million, respectively, which approximated fair value.

In December 2002, Isis obtained a credit facility evidenced by promissory notes of up to $6.7 million from a bank to refinance two existing notes, secured by Isis' real property. During 2005, Isis sold the real property and

paid the notes in full. The carrying value of this loan at December 31, 2005 and 2004 was $0 and $6.1 million, respectively, which approximated fair value. (*Note 8—Restructuring Activities).*

Convertible Subordinated Notes

In May 2002, Isis completed a $125.0 million convertible debt offering, which raised proceeds of approximately $120.9 million, net of $4.1 million in issuance costs. Isis includes the issuance costs in the balance sheet under Deposits and Other Assets and is amortizing these issuance costs to interest expense over the life of the debt. The subordinated notes mature in 2009 and bear interest at 5.5%, which is payable semi-annually. The notes are convertible, at the option of the note holders, into approximately 7.5 million shares of common stock at a conversion price of $16.625 per share. At both December 31, 2005 and 2004, the principal and accrued interest outstanding on the notes was $125.0 million and $1.1 million, respectively. The fair value of the subordinated notes was $110.5 million and $104.9 million as of December 31, 2005 and 2004, respectively. Isis did not include these convertible notes in the computation of diluted net loss per share because the effect would be anti-dilutive.

Capital Leases and Other Obligations

At December 31, 2005 and 2004, Isis had approximately $2.6 million and $5.8 million outstanding, respectively, under various capital equipment leases, which bear interest at rates ranging from 7.25% to 8.78% and mature at various dates through 2008. At December 31, 2005 and 2004, Isis had approximately $160,000 and $900,000, respectively, under various contractual obligations. *(Note 6—Collaborative Arrangements and Licensing Agreements).*

Annual debt and other obligation maturities at December 31, 2005 are as follows (in thousands):

2006	$ 7,835
2007	7,528
2008	7,387
2009	125,000
2010	—
Total	$ 147,750

Isis leases equipment and certain office and lab space under non-cancelable operating and capital leases with terms through September 2020. Three of the building leases have two extension options for five years each. In connection with the sale of our 28,704 square foot manufacturing facility, the Company leased back the property for an initial term of fifteen years with an initial rent of $2.60 per rentable square foot. Under the terms of the lease, the monthly rent will increase five percent every two years. The future contractual obligations of this lease are included in the operating lease caption of the Contractual Obligations table shown above. The lease provides Isis an option to extend the lease for up to two five-year periods. In connection with the lease, Isis executed a stand by letter of credit for $500,000. Annual future minimum payments under capital and operating leases as of December 31, 2005 are as follows (in thousands):

	Operating Leases	Capital Leases
2006	$ 3,458	$ 1,571
2007	2,491	869
2008	1,699	190
2009	1,627	0
2010	1,231	0
Thereafter	10,896	0
Total minimum payments	$ 21,402	$ 2,630
Less amount representing interest		(197)
Present value of future minimum payments		$ 2,433
Less current portion		(1,425)
Long-term portion		$ 1,008

Rent expense for the years ended December 31, 2005, 2004, and 2003 was $2.6 million, $3.1 million, and $3.2 million, respectively. Cost of equipment under capital leases at December 31, 2005 and 2004 was $23.9 million, respectively. Accumulated depreciation of equipment under capital leases at December 31, 2005 and 2004 was approximately $19.7 million and $16.9 million, respectively.

4. Stockholders' Equity

Preferred Stock

Isis is authorized to issue up to 15,000,000 shares of "blank check" Preferred Stock. As of December 31, 2005 and 2004, there was no Series A Convertible Exchangeable 5% Preferred Stock or Series B Convertible Exchangeable 5% Preferred Stock shares outstanding. Series C Junior Participating Preferred Stock is designated but not outstanding.

Series B Convertible Exchangeable 5% Preferred Stock

In June 2004, the holder of the Company's Series B Convertible Exchangeable Preferred Stock transferred its shares to a third party. Immediately upon transfer, these shares converted into 1,055,502 shares of Isis common stock, eliminating the 5% in-kind dividend, thereby reducing future dilution of approximately 86,000 shares of Isis common stock. Isis also cancelled a warrant the holder of the Company's Series B Convertible Exchangeable Preferred Stock held to purchase 14,881 shares of Isis common stock. In addition, a warrant the holder of the Company's Series B Convertible Exchangeable Preferred Stock held to purchase 215,000 shares of Isis common stock, expired unexercised in April 2004.

Series C Junior Participating Preferred Stock

In December 2000, Isis adopted a Preferred Share Purchase Rights Plan ("Plan"). The Plan provides for a dividend distribution of one preferred stock purchase right ("Right") for each outstanding share of Isis common stock, par value $0.001 per share ("Common Shares"), held of record at the close of business on January 10, 2001, and on each subsequently issued share of Isis common stock. The Rights are not currently exercisable. Under certain conditions involving an acquisition or proposed acquisition by any person or group holding 20% or more of Isis' common stock, the Rights permit the holders (except the 20 percent holder) to purchase one one-hundredth of a share of Series C Junior Preferred Stock, par value $0.001 per share ("Preferred Shares"), at a price of $85 per one one-hundredth of a Preferred Share, subject to adjustment. Each one one-hundredth of a share of Preferred Shares has designations and powers, preferences and rights, and qualifications, limitations and restrictions that make its value approximately equal to the value of a Common Share. Certain conditions allow the Isis Board of Directors to redeem

Common Stock

At December 31, 2005 and 2004, Isis had 100,000,000 shares of common stock authorized, of which 72,201,505 and 57,447,333 were issued and outstanding, respectively. As of December 31, 2005, total common shares reserved for future issuance was approximately 24,784,985.

The above amount includes 12 million shares of common stock issued in August 2005. Isis raised $51 million in a private placement of 12 million shares of its common stock at a price of $4.25 per share, which was a 2.3% discount from the Company's 60-day average trading price. Investors in the financing also received five-year warrants to purchase approximately 3 million shares of common stock at an exercise price of $5.24 per share. The net proceeds from the offering were $48.2 million.

Additionally, Isis converted the $100.0 million Lilly loan into 2.5 million shares of the Company's common stock. The impact to the balance sheet was a reduction in long term debt and an increase in stockholders' equity.

Stock Option Plans

1989 Stock Option Plan and Other Employee Option Grants

In June 1989 and as amended, Isis' Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that provides for the issuance of non-qualified and incentive stock options for the purchase of up to 13,200,000 shares of common stock to its employees, directors, and consultants. The term of the plan is scheduled to end in January 2014. The 1989 Plan does not allow Isis to grant stock bonuses or restricted stock awards and prohibits Isis from repricing any options outstanding under the plan unless the Company's stockholders approve the repricing. Options granted after December 31, 1995 vest over a four-year period, with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted before January 1, 1996 generally vested over a five-year period. Options granted after May 26, 2004 have a term of seven years while options granted before May 26, 2004 have a term of ten years. At December 31, 2005, a total of 4,032,000 options were outstanding, options to purchase 2,157,000 shares were exercisable, and 4,122,000 shares were available for future grant.

2000 Broad Based Equity Incentive Plan

In January 2000, Isis adopted the 2000 Broad-Based Equity Incentive Plan (the "2000 Plan"), which provides for the issuance of non-qualified stock options for the purchase of up to 3,990,000 shares of common stock to its employees, directors, and consultants. In May 2002, the Board of Directors increased the 2000 Plan by 2,000,000 shares, authorizing up to 5,990,000 shares of common stock under the 2000 Plan for issuance to

employees, directors, and consultants. Typically options expire 10 years from the date of grant. Options granted under this plan generally vest over a four-year period, with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted under this plan pursuant to the April 2003 stock option exchange program expire on December 31, 2008 and vested 33.34% on January 1, 2004 and then at the rate of 2.78% per month during the option holder's employment or service as a consultant, employee or director. At December 31, 2005, a total of 3,588,000 options were outstanding, 3,116,000 shares were exercisable, and 1,976,000 shares were available for future grant.

In the event of:

- a sale, lease or other disposition of all or substantially all of our assets;
- a merger or consolidation in which we are not the surviving corporation; or
- 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,

then any surviving corporation or acquiring corporation will assume any stock awards outstanding under the 2000 Plan or will substitute similar stock awards (including an award to acquire the same consideration paid to the shareholders in the transaction for those outstanding under the 2000 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar stock awards for those outstanding under the 2000 Plan, then with respect to stock awards held by participants whose continuous service has not terminated, such stock awards automatically vest in full (and, if

applicable, the time during which such stock awards may be exercised) and the stock awards will terminate if not exercised (if applicable) at or prior to such event. With respect to any other stock awards outstanding under the 2000 Plan, such stock awards will terminate if not exercised (if applicable) prior to such event. In addition, as of December 31, 2005, approximately 3,588,000 stock awards granted under the 2000 Plan will be accelerated in full if a transaction described above occurs, even if the surviving corporation assumes such award.

2002 Non-Employee Directors' Stock Option Plan

In September 2001, Isis' Board of Directors adopted, and the stockholders subsequently approved, an amendment and restatement of the 1992 Non-Employee Directors' Stock Option Plan, which provides for the issuance of non-qualified stock options to Isis' non-employee directors. The name of the resulting new plan is the 2002 Non-Employee Directors' Stock Option Plan, and it has an aggregate of 600,000 shares of common stock authorized for issuance. Options under this plan expire 10 years from the date of grant. Options granted become exercisable in four equal annual installments beginning one year after the date of grant. At December 31, 2005, a total of 360,000 options were outstanding, 180,000 of the shares issued under this plan were exercisable and 131,000 shares were available for future grant.

The following table summarizes stock option activity for the years ended December 31, 2003 through December 31, 2005 (in thousands, except per share data):

	Number of Shares	Price Per Share	Weighted Average Price Per Share
Outstanding at December 31, 2002	9,256	$ 3.75 to $26.65	$ 11.34
Granted	2,724	$ 3.12 to $7.85	
Exercised	(35)	$ 4.00 to $6.81	
Terminated	(3,734)	$ 3.75 to $26.65	
Outstanding at December 31, 2003	8,211	$ 3.12 to $26.65	$ 8.66
Granted	2,163	$ 4.30 to $9.50	
Exercised	(508)	$ 3.12 to $8.15	
Terminated	(1,199)	$ 3.75 to $22.19	
Outstanding at December 31, 2004	8,667	$ 3.12 to $26.65	$ 8.34
Granted	1,571	$ 2.86 to $5.90	
Exercised	(32)	$ 3.12 to $5.15	
Terminated	(2,227)	$ 3.75 to $26.65	
Outstanding at December 31, 2005	7,979		$ 7.86

The following table summarizes information concerning currently outstanding and exercisable options (in thousands, except contractual life and exercise price data):

	Options Outstanding			Options Exercisable	
Range of Exercise Price	Number Outstanding As of 12/31/05	Weighted Average Remaining Contractual Life	Weighted Average Exercise Price	Number Exercisable As of 12/31/05	Weighted Average Exercise Price
$ 2.86 - $5.76	1,467	5.09	$ 4.93	960	$ 5.08
$ 5.80 - $6.50	1,480	6.15	$ 5.90	179	$ 6.23
$ 6.59 - $6.81	1,773	6.10	$ 6.79	1,309	$ 6.79
$ 6.82 - $9.63	1,796	5.68	$ 7.93	1,567	$ 7.99
$ 9.75 - $22.83	1,463	4.05	$ 14.00	1,439	$ 13.97
	7,979			5,454	

Employee Stock Purchase Plan

In 2000, Isis' Board of Directors adopted, and the stockholders subsequently approved, the 2000 Employee Stock Purchase Plan and Isis reserved 200,000 shares of common stock for issuance thereunder. In each of the subsequent years, an additional 200,000 shares of common stock were reserved for the 2000 Employee Stock Purchase Plan, resulting in a total of 800,000 shares authorized in the plan. The plan permits full-time employees to purchase common stock through payroll deductions (which cannot exceed 10% of each employee's compensation) at the lower of 85% of fair market value at the beginning of the offering period or the end of each six-month purchase period. During 2005, 222,049 shares were purchased and issued under this plan to employees at prices ranging from $3.36 to $4.67 per share. At December 31, 2005, 50,944 shares were available for purchase under this plan.

Warrants

In 2002, Isis issued a warrant to purchase 6,304 shares of common stock to Elan for the achievement of a development milestone related to the HepaSense joint venture between Isis and Elan. As of December 31, 2005, this warrant remained outstanding at an exercise price of $59.48 per share. The warrant expires April 25, 2007.

In connection with the August 2005 private placement financing, investors received five-year warrants to purchase approximately 3 million shares of common stock at an exercise price of $5.2395 per share. The warrants issued in the private placement provide a call right in favor of Isis to the extent that the price per share of Isis's common stock exceeds $14.41 per share for twenty (20) consecutive trading days, subject to certain circumstances. Isis cannot exercise this call right prior to August 2008.

Prior to the registration statement for the August private placement financing becoming effective, the potential existed for Isis to pay liquidated damages if such effectiveness did not occur. Accordingly, as required by EITF 00-19, *"Accounting for Derivative Financial Instruments Indexed to, and Potentially Settled in, a Company's Own Stock,"* Isis periodically revalued the Warrants as a derivative instrument by computing the value in connection with changes in the underlying stock price and other assumptions, with the change in value recorded as interest expense or interest income. Before November 1, 2005, the effective date of the underlying registration statement, the warrant liability was recorded at fair value based on the methodology described below. Changes in fair value during each period were recorded as interest income. On November 1, 2005, the effective date of the underlying registration statement, the warrant liability was reclassified into stockholders' equity.

The fair value of the warrants was estimated using the Black-Scholes option-pricing model ("Black Scholes") with the following assumptions: no dividends, a risk-free interest rate of 4.2%, a contractual life of 5 years and volatility of 54%. The fair value of the Warrants was estimated to be $7.6 million on the closing date of the transaction. In the fourth quarter of 2005, the warrant liability was re-measured and the resulting amount of $5.6 million was reclassified into stockholders' equity. The change in the warrant liability was recorded as interest income. The $2.0 million change in fair value of the warrants was recorded as an increase in interest income in the statements of operation in 2005. (*Note 11—Private Placement Financing*)

5. Income Taxes

Significant components of Isis' deferred tax assets as of December 31, 2005 and 2004 are shown below (in thousands). Isis recognized valuation allowances of $270.5 million and $283.7 million for 2005 and 2004, respectively, to offset the net deferred tax assets as realization of such assets is uncertain.

	2005	2004
Deferred tax assets:		
Capitalized research expense	$ 40,465	$ 43,132
Net operating loss carryforwards	185,788	189,148
Research and development credits	36,782	33,966
Deferred revenue	617	5,998
Accrued restructuring	9,213	13,335
Other, net	6,537	7,525
Total deferred tax assets	279,402	293,104
Deferred tax liabilities:		
Intangible Assets	(8,907)	(9,393)
Total deferred tax liabilities	(8,907)	(9,393)
Total net deferred tax assets	270,495	283,711
Valuation allowance for deferred tax assets	(270,495)	(283,711)
Net deferred tax assets	$ —	$ —

At December 31, 2005, approximately $7.2 million of the valuation allowance for deferred tax assets related to stock option deductions which, when recognized, will be allocated directly to additional paid-in capital.

At December 31, 2005, Isis had federal, foreign and California tax net operating loss carryforwards of approximately $510.5 million, $1.0 million and $120.0 million, respectively. Isis also had federal and California research credit carryforwards of approximately $25.0 million and $17.5 million, respectively. The difference between the tax loss carryforwards for federal and California purposes is attributable to the capitalization of research and development expenses for California tax purposes and a required 50% to 60% limitation on the utilization of prior years California loss carryforwards. Unless previously utilized, the expiration of the federal tax loss carryforwards begins in 2007. The research credit carryforwards begin expiring in 2006, unless utilized. The foreign tax losses may be carried forward indefinitely and used to offset future taxable profits, provided there is no substantial change in ownership. The California tax loss carryforwards begin expiring in 2006, unless utilized.

Pursuant to Sections 382 and 383 of the Internal Revenue Code, annual use of Isis' net operating loss and credit carryforwards may be limited due to cumulative changes in ownership of more than 50%. Isis believes that changes in ownership have occurred, but believes that such limitations will not have a material impact upon the utilization of the carryforwards.

6. Collaborative Arrangements and Licensing Agreements

Antisense Drug Discovery Collaborations

Amgen

In December 2001, Isis entered into a three-year collaboration with Amgen, Inc. to discover new antisense drugs. Amgen had the right to develop and commercialize antisense drugs resulting from the collaboration. Under

the terms of the agreement, Isis was entitled to receive milestone payments upon key clinical, research and commercial achievements, as well as royalties on sales of any products resulting from the collaboration. During 2004, Isis earned revenue of $783,000 related to quarterly research support and progress research milestones under this drug discovery collaboration. In December 2004, Isis' collaboration with Amgen ended in accordance with its terms.

Eli Lilly and Company

In August 2001, Isis entered into a broad strategic relationship with Lilly, which included four key components.

- Lilly purchased $75.0 million of Isis' common stock at $18 per share.
- Isis licensed to Lilly rights to Affinitak, which Lilly decided to discontinue funding. Lilly paid Isis $25.0 million in upfront fees for Affinitak and reimbursed Isis for Isis' Affinitak development costs. During 2003, Isis earned $11.1 million related to the reimbursement of Affinitak costs. Isis earned no revenue related to Affinitak in 2004 or 2005.
- The companies entered into a joint antisense research collaboration in the areas of cancer, metabolic and inflammatory diseases and a related gene functionalization and target validation collaboration to determine the function of up to 1,000 genes.
- Lilly provided Isis a $100 million loan to fund its obligations under the research collaboration.

In August 2005, Isis extended the research collaboration with Lilly for approximately 24 months to focus on a select number of targets. During the extension, Isis and Lilly will continue to advance antisense drugs identified during the initial collaboration, and continue their efforts to develop and refine antisense technologies. During the extension, Isis will use collaboration funds to support its scientists and Lilly will support Lilly scientists.

- *LY2181308*—As part of the collaboration, Lilly licensed LY2181308, Isis' antisense inhibitor of survivin, in 2002. To date, Isis has earned $4.1 million in license fees and milestone payments related to the continued development of LY2181308, including the $1.5 million milestone payment Isis earned in November 2004 when Lilly initiated Phase 1 clinical trials of LY2181308. Isis will receive additional milestone payments aggregating up to $25.0 million if LY2181308 achieves specified regulatory and commercial milestones, and royalties on future product sales of this drug.
- *LY2275796*—Lilly also licensed LY2275796, an antisense inhibitor of eIF-4E, which was discovered through the research collaboration. Isis earned a $750,000 payment from Lilly for the license. In January 2006, Lilly initiated clinical trials of LY2275796 for which Isis received a $750,000 milestone payment. Isis will also receive additional milestone payments aggregating up to $19.5 million if LY2275796 achieves specified regulatory and commercial milestones, and royalties on future product sales of this drug.

- *STAT-3*—As part of the recent extension, Isis is exploring with Lilly antisense drugs targeting Signal Transducer and Activator of Transcription 3 (STAT-3), a protein that regulates cell division and growth, and prevents cell death. Isis is working closely with Lilly to advance an improved STAT-3 candidate into development. Isis will receive milestone payments of up to $28.0 million as an antisense drug targeting STAT-3 advances through various stages of development, and royalties on future product sales of this drug.
- *Antisense Drug Discovery*—The extended collaboration provides Lilly access to Isis' patents to support Lilly's internal antisense drug discovery and development program for a limited number of targets. As part of the extension, Isis and Lilly will continue to characterize and develop RNase H, siRNA, and splicing modulating inhibitors for the treatment of cancer using advanced generation chemistries.

In connection with the extension, Isis converted the $100 million loan that Lilly provided to Isis into 2.5 million shares of the Company's common stock. In connection with the extension and the conversion, Lilly agreed not to sell the conversion shares until at least the fourth quarter of 2006, assuming the collaboration is not terminated earlier, in exchange for certain credits against milestone payments and royalties in the event of a stock price decline.

Isis' relationship with Lilly historically provided several revenue sources, including research funding related to the $100.0 million research loan, development milestones similar to the milestones for LY2181308 and LY2275796, and revenue related to Affinitak. During 2005, 2004 and 2003, Isis generated revenue from its relationship with Lilly totaling $10.8 million, $15.7 million, and $30.9 million, respectively, which comprised 27%, 37%, and 62%, respectively, of Isis' total revenue during those same periods.

Industrial and Technology Research Institutes of Taiwan

In June 2003, Isis initiated a collaboration with the Industrial and Technology Research Institutes of Taiwan to identify antisense candidates targeting the coronavirus associated with Severe Acute Respiratory Syndrome, or SARS. The collaboration entitled Isis to an upfront payment, milestone payments, and the potential for future funding. During 2003, Isis earned revenue under this collaboration of $2.0 million, comprised of $1.0 million for an upfront payment and $1.0 million related to the achievement of certain milestones. The milestones related to the identification of second generation antisense drugs that inhibit SARS virus replication and the successful completion of preclinical studies evaluating aerosol and parenteral delivery of antisense drugs as specified under the agreement. Isis earned no revenue during 2004 or 2005 under this collaboration. This collaboration has ended in accordance with its terms.

The Ludwig Institute; Center for Neurological Studies

In October 2005, Isis entered a collaboration agreement with the Ludwig Institute, the Center for Neurologic Study (CNS) and researchers from these institutions to discover and develop antisense drugs in the areas of amyotrophic lateral sclerosis and other neurodegenerative diseases. Under this agreement, Isis agreed to pay the Ludwig Institute and CNS royalties and modest milestones on any antisense drugs discovered and developed within the collaboration. The researchers from the Ludwig Institute and CNS, through funding from the ALS Association, will conduct preclinical safety and efficacy studies of ISIS 333611.

Pfizer, Inc

In May 2005, Isis entered into a multi-year drug discovery collaboration with Pfizer to identify second generation antisense drugs for the treatment of ophthalmic disease. Under the terms of the agreement, Isis received a technology access fee of $1.0 million. In 2005, Isis earned milestone payments of $1.2 million through the collaboration. Pfizer will also pay Isis additional milestone payments for the achievement of key research,

clinical, regulatory and sales milestones, and provide research funding. Assuming that Pfizer successfully develops and commercializes the first drug for the first indication, Isis will earn milestone payments totaling up to $25.6 million. In addition, Isis will receive royalties on the sale of drugs resulting from the collaboration.

Singapore Economic Development Board

In November 2003, Isis received a grant of up to $8.0 million over three years from the Singapore Economic Development Board ("Singapore EDB"), which was intended to fund, in part, the broadening of two of Isis' RNA-based drug discovery and development programs: micro-RNA drug discovery and antisense drug discovery targeting the coronavirus associated with SARS. In connection with this grant, Isis established Isis Pharmaceuticals Singapore Pte Ltd, a wholly-owned subsidiary of Isis Pharmaceuticals, Inc. During 2004, Isis earned revenue of $1.5 million from this grant.

As part of the Company's reorganization, Isis decided to close its research and development laboratory in Singapore during the first quarter of 2005 and terminate its agreement with the Singapore EDB. Isis received $1.5 million in cash payments under this $8.0 million grant from the Singapore EDB and does not anticipate any additional payments, or additional revenue, under the agreement.

Satellite Company Collaborations

Achaogen, Inc.

In January 2006, Isis licensed its proprietary aminoglycosides program to Achaogen, a biotechnology company pursuing unique strategies to combat drug-resistant pathogens. Aminoglycosides are a group of antibiotics that inhibit bacterial protein synthesis and are used to treat serious bacterial infections. The program Isis licensed to Achaogen resulted from research conducted in Isis' Ibis division to identify drugs to treat antibiotic-resistant infections.

In exchange for the exclusive, worldwide license to Isis' aminoglycoside program, Achaogen issued to the Company $1.5 million of Achaogen Series A Preferred stock. Isis has not yet determined a value for the Achaogen stock. In addition, assuming Achaogen successfully develops and commercializes the first drug in the first major market, Isis will receive milestone payments totaling up to $34.5 million for the achievement of key clinical, regulatory and sales milestones. In addition, Isis will receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of the aminoglycoside program and products.

Alnylam Pharmaceuticals, Inc.

In March 2004, Isis entered into a strategic alliance with Alnylam to develop and commercialize RNAi therapeutics. Under the terms of the agreement, Isis exclusively licensed to Alnylam its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5.0 million technology access fee, participation in fees for Alnylam's partnering programs, as well as future milestone and royalty payments. For each drug Alnylam develops under this alliance, the potential milestone payments total $3.4 million and are payable to Isis upon the occurrence of specified development and regulatory events. Isis will retain rights to a limited number of RNAi therapeutic targets and all rights to single-stranded RNAi therapeutics. In addition, Alnylam and Isis will share the proceeds of any licenses Alnylam grants under its previously announced Interfe*Rx* program that include sublicenses to Isis' patents. Isis agreed to provide Alnylam with access to its resources for development and commercialization of RNAi therapeutics, including process development, bioanalytic methods, quality control and manufacturing. Isis also made a $10 million equity investment in Alnylam.

In turn, Alnylam nonexclusively licensed Isis its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded RNAi therapeutics and to research double-stranded RNAi compounds. Isis also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on either an exclusive or co-exclusive basis depending on the target. If Isis develops or commercializes an RNAi-based drug using Alnylam's technology, Isis will pay Alnylam milestones and royalties. For each drug we develop under this alliance, the potential milestone payments total $3.4 million and are payable upon the occurrence of specified development and regulatory events. As of December 31, 2005, Isis did not have an RNAi-based drug in clinical development. As part of the collaboration, each party granted the other party a nonexclusive cross license to its respective patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for microRNA therapeutics.

Isis' Alnylam alliance provides the Company with an opportunity to realize substantial value from its pioneering work in antisense mechanism and obigonucleotide chemistry and is an example of Isis' strategy to participate in all areas of RNA-based drug discovery. For example, in October 2005, Isis earned $3.7 million associated with the inclusion of Isis' technology in Alnylam's collaboration with Novartis. In addition, Isis has the potential to earn additional revenue in the form of milestones and royalty payments on drugs which utilize the Isis technology sub-licensed by Alnylam to Novartis. In 2004, Isis earned $500,000 from Alnylam for the inclusion of Isis' technology in Alnylam's ocular alliance with Merck.

During 2005 and 2004, Isis generated revenue from its relationship with Alnylam totaling $3.7 million and $5.5 million, respectively, representing 9% and 13%, respectively, of the Company's total revenue.

In September 2004, Isis recorded a non-cash loss on investment of $5.0 million related to the impairment of its equity investment in Alnylam. The loss on investment reflected a decrease in the market value of Alnylam's stock in 2004, which Isis believes was primarily a result of financial market conditions related to biotechnology companies. Isis' balance sheet at December 31, 2005 and 2004, includes a short-term investment at carrying value amounts of approximately $3.5 million and $2.0 million, respectively, and a long-term investment at carrying value of $3.5 million and $3.9 million, respectively. During 2005, Isis sold a portion of its Alnylam stock for cash proceeds of $2.6 million. Isis still holds more than 580,000 shares of Alnylam's stock.

Antisense Therapeutics Ltd., Inc.

In December 2001, Isis licensed its compound, ATL1102 to Antisense Therapeutics Limited, a publicly-traded company listed on the Australian Stock Exchange. Isis was responsible for the required preclinical studies for ATL1102 and for manufacturing the drug for human clinical trials at ATL's expense. ATL agreed to undertake the future clinical development and commercialization of the drug. In June 2004, ATL announced the results of a Phase 1 clinical trial of ATL1102, in which ATL1102 was well tolerated. In December 2004, ATL initiated a Phase 2 clinical trial of ATL1102 in patients with multiple sclerosis. In light of the publicly announced safety issues associated with one other VLA-4 inhibitor that works through a different mechanism, ATL

suspended the trial in March 2005 to convene an advisory group to consider the potential development path for ATL1102. In January 2006, ATL received approval to restart the Phase 2 trial for patients with relapsing-remitting multiple sclerosis. In addition, Isis is participating with ATL in a five-year antisense drug discovery and development collaboration. ATL pays Isis for access to its antisense expertise and for research and manufacturing services Isis may provide to ATL during the collaboration. ATL has the option to license additional drugs from Isis. Additionally, ATL will pay Isis royalties on any antisense drugs discovered and developed within the partnership.

In connection with this collaboration, Isis received 30.0 million shares of ATL common stock upon completion of ATL's initial public offering ("IPO"), representing an initial ownership percentage of approximately 14%, and options to purchase an additional 20.0 million shares of ATL common stock, which expire in 2008. Isis valued its initial ownership at $2.8 million, and is recognizing revenue based on this amount over the term of the agreement. For the years ended December 31, 2005, 2004 and 2003, Isis recorded revenue of $698,000, $1.4 million, and $811,000, respectively, related to this collaboration. As of December 31, 2005, Isis' ownership percentage in ATL, including 10.3 million shares Isis purchased subsequent to shares it acquired in the IPO, was approximately 11%. If all of ATL's options, including Isis', were exercised, Isis' ownership in ATL would be approximately 14%. Isis' balance sheets at December 31, 2005 and 2004 included a short-term investment at fair market value of $1.2 million and $3.8 million, respectively, related to this equity investment.

Ercole Biotech, Inc.

In May 2003, Isis and Ercole initiated a multi-year collaboration to discover antisense drugs that regulate alternative RNA splicing. As part of the collaboration, the two parties cross-licensed their respective splicing-related intellectual property. As part of this collaboration, Isis granted Ercole a license to its Bcl-x molecule and certain of its chemistry patents. In addition, Isis took an equity ownership position in Ercole, with the initial funding in the form of a convertible note, which the companies anticipate will convert into securities that Ercole issues in its next venture capital financing. Isis also has the option to make an additional equity investment in Ercole. Pursuant to the terms of a Note and Warrant Purchase Agreement, during 2003 and early 2004, Isis made cash payments to Ercole of $500,000 and $250,000, respectively in exchange for a convertible note. Isis expensed the payments when made. The note is secured by all of Ercole's assets, including intellectual property and licenses. The note will convert into securities that Ercole issues in a qualified financing, as defined by the agreement.

iCo Therapeutics, Inc.

In August 2005, Isis granted a license to iCo for the development and commercialization of iCO 007, a second generation antisense drug. iCo is initially developing iCO 007 for the treatment of various eye diseases, such as diabetic macular edema age-related macular degeneration and diabetic retinopathy, caused by the formation and leakage of new blood vessels. iCo paid Isis a $500,000 upfront fee consisting of $250,000 in cash and a $250,000 convertible note, which will convert into iCo stock upon iCo's completion of a qualified financing. Isis has recognized a valuation allowance of $250,000 to offset the note as realization of this asset is uncertain. iCo will also pay Isis milestone payments totaling up to $23.2 million for the achievement of key clinical and regulatory milestones, and royalties on any product sales of this drug. Under the terms of the agreement, iCo is solely responsible for the clinical development and commercialization of the drug.

In December 2005, the Company entered into a manufacturing and supply agreement with iCo. Under the agreement, iCo will purchase drug manufactured by Isis for $700,000. iCo made a $525,000 prepayment to Isis consisting of $175,000 in cash and a $350,000 convertible note, which will convert into iCo stock upon iCo's completion of a financing. The remaining $175,000 will be paid upon shipment of the drug. Isis has recognized a valuation allowance of $350,000 to offset the note, as realization of this asset is uncertain.

OncoGenex Technologies Inc.

In November 2001, Isis established a drug development collaboration with OncoGenex Technologies Inc., a privately-held biotechnology company committed to the development of cancer therapeutics for patients with drug resistant and metastatic cancers, to co-develop and commercialize the anti-cancer antisense drug, OGX-011. Isis shares in the costs of developing OGX-011. In exchange, Isis shares in any revenue generated by OncoGenex

for OGX-011. In September 2003, the companies expanded their drug development collaboration, to include the development of a second anti-cancer antisense drug, OGX-225. Under the terms of the collaboration, during 2003, OncoGenex paid Isis an upfront fee and Isis acquired an ownership interest in OncoGenex of less than 10%. In addition, OncoGenex will pay to Isis milestone payments totaling up to $3.5 million for the achievement of key clinical and regulatory milestones, and royalties on product sales. As of December 31, 2005, OncoGenex had not triggered any of these milestone payments related to OGX-225.

In January 2005, Isis further broadened its antisense drug development partnership with OncoGenex to allow for the development of two additional second generation antisense anti-cancer drugs. In April 2005, OncoGenex selected its first drug under this expanded partnership, OGX-427. OGX-427 targets heat shock protein 27, or Hsp27, which is over-expressed in numerous tumor types and is associated with treatment resistance through its ability to help cancer cells survive stress-induced injury. OncoGenex paid

Isis an upfront fee with a convertible note, which, in August 2005, converted into 244,300 shares of OncoGenex's preferred stock. OncoGenex will also pay Isis milestone payments totaling up to $5 million for the achievement of key clinical and regulatory milestones, and royalties on future product sales of these drugs.

For the years ended December 31, 2005 and 2004, Isis earned revenue of $2.7 million and $669,000, respectively, related to its collaboration with OncoGenex. Isis' balance sheets at December 31, 2005 and 2004 include a long-term investment of $750,000 related to this equity investment, reflecting the value of Isis' initial investment. While there is no readily determinable market value for these securities, there has been no indication that Isis' investment in OncoGenex has been impaired; accordingly, Isis believes that the carrying value of this investment is equal to or below its current fair market value. As of December 31, 2004, Isis' balance sheet included deferred revenue of $1.6 million with corresponding finished goods inventory of $1.4 million on its balance

sheet related to an agreement to supply clinical trial material to OncoGenex for which Isis had continuing obligations. In 2005, Isis satisfied these continuing obligations, and as such, recognized the $1.6 million in revenue and related costs of $1.4 million.

Rosetta Genomics, Inc.

In January 2006, Isis initiated a joint research collaboration with Rosetta Genomics to discover and develop antisense drugs that regulate microRNAs for the treatment of the most prevalent type of liver cancer, hepatocellular carcinoma. For each drug that meets specific success factors outlined in the collaboration, Isis and Rosetta will mutually agree on a development strategy for the drug. This collaboration has an initial term of two years.

Santaris Pharma A/S

In November 1998 and September 2000, Isis entered into license agreements with Santaris, a privately-held company, formerly Pantheco A/S, a privately-held company. The agreement was amended in May 2003. Under the terms of the amended and restated license agreements, Isis licensed its novel antisense chemistry, Peptide Nucleic Acid, or PNA, to Santaris on a limited exclusive basis to develop products. The license restricts Santaris to a limited number of molecular targets that are subject to Isis' approval. Santaris has agreed to pay Isis royalties on any products developed under the license.

As part of its original license agreements with Pantheco, Isis received shares of Pantheco stock. In May 2003, Pantheco and Cureon A/S merged to form Santaris. Prior to the merger, Isis purchased additional shares of Pantheco for $55,000 as a result of anti-dilution provisions related to Pantheco's stock. After the merger and as of December 31, 2005 and 2004, Isis' ownership interest in Santaris was less than 10%. Isis' balance sheets at December 31, 2005 and 2004 included a long-term investment of $625,000, respectively, related to this

equity investment, reflecting the value of Isis' initial investment. While there is no readily determinable market value for these securities, there has been no indication that Isis' investment in Santaris has been impaired; accordingly, Isis believes that the carrying value of this investment is equal to or below its current fair market value.

Sarissa, Inc.

In February 2005, Isis licensed an anti-cancer antisense drug to Sarissa, Inc., a biotechnology company emerging from the University of Western Ontario. The drug is an antisense inhibitor of thymidylate synthase, or TS, a well-known drug target that protects cancer cells from the effects of several chemotherapy treatments. In preclinical studies, antisense inhibition of TS suppressed human tumor cell growth and overcame tumor cell resistance to marketed TS-targeted drugs.

Sarissa paid Isis a $1.0 million upfront fee with a convertible note, which will convert into Sarissa stock upon Sarissa's completion of a financing. Isis has recognized a valuation allowance of $1.0 million to offset the note as realization of this asset is uncertain. Sarissa will also pay Isis milestone payments totaling up to $5.5 million for the achievement of key clinical and regulatory milestones, and royalties on any product sales of this drug. Under the terms of the agreement, Sarissa is solely responsible for preclinical and clinical development of the drug.

Licensing Agreements and Royalty Factoring Agreements

Drug Royalty Corporation

In December 2004, Isis sold a portion of its royalty rights in Macugen to Drug Royalty USA, Inc. ("DRC). In exchange for this sale, DRC paid Isis $7.0 million in October 2005 and agreed to pay Isis an additional $17.0 million over the next two years. Under the terms of the agreement, Isis and DRC share the royalty rights on Macugen through 2009. After 2009, Isis retains all royalties for Macugen under its Eyetech agreement. Under the agreement, through 2009, DRC will receive the royalties on the first $500.0 million of annual sales of Macugen. Isis and DRC will each receive 50 percent of royalties on annual sales between $500.0 million and $1.0 billion. Isis retains 90 percent of all royalties on annual sales in excess of $1.0 billion and 100 percent of all royalties after 2009. Isis has retained all milestones payable to Isis by Eyetech under the companies' original license agreement.

As part of the sale, Isis agreed to pay DRC liquidated damages if any one of a defined set of defaults occurs. The amount of liquidated damages will be calculated such that DRC will receive a ten percent per annum return, compounded quarterly on the total of all purchase price payments made by DRC to Isis through the default date minus the total of any royalties received by DRC through the default date. To date, DRC has received $3.7 million in royalties. In addition, DRC may withhold any installment of the purchase price if immediately prior to such payment, Isis fails to meet a minimum liquidity requirement equal to the then outstanding balance on its loan with Silicon Valley Bank; plus the potential amount of liquidated damages, assuming that DRC has paid the impending purchase price installment; plus its cash burn over the most recent three months. As collateral for its obligations under the sale agreement, Isis granted DRC a first priority security interest in the patents licensed by Isis to Eyetech under the license agreement and in the license agreement itself.

Eyetech Pharmaceuticals, Inc.

In December 2001, Isis licensed to Eyetech Pharmaceuticals, Inc., a wholly-owned subsidiary of OSI Pharmaceuticals, Inc., certain of its patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense drug for the treatment of wet age-related macular degeneration, that Eyetech is co-developing and

commercializing with Pfizer. Eyetech paid Isis a $2.0 million upfront fee and agreed to pay Isis milestone and royalty payments in exchange for non-exclusive, worldwide rights to the intellectual property licensed from Isis.

During 2004, Isis earned $4.0 million in milestones associated with the filing of an NDA and FDA approval for Macugen for the treatment of wet age-related macular degeneration. Isis' license with Eyetech will also generate additional milestone payments aggregating up to $2.8 million for the achievement

of specified regulatory milestones with respect to the use of Macugen for each additional therapeutic indication. In 2005, Isis earned no revenue from Eyetech.

Hybridon, Inc.

In May 2001, Isis entered into an agreement with Hybridon under which Isis acquired an exclusive license to all of Hybridon's antisense chemistry and delivery patents and technology. Hybridon retained the right to practice its licensed antisense patent technologies and to sublicense it to collaborators under certain circumstances. In addition, Hybridon received a non-exclusive license to Isis' suite of RNase H patents. In exchange for the license to Hybridon's antisense patents, Isis paid $15.0 million in cash and agreed to pay Hybridon $19.5 million in Isis common stock before May 2003. In return for access to Isis' patents, Hybridon agreed to pay Isis $6.0 million in Hybridon common stock before May 2004. In September 2001 and October 2001, Isis issued to Hybridon 357,143 shares of its common stock valued at $5.0 million and 500,000 shares of its common stock valued at $10.0 million, respectively. In May 2002, Hybridon issued to Isis 1,005,499 shares of its common stock valued at $1.3 million and paid Isis $700,000 in cash. In August 2002, Hybridon and Isis cancelled the remaining reciprocal financial obligations related to this agreement. The cancellation of the obligations resulted in a decrease to Isis' carrying value for the license in the amount of $500,000. Isis' balance sheet at December 31, 2005 and 2004 reflected a licensing asset, net of amortization, of $19.5 million and $21.3 million, respectively. Isis' balance sheet at December 31, 2004 also reflected a short-term investment at fair market value of $474,000, related to this agreement. During 2004 and 2005, Isis sold its short term investment in Hybridon for net proceeds of approximately $665,000.

Integrated DNA Technologies, Inc.

In March 1999, Isis licensed certain antisense patents from Integrated DNA Technologies, Inc. ("IDT"), a leading supplier of antisense inhibitors for research. These patents are useful in functional genomics and in making certain antisense drugs. In December 2001, Isis expanded this license agreement to allow Isis to exclusively sublicense this intellectual property for functional genomics purposes. Under the license, Isis paid IDT $4.9 million through December 31, 2005. Isis will pay IDT royalties on drugs utilizing the technology IDT licensed to Isis.

In addition, in December 2001 Isis established a long-term research-scale antisense inhibitor supply agreement with IDT. In this supply agreement IDT agreed to manufacture research-scale antisense inhibitors and research reagents to Isis' specifications. Isis paid IDT $5.0 million toward the future purchase of antisense inhibitors. During the fourth quarter of 2004, Isis recorded a non-cash charge of $4.2 million to write off this unused portion as part of its restructuring activities (*Note 8—"Restructuring Activities"*).

Ibis Division

To develop the TIGER biosensor system and applications, Isis' Ibis division has received contracts and grants from a number of government agencies, including DARPA, the DHS, the CDC, the FBI and the NIAID, a part of the NIH. Each of these agencies represents a significant source of funding for Isis' TIGER program. As of December 31, 2005, Isis had earned $47.9 million in revenue under itsr government contracts and grants and had an additional $8.4 million committed under its existing contracts and grants. In 2005, Isis' Ibis scientists advanced application development for the TIGER biosensor system through contracts with its government partners in the areas of biowarfare defense, microbial forensics, epidemiological surveillance and pharmaceutical process control.

Biowarfare Defense

The earliest application of Isis' TIGER biosensor system to be funded by the government focused on bioweapons detection. In March 2004, Isis' Ibis division received a two-year contract from DARPA under a subcontract from SAIC to further develop the TIGER biosensor system to identify infectious agents in biological warfare attacks. As part of this program, Ibis successfully demonstrated proof-of-principle of the TIGER biosensor system by identifying a variety of bacteria and viruses in both environmental and human clinical samples. In 2005, under a subcontract from SAIC and with support from DARPA, Ibis delivered its first TIGER biosensor system to USAMRIID for use in biowarfare defense.

Microbial Forensics

Microbial forensics is a type of forensics used to investigate crimes involving infectious organisms. Microbial forensics uses the "biological fingerprint" of an infectious organism to help pinpoint the source, allowing law enforcement and public health officials to effectively respond to a biological threat. Additionally, through an award from the FBI, Ibis is continuing its ongoing development of the Microbial Rosetta Stone (MRS) informational databases on microbial agents. The MRS program is a database of biological threat agents, their DNA sequences and effects, that law enforcement officials can use to confer deterrence and support forensic investigations. In 2005, under a subcontract from SAIC and with support from DARPA, Ibis deployed its second TIGER biosensor system to the DHS's National Bioforensic Analysis Center for use in bioforensics.

Epidemiological Surveillance

Isis' Ibis division continues to develop with its government partners applications for its TIGER biosensor system to rapidly identify, monitor and control infectious diseases. Specifically, in August 2005 Ibis received a three-year grant worth up to $4.9 million from the NIAID, a part of the NIH. The grant funds the continued development of applications to diagnose infectious diseases and to identify and control hospital-associated infections using the TIGER biosensor system. In addition, in September 2003, Ibis received a three-year grant for up to $6.0 million from the CDC to develop and apply its TIGER technology to the surveillance of human infectious disease in the United States. Ibis expects to deploy a third TIGER biosensor system to the CDC later this year under this contract. In addition, we are currently working with the Naval Health Research Center using the TIGER biosensor system in respiratory disease surveillance and

have analyzed hundreds of samples on the TIGER system at our facility. We plan to move the system hardware to the Navy's new laboratory facility, when it's finished.

Pharmaceutical Process Control

Government agencies such as the NIAID have engaged Ibis to develop applications to improve the safety of biological pharmaceutical products, such as vaccines. In 2004, Ibis received funding from the NIAID to develop a TIGER application to specifically address safety issues unique to cell substrates used in vaccine manufacturing, such as the identification of unknown or novel microbes that have the potential to contaminate vaccine cell lines and substrates.

Joint Ventures

Elan Corporation

Isis and Elan formed Orasense, a joint venture to develop technology for the formulation of oral drugs, and HepaSense, a joint venture to develop an antisense drug to treat patients chronically infected with the Hepatitis C virus, or HCV, during 1999 and 2000, respectively. In late 2002, Elan concluded its participation in both of the related collaborations. Pursuant to a June 2004 agreement, Isis acquired Elan's minority interest in Orasense and HepaSense. As part of the agreement, Isis eliminated all future royalties to Elan related to these joint ventures**.** As of December 31, 2005 and 2004, Isis had no receivable or funding obligation related to Orasense or HepaSense. On July 25, 2005, Isis dissolved the Hepasense, Ltd. subsidiary. In 2004, Orasense incurred approximately $811,000 in research and development expenses through the date of Isis' acquisition of Elan's minority interest in Orasense.

7. Segment Information and Concentration of Business Risk

Segment Information

The Company reports its financial results in two reportable segments, Drug Discovery and Development, and its Ibis division. Segment operating loss includes research and development, general and administrative expenses, and other charges attributable to the segment. Costs excluded from the segments consist of compensation expense (benefit) related to stock options and restructuring activities.

The Drug Discovery and Development segment generates revenue from collaborations with corporate partners and from licensing proprietary patent rights. Revenue from collaborations with corporate partners may consist of upfront payments, funding for research and development activities, milestones and royalties. This segment's proprietary technology to discover and characterize novel antisense inhibitors has enabled its scientists to modify the properties of its antisense drugs for optimal use with particular targets and thus, to produce a broad proprietary portfolio of compounds applicable to many disease targets.

The Ibis division generates revenue from grants and contracts from United States government agencies, including DARPA, the DHS, the CDC, the FBI and the NIAID, a part of the NIH. Isis' Ibis division has developed a revolutionary system, called TIGER, that can simultaneously identify thousands of infectious organisms in a sample, without needing to know beforehand what might be present in the sample. Ibis plans to commercialize the TIGER biosensor system to government customers for use in biowarfare defense, epidemiological surveillance and forensics; and to non-government customers for use in pharmaceutical process control, hospital-associated infection control and infectious disease diagnostics.

Isis does not include asset or liability information by reportable segment since Isis does not currently segregate this information by segment and it is not used for purposes of making decisions about allocating resources to the segments and assessing their performance.

The following is information for net sales and operating income by segment for the years ended December 31, 2005 and 2004.

December 31, 2005	Drug Discovery and Development	Ibis	Corporate	Total
Revenue:				
Research and development	$ 16,817	$ 11,793	$ —	$ 28,610
Licensing and royalty	11,523	—	—	11,523
Total segment revenue	$ 28,340	$ 11,793	$ —	$ 40,133
Loss from operations	$ (48,297)	$ (2,228)	$ (6,657)	$ (57,182)

December 31, 2004	Drug Discovery and Development	Ibis	Corporate	Total
Revenue:				
Research and development	$ 21,684	$ 10,933	$ —	$ 32,617
Licensing and royalty	10,007	—	—	10,007
Total segment revenue	$ 31,691	$ 10,933	$ —	$ 42,624
Loss from operations	$ (82,135)	$ (3,297)	$ (32,421)	$ (117,853)

Concentrations of Business Risk

Isis does not generate sales from products but has historically funded its operations in part from collaborations with corporate partners and various government agencies. A relatively small number of partners historically have accounted for a significant percentage of Isis' revenue. Revenue from significant partners as a percentage of total revenue was as follows:

	2005	2004	2003
Partner A	27%	37%	62%
Partner B	14%	18%	16%
Partner C	9%	13%	0%
Partner D	17%	0%	0%

During 2005, 2004, and 2003, Isis derived approximately 30%, 28%, and 20%, respectively, of its revenue from agencies of the United States Government, including approximately 14%, 18%, and 16%, respectively, of revenue from one significant customer.

Contract receivables from four significant partners comprised approximately 39%, 13%, 12% and 12% of contract receivables at December 31, 2005. Contract receivables from four significant partners comprised approximately 30%, 20%, 17% and 10% of contract receivables at December 31, 2004.

8. Restructuring Activities

During the fourth quarter of 2004, Isis recorded a $32.4 million charge for restructuring activities resulting from its strategic decision to reorganize and focus its resources on key programs. The 2004 charge for restructuring activities consisted of non-cash write-downs of tangible and intangible assets that the Company considered to be non-essential to its new focus, including excess or idle equipment, inventories, patent costs, and certain prepaid expenses. For the year ended December 31, 2005, Isis recorded $7.0 million in costs associated with its restructuring activities, net of the gain on the sale of property of $1.5 million discussed below. In January 2005, Isis commenced several cost containment measures, including a reduction in workforce of approximately 160 employees, the consolidation of its facilities in the United States, and the closure of the Company's research and development laboratory in Singapore.

In connection with the consolidation of its U.S. facilities, during 2005 Isis completed the sale of its real properties located at 2292 Faraday Avenue, 2280 Faraday Avenue and 2282 Faraday Avenue, all in Carlsbad, California. The real properties included three buildings, two of which Isis primarily used for office space and laboratory space and the third which Isis uses for manufacturing. After repaying approximately $5.8 million of debt, which was secured by the properties, and after deducting commissions and other expenses, Isis received net proceeds of approximately $7.9 million for the sale of the properties. Isis included a net gain of approximately $1.5 million in restructuring activities in 2005.

Pursuant to SFAS No. 146, *"Accounting for Costs Associated with Exit or Disposal Activities,"* the following table sets forth the activity in the restructuring reserve, which is included in accrued liabilities at December 31, 2005 (in thousands).

	Facility Consolidation and Closure Related Costs	Employee Separation Costs	Contract Termination Costs	Other Costs	Total
Balance at December 31, 2004	$ —	$ —	$ —	$ —	$ —
Accrued and expensed	1,709	3,751	910	590	6,960
Charged against accrual	853	3,751	145	464	5,213
Balance at December 31, 2005	$ 856	$ —	$ 765	$ 126	$ 1,747

9. Employee Post Employment Benefits

Isis has an employee 401(k) salary deferral plan, covering all domestic employees. Employees may make contributions by withholding a percentage of their salary up to the IRS annual limit ($14,000 and $18,000 in 2005 for employees under 50 years old and over 50 years old, respectively). Isis made approximately $404,000, $478,000 and $463,000 in matching contributions for the years ended December 31, 2005, 2004 and 2003, respectively.

10. Affiliate Supplementary Disclosure

Orasense

In April 1999 and January 2000, Isis and Elan formed Orasense, Ltd. and Hepasense, Ltd., respectively, both Bermuda limited companies. Each joint venture was owned 80.1% by Isis and 19.9% by Elan. In 2002, Elan concluded its participation in both the Orasense and HepaSense collaborations. Additionally, Isis regained all rights to ISIS 104838, the compound that Elan and Isis were developing within Orasense. In June 2004, Isis acquired Elan's minority interest in Orasense and HepaSense and eliminated all future royalties to Elan related to the technology for the formulation of oral drugs developed within the Orasense collaboration. As a result, Isis owned 100% of Orasense and HepaSense at December 31, 2004. Isis dissolved the Hepasense subsidiary in July 2005. At December 31, 2005, Isis owned 100% of Orasense. In 2004, Orasense incurred approximately $811,000 in research and development expenses through the date of Isis' acquisition of Elan's minority interest in Orasense.

11. Private Placement Financing

In August 2005, the Company raised $51 million in a private placement of 12 million shares of its common stock at a price of $4.25 per share, which was a 2.3% discount from the Company's 60-day average trading price. In addition, investors in the financing received five-year warrants to purchase approximately 3 million shares of common stock at an exercise price of $5.24 per share. The net proceeds from the offering were $48.2 million. The warrants issued in the transaction provide a call right in favor of the Company to the extent that the price per share of the Company's common stock exceeds $14.41 per share for 20 consecutive trading days, subject to certain circumstances. The Company cannot exercise this call right prior to August 2008.

Pursuant to the terms of the registration rights agreement entered into in connection with the above transaction, within defined timelines the Company was required to file with the SEC a registration statement under the Securities Act of 1933, as amended, covering the resale of all of the common stock purchased and the common stock underlying the warrants. The registration rights agreement further provides that if a registration statement is not filed, or does not become effective, within the defined time period, then in addition to any other rights the holders may have, the Company would be required to pay each holder an amount in cash, as liquidated damages, equal to 1% per month of the aggregate purchase price paid by such holder in the private placement for the common stock and warrants then held. The registration statement was filed within the allowed time, and was declared effective by the SEC on November 1, 2005. As a result, the Company was not required to pay any liquidated damages in connection with the initial registration.

Because of the potential to pay liquidated damages, Isis allocated a portion of the offering proceeds to the warrants based on their fair value in accordance with EITF 00-19, "Accounting for Derivative Financial Instruments Indexed to, and Potentially Settled in, a Company's Own Stock,". The related registration statement was declared effective by the SEC within the contractual deadline and the Company incurred no penalties. The adjustments for EITF 00-19 had no impact on the Company's working capital, liquidity or business operations.

12. Legal Proceedings.

Ajinomoto Co., Inc. v. Isis Pharmaceuticals, Inc. On or about January 27, 2005, Ajinomoto Co., Inc., or Ajinomoto filed a Demand for Arbitration against us with the American Arbitration Association in San Diego, California. The Demand relates to a February 17, 1994 license agreement between Ajinomoto and us, that purports to license certain intellectual property, including United States Patent No. 5,013,830, or the '830 patent, in exchange for initial payments, royalties and certain milestone payments relating to the development of products covered by the license. Ajinomoto alleges that several products developed by us are covered by the '830

patent, and thus by the license. Ajinomoto seeks a determination of products covered by the license, along with an accounting of any sums due as a result. In October 2005, we filed our answering statement. We believe that Ajinomoto's claims are without merit, and we intend to vigorously defend our position. Ajinomoto and Isis agreed to a bifurcated arbitration process in which the arbitrator would first hear contract arguments and will then hear the patent arguments, if necessary, at a later date. The contract argument portion of the arbitration proceeding took place on February 22, 2006. We expect a ruling from the arbitrator on the first part of this proceeding in the middle of April 2006.

Isis estimates that the potential range of loss on this claim is zero to $2.1 million, and believes it is reasonably possible, not probable, that it will ultimately pay any amounts to Ajinomoto related to this claim. As such, Isis has not recorded a loss related to this claim as of December 31, 2005.

13. Quarterly Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods. Summarized quarterly data for the years ended December 31, 2005, and 2004 are as follows (in thousands, except per share data).

2005 Quarters	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Revenue	$ 7,442	$ 10,592	$ 7,458	$ 14,641
Operating expenses(1)	30,949	23,515	19,602	23,249
Loss from operations(1)	(23,507)	(12,923)	(12,144)	(8,608)
Net loss applicable to common stock(1)	$ (29,658)	$ (19,659)	$ (15,172)	$ (7,912)
Basic and diluted net loss per share(3)	$ (0.52)	$ (0.34)	$ (0.24)	$ (0.11)

2004 Quarters	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Revenue	$ 12,303	$ 9,843	$ 9,093	$ 11,385
Operating expenses(2)	34,638	31,183	31,473	63,183
Loss from operations(2)	(22,335)	(21,340)	(22,380)	(51,798)
Net loss(2)	(26,306)	(25,949)	(32,708)	(57,540)
Accretion of dividends on preferred stock	(181)	(180)	—	—
Net loss applicable to common stock(2)	$ (26,487)	$ (26,129)	$ (32,708)	$ (57,540)
Basic and diluted net loss per share(3)	$ (0.47)	$ (0.47)	$ (0.57)	$ (1.00)

(1) Includes charges related to restructuring activities of $7.0 million incurred during the year ended December 31, 2005.

(2) Includes charges related to restructuring activities of $32.4 million incurred during the quarter ended December 31, 2004.

(3) Net loss per share is computed independently for each of the quarters presented. Therefore, the sum of the quarterly net loss per share will not necessarily equal the total for the year.

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the Registration Statements (Form S-3 Nos. 33-55790, 33-72124, 33-75068, 33-96138, 333-71911, 333-90811, 333-38844, 333-71116, 333-71176, 333-89066, 333-89626, 333-128156, 333-130639, 333-134380 and Form S-8 Nos. 33-42356, 33-42970, 33-51236, 33-54840, 33-58450, 33-75150, 33-90780, 333-05825, 333-55683, 333-40336, 333-59296, 333-91572, 333-106859, 333-116962, 333-125911, 333-133853) of Isis Pharmaceuticals, Inc. and in the related Prospectuses of our reports dated March 7, 2006 except for note 2 as to which the date is August 4, 2006, with respect to the consolidated financial statements of Isis Pharmaceuticals, Inc., Isis Pharmaceuticals, Inc.'s management's assessment of the effectiveness of internal control over financial reporting, and the effectiveness of internal control over financial reporting of Isis Pharmaceuticals, Inc., included in this Annual Report (Form 10-K/A) for the year ended December 31, 2005.

/s/ ERNST & YOUNG LLP

San Diego, California
August 4, 2006

Exhibit 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

1. I have reviewed this Annual Report on Form 10-K/A of Isis Pharmaceuticals, Inc.;
2. Based on my knowledge, this annual report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this annual report;
3. Based on my knowledge, the consolidated financial statements, and other financial information included in this annual report, fairly present in all material respects the financial condition, consolidated results of operations and consolidated cash flows of the registrant as of, and for, the periods presented in this annual report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):
   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: August 9, 2006

/s/ STANLEY T. CROOKE

Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

Exhibit 31.2

CERTIFICATION

I, B. Lynne Parshall, certify that:

1. I have reviewed this Annual Report on Form 10-K/A of Isis Pharmaceuticals, Inc.;
2. Based on my knowledge, this annual report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this annual report;
3. Based on my knowledge, the consolidated financial statements, and other financial information included in this annual report, fairly present in all material respects the financial condition, consolidated results of operations and consolidated cash flows of the registrant as of, and for, the periods presented in this annual report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):
   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: August 9, 2006

/s/ B. LYNNE PARSHALL

B. Lynne Parshall, J.D.
Chief Financial Officer

Exhibit 32.1

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Stanley T. Crooke, the Chief Executive Officer of Isis Pharmaceuticals, Inc. (the "Company"), and B. Lynne Parshall, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Annual Report on Form 10-K, as amended for the period ended December 31, 2005, to which this Certification is attached as Exhibit 32.1 (the "Annual Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

2. The information contained in the Annual Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Annual Report and the results of operations of the Company for the period covered by the Annual Report.

Dated: August 9, 2006

/s/ STANLEY T. CROOKE	/s/ B. LYNNE PARSHALL
Stanley T. Crooke, M.D., Ph.D.	B. Lynne Parshall, J.D.
Chief Executive Officer	*Chief Financial Officer*

A signed original of this written statement required by Section 906 has been provided to Isis Pharmaceuticals, Inc. and will be retained by Isis Pharmaceuticals, Inc. and furnished to the Securities and Exchange Commission or its staff upon request**.**

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of Isis Pharmaceuticals, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.