UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

Form 10-Q

(Mark One)
☒ QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the Quarterly Period Ended March 31, 2005

OR

o TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF SECURITIES EXCHANGE ACT OF 1934

For the transition period from to

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 (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 ☒ No o

Indicate by check mark whether the registrant is an accelerated filer (as defined in Rule 12(b)-2 of the Securities Exchange Act of 1934). Yes ☒ No o

The number of shares of voting common stock outstanding as of May 2, 2005 was 57,527,999.

ISIS PHARMACEUTICALS, INC.
FORM 10-Q

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TRADEMARKS

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

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

	March 31, 2005 (Unaudited)	December 31, 2004
ASSETS		
Current assets:		
Cash and cash equivalents	$ 12,006	$ 27,250
Short-term investments	70,778	76,633
Contracts receivable	2,911	10,048
Inventory	2,722	2,722
Other current assets	8,574	8,956
Total current assets	96,991	125,609
Property, plant and equipment, net	26,665	28,454
Licenses, net	25,521	26,104
Patents, net	19,745	19,097
Deposits and other assets	3,422	3,854
Long-term investments	3,304	5,307
Total assets	$ 175,648	$ 208,425
LIABILITIES AND STOCKHOLDERS' DEFICIT		
Current liabilities:		
Accounts payable	$ 2,240	$ 6,967
Accrued compensation	1,811	3,475
Accrued liabilities	11,902	8,238
Current portion of long-term obligations	9,674	10,546
Current portion of deferred contract revenue	10,435	14,190
Total current liabilities	36,062	43,416
5 ½% convertible subordinated notes	125,000	125,000
Long-term obligations, less current portion	118,358	111,611
Long-term deferred contract revenue, less current portion	378	531

Stockholders' deficit:		
Common stock, $0.001 par value; 100,000,000 shares authorized, 57,523,924 shares and 57,447,333 shares issued and outstanding at March 31, 2005 and December 31, 2004, respectively	58	57
Additional paid-in capital	623,361	623,706
Deferred compensation	(8)	(72)
Accumulated other comprehensive income	544	2,623
Accumulated deficit	(728,105)	(698,447)
Total stockholders' deficit	(104,150)	(72,133)
Total liabilities and stockholders' deficit	$ 175,648	$ 208,425

See accompanying notes

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

	Three Months Ended March 31,	
	2005	2004
Revenue:		
Research and development revenue under collaborative agreements	$ 7,135	$ 6,998
Licensing and royalty revenue	307	5,305
Total revenue	7,442	12,303
Operating expenses:		
Research and development	22,361	28,947
General and administrative	2,137	2,453
Compensation expense (benefit) related to stock options	(633)	3,238
Restructuring activities	7,084	—
Total operating expenses	30,949	34,638
Loss from operations	(23,507)	(22,335)
Other income (expenses):		
Investment income	504	1,133
Interest expense	(6,655)	(5,104)
Net loss	(29,658)	(26,306)
Accretion of dividends on preferred stock	—	(181)
Net loss applicable to common stock	$ (29,658)	$ (26,487)
Basic and diluted net loss per share	$ (0.52)	$ (0.47)
Shares used in computing basic and diluted net loss per share	57,521	55,858

See accompanying notes

ISIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)
(Unaudited)

	Three Months Ended March 31,	
	2005	2004
Net cash used in operating activities	$ (22,032)	$ (23,467)
Investing activities:		
Purchase of short-term investments	(3,306)	(23,182)
Proceeds from the sale of short-term investments	8,985	64,181
Purchase of property, plant and equipment	(277)	(103)
Proceeds from the sale of property, plant and equipment	165	—
Other assets	(1,173)	(1,837)
Strategic investments	—	(10,000)
Net cash provided by investing activities	4,394	29,059

Financing activities:		
Net proceeds from issuance of equity	353	2,172
Proceeds from long-term borrowings	5,000	7,574
Principal payments on debt and capital lease obligations	(2,959)	(8,698)
Net cash provided by financing activities	2,394	1,048
Net increase (decrease) in cash and cash equivalents	(15,244)	6,640
Cash and cash equivalents at beginning of period	27,250	33,117
Cash and cash equivalents at end of period	$ 12,006	$ 39,757
Supplemental disclosures of cash flow information:		
Interest paid	$ 522	$ 570

See accompanying notes

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
March 31, 2005
(Unaudited)

1. Basis of Presentation

The unaudited interim consolidated financial statements for the three-month periods ended March 31, 2005 and 2004 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2004. The financial statements include all adjustments, which Isis considers necessary for a fair presentation of the financial position at such dates and the operating results and cash flows for those periods. Results for the interim periods are not necessarily indicative of the results for the entire year. For more complete financial information, these financial statements, and notes thereto, should be read in conjunction with the audited financial statements for the year ended December 31, 2004 included in Isis' Annual Report on Form 10-K filed with the Securities and Exchange Commission.

The condensed consolidated financial statements include the accounts of Isis and its wholly-owned subsidiaries, Isis Pharmaceuticals Singapore Pte Ltd., Hepasense, Ltd., and Orasense, Ltd.

2. Significant Accounting Policies

Revenue Recognition

Isis recognizes revenue when it has satisfied all contractual obligations and Isis is reasonably certain it can collect the receivable.

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 records revenue from federal research grants during the period in which it incurs 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. As of March 31, 2005, Isis had drawn down the entire $100.0 million on this loan. Isis has discounted the $100.0 million loan to its 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 accretes 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 represents value Lilly gave to Isis to help fund the research collaboration. Isis accounts for this value as deferred revenue and recognizes it as revenue over the period of performance.

Licensing and royalty revenue

Isis recognizes licensing and royalty revenue immediately, if collectibility is reasonably assured, for arrangements in which 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 established 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 quarter. Isis uses the specific identification method to determine the cost of debt securities sold. Isis includes gross realized gains and losses in investment income and these amounts have not been material. Isis determined that there were no other-than-temporary declines in value of its investments during the three months ended March 31, 2005 and 2004.

Valuation of Inventory

We include 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. We expense these costs when we deliver our drugs to partners, or as we use these drugs in our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce our carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf lives of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. During the fourth quarter of 2004, we recorded a charge of approximately $21.0 million for the write-down of inventory to its estimated net realizable value related to our strategic decision to reorganize and refocus our resources to advance our most promising second-generation drugs.

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

	March 31, 2005	December 31, 2004
Raw materials	$ 1,329	$ 1,329
Finished goods	1,393	1,393
	$ 2,722	$ 2,722

Licenses

Isis obtains licenses from third parties and capitalizes the cost related to exclusive licenses. Isis amortizes capitalized licenses over their estimated useful life or term of the agreement, which for current licenses is between 7 years and 15 years.

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.

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

Pursuant to the provisions of SFAS No. 144, *Accounting for the Impairment of Long-Lived Assets*, Isis evaluates carrying values of long-lived assets including property, plant and equipment and intangible assets, on at least a quarterly basis, and when events and circumstances indicate that these assets may be impaired. In the first quarter of 2005, Isis incurred a charge related to restructuring activities of $1.4 million primarily for the write-down of capitalized leasehold improvements in a building which Isis vacated during March 2005.

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 condensed consolidated financial statements and accompanying notes. Actual results could differ from those estimates.

Long-Term Debt

Isis has a $100.0 million Lilly research collaboration loan, of which $100.0 million was outstanding as of March 31, 2005, that is due in August 2005. Isis can repay this loan at its option in either cash or its common stock at a fixed conversion price of $40 per share. Accordingly, the outstanding balance on this loan has been classified as a long-term obligation in the current quarter.

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 March 31, 2005, Isis had collaborative arrangements with two entities which 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 promissory note (the "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 result of operations under FIN No. 46 as it 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 promissory note (the "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 debt instrument, as realization of this asset is uncertain. Isis is not required to consolidate Sarissa's results of operations under FIN No. 46 as it is not the primary beneficiary.

Stock-Based Compensation

In April 2003, Isis implemented an employee stock option exchange program ("2003 option exchange program") to maintain one of Isis' key assets, its employee base, in a manner that was sensitive to shareholder interests. 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 using variable accounting consistent with the provisions of Accounting Principles Board ("APB")

Opinion No. 25 and FIN No. 44, and will continue to account for the affected options using variable accounting until all these options have been exercised or cancelled. As a result, Isis recorded compensation benefit of approximately $633,000 during the three months ended March 31, 2005 and compensation expense of $3.2 million for the same period in 2004.

Isis has adopted the disclosure-only provision of SFAS No. 123, *Accounting for Stock-Based Compensation* ("SFAS 123"). Accordingly, Isis has not recognized compensation expense for the Isis stock option plans, except for compensation expense primarily related to the affected options from the 2000 and 2003 option exchange programs. Had Isis determined compensation expense consistent with SFAS No. 123, Isis would have reported the following proforma amounts for net loss and basic and diluted net loss per share (in thousands, except per share amounts):

	Three Months Ended March 31,	
	2005	2004
Net loss applicable to common stock—as reported	$ (29,658)	$ (26,487)
Net loss applicable to common stock—pro forma	$ (31,965)	$ (25,100)
Basic and diluted net loss per share—as reported	$ (0.52)	$ (0.47)
Basic and diluted net loss per share—pro forma	$ (0.55)	$ (0.45)

For purposes of proforma disclosures, Isis estimated the fair value of each option grant on the date of grant using the Black-Scholes option pricing model with the following weighted-average assumptions:

	March 31,	
	2005	2004
Risk-free interest rate	4.5%	3.8%
Dividend yield	0.0%	0.0%
Volatility	41.6%	74.6%
Expected Life	6.5 years	6.2 years

The weighted average fair values of options granted were $5.71 and $6.91 for the three months ended March 31, 2005 and 2004, respectively.

Comprehensive Loss

SFAS No. 130, *Reporting Comprehensive Income,* requires Isis to report, in addition to net loss, comprehensive loss and its components. A summary follows (in thousands):

	Three Months Ended March 31,	
	2005	2004
Comprehensive loss:		
Change in unrealized gains (losses)	$ (2,079)	$ 1,271
Net loss applicable to common stock	(29,658)	(26,487)

Comprehensive loss	$ (31,737)	$ (25,216)

Impact of Recently Issued Accounting Standards

On December 16, 2004, the Financial Accounting Standards Board ("FASB") issued SFAS 123(R), *Share-Based Payment* ("SFAS 123(R)"), which is a revision of SFAS 123. Generally, the approach in SFAS 123(R) is similar to the approach described in SFAS 123. However, SFAS 123(R) requires all share-based payments to employees, including grants of employee stock options, to be recognized in the income statement based on their fair values. Pro forma disclosure is no longer an alternative. This statement also eliminates the ability to account for share-based compensation transactions using APB Opinion No. 25. On April 14, 2005, the SEC deferred the effective date of SFAS 123(R). In accordance with the SEC's new effective date, Isis expects to adopt SFAS 123(R) on January 1, 2006.

SFAS 123(R) permits public companies to adopt its requirements using one of two methods: 1) A "modified prospective" method in which compensation cost is recognized beginning with the effective date (a) based on the requirements of SFAS 123(R) for all share-based payments granted after the effective date and (b) based on the requirements of SFAS 123 for all awards granted to employees prior to the effective date of SFAS 123(R) that remain unvested on the effective date, 2) A "modified retrospective" method which includes the requirements of the modified prospective method described above, but also permits entities to restate based on the amounts previously recognized under SFAS 123 for purposes of pro forma disclosures either (a) all prior periods presented or (b) prior interim periods of the year of adoption. Isis has not yet determined what method it will use.

As permitted by SFAS 123, Isis currently accounts for share-based payments to employees using APB Opinion No. 25's intrinsic value method and, as such, generally recognizes no compensation cost for employee stock options. Accordingly, the adoption of SFAS 123(R)'s fair value method may have a significant impact on Isis' results of operations, although it will have no impact on its overall financial position. The impact of adoption of SFAS 123(R) cannot be predicted at this time because it will depend on levels of share-based payments granted in the future. However, had Isis adopted SFAS 123(R) in prior periods, the impact of that standard would have approximated the impact of SFAS 123 as described in the disclosure of pro forma net income and earnings per share in Note 1 to the condensed consolidated financial statements. SFAS 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* ("SFAS 151"), 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.

In March 2004, the FASB issued EITF 03-1, *The Meaning of Other-Than-Temporary Impairment and Its Application to Certain Investments*. EITF 03-1, which was originally effective for interim and annual reporting periods beginning after June 15, 2004 requires a three-step model to determine other-than-temporary impairments for all current and future investments in marketable securities. In September 2004, the FASB delayed the requirement to record impairment losses under EITF 03-1 until new guidance is issued. Isis does not expect that the adoption of EITF 03-1 will have a material impact on its operating results and financial position.

3. Strategic Alliances

OncoGenex Technologies Inc

In January 2005, Isis broadened its antisense drug development partnership with OncoGenex to allow for the development of two additional second-generation antisense anti-cancer drug candidates. In April 2005, OncoGenex selected its first drug candidate under this expansion, 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 up-front fee with a debt instrument, which, at OncoGenex's discretion is payable in cash or will convert into OncoGenex stock upon OncoGenex's completion of its next stock financing. OncoGenex will also pay Isis milestone payments totaling up to $5 million for key clinical and regulatory achievements, and royalties on future product sales of these drugs. Under the terms of the agreement, OncoGenex will be responsible for the preclinical and clinical development of the drug.

Sarissa, Inc.

In February 2005, Isis licensed one of its anti-cancer antisense drugs to Sarissa, 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 debt instrument, 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 debt instrument as realization of this asset is uncertain. Sarissa will also pay Isis milestone payments totaling up to $5.5 million for key clinical and regulatory achievements and royalties on any product sales of this drug. Under the terms of the agreement, Sarissa will be solely responsible for preclinical and clinical development of the drug.

Department of Homeland Security

In April 2005, Isis received two contracts totaling $1.5 million for the development of a new microbial forensics application for the TIGER biosensor system for use in the investigation of crimes involving infectious agents which compares the genetic "fingerprint" of an infectious agent to that of a potential source. The new awards will also support further enhancement of the Microbial Rosetta Stone (MRS) database to include additional genetic information on infectious agents. The MRS database is a key component of the TIGER biosensor system. These new contracts broaden TIGER's commercial applications and product opportunities for use by government and non-government customers.

4. Segment Information and Concentration of Business Risk

Segment Information

The following is information for revenue and loss from operations by segment.

	Drug Discovery and Development	Ibis	Corporate	Total
Three Months Ended March 31, 2005				
Revenue:				
Research and development	$ 4,810	$ 2,325	$ —	$ 7,135
Licensing and royalty	307	—	—	307
Total segment revenue	$ 5,117	$ 2,325	$ —	$ 7,442
Loss from operations	$ (15,944)	$ (1,112)	$ (6,451)	$ (23,507)
Three Months Ended March 31, 2004				
Revenue:				
Research and development	$ 4,201	$ 2,797	$ —	$ 6,998
Licensing and royalty	5,305	—	—	5,305
Total segment revenue	$ 9,506	$ 2,797	$ —	$ 12,303
Loss from operations	$ (17,941)	$ (1,156)	$ (3,238)	$ (22,335)

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.

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:

	Three Months Ended March 31,	
	2005	2004
Partner A	—	41%
Partner B	57%	23%
Partner C	9%	18%

For the three months ended March 31, 2005 and 2004, Isis derived approximately 34%, and 24%, respectively, of its revenue from agencies of the United States Government, including approximately 9% and 18% respectively, of revenue from one significant customer.

Contract receivables from three significant partners comprised approximately 29%, 24%, and 15% of contract receivables at March 31, 2005. Contract receivables from four significant partners comprised 30%, 20%, 17% and 10% of contract receivables at December 31, 2004.

5. Restructuring Activities

In connection with the decision to reorganize and refocus the Company's resources, 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. Isis expects to substantially complete these restructuring efforts by the end of the second quarter 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 March 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	1,642	3,900	1,079	463	7,084
Charged against accrual	(340)	(2,622)	(89)	(337)	(3,388)
Balance at March 31, 2005	$ 1,302	$ 1,278	$ 990	$ 126	$ 3,696

ITEM 2. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

In addition to historical information contained in this Report on Form 10-Q, this Report contains forward-looking statements regarding our business, the financial position of Isis Pharmaceuticals, Inc. 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 Isis' clinical 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 technology and systems used to identify infectious agents, and in the endeavor of building a business around such products and services. 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 Annual Report on Form 10-K for the year ended December 31, 2004, which is on file with the U.S. Securities and Exchange Commission, and those identified in the section of Item 2 entitled "Risk Factors" beginning on page 27 of this Report. 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.

Overview

Since our inception in 1989, we have pioneered the science of antisense for the development of a new class of drugs. We have designed antisense drugs to treat a wide variety of diseases. Due to their gene selectivity, antisense drugs have the potential to be highly effective and less toxic than traditional drugs. We have made significant progress in understanding the capabilities of antisense drugs in treating disease. We have developed new chemistries and novel formulations to enhance the potency and utility of antisense drugs, and we have successfully turned our expertise into one marketed product and 11 antisense drugs, which we and our partners are advancing in pre-clinical and clinical development, the majority of which are in Phase I or Phase II human clinical trials. Our products in development address numerous therapeutic areas with major market potential, including inflammatory, metabolic, and cardiovascular diseases, and cancer. We are expanding the therapeutic opportunities for antisense drugs by developing a variety of formulations to enhance patient convenience and compliance, including intravitreal, subcutaneous, topical cream, enema, aerosol, and oral formulations. In addition, our pipeline has matured to consist primarily of drugs based on our proprietary second-generation chemistry. Our second-generation antisense drugs offer a number of advantages over prior chemistries. Specifically, these drugs offer the potential for improved safety, increased potency and a longer half-life, which correlates with durability of therapeutic response and the potential for less frequent dosing. Physicians may be able to dose our second-generation drugs as infrequently as once every two weeks to once a month. We are also making progress on developing oral formulations of our second-generation antisense drugs. Recently, we expanded the clinical development program for our second-generation inhibitor of apoB-100 for the lowering of cholesterol, ISIS 301012, with the initiation of a Phase 1 study of an oral capsule formulation of ISIS 301012. Our oral formulations may increase the commercial value of our antisense drugs. We achieved marketing clearance for the world's first antisense drug, Vitravene (fomivirsen), in 1998.

Our Ibis division has invented the TIGER (Triangulation Identification for Genetic Evaluation of Risks) biosensor system, a system that has the potential to revolutionize the identification of infectious diseases. The Ibis division was founded to take advantage of our expertise in RNA and utilize that knowledge and innovation to create a fundamentally different approach for the identification of bacterial and viral organisms. Our scientists have applied proprietary technologies to develop a biological sensor to identify a broad range of infectious organisms contained in a sample, including those that are newly-emerging, genetically altered and unculturable. The division has successfully demonstrated proof-of-principle of the TIGER biosensor system with the identification of a variety of bacteria and viruses in both environmental and human clinical samples. In addition to bioweapons defense, Ibis has advanced the development of the TIGER biosensor system to include epidemiological surveillance, biological products screening and microbial forensics applications. These applications represent the first of many we plan to add to the TIGER biosensor system to enhance its commercial value and opportunity in the government, research, medical and diagnostic markets.

To develop TIGER technology and applications, our Ibis division has received contracts from a number of government agencies, including the Defense Advanced Research Projects Agency (DARPA), the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), the Federal Bureau of Investigation (FBI), and the Department of Homeland Security (DHS). From inception through March 31, 2005, Ibis has earned $38.5 million in revenue from government partners. An additional $9.0 million was committed under existing contracts and grants, with the potential for added funding.

We have a broad patent portfolio covering our technologies. We own or exclusively license more than 1,500 issued patents, which we believe represents the largest antisense and RNA-oriented patent estate in the pharmaceutical industry. Our intellectual property is a strategic asset that we are exploiting to generate near-term revenue and that we expect will also provide us with revenue in the future. To date, we have generated nearly $71 million from our intellectual property licensing program that helps support our internal drug discovery and clinical development programs.

The principal purpose of our intellectual property portfolio is to protect our products and those of our partners. Our intellectual property portfolio also enables us to expand our pipeline by granting other companies limited access to antisense technology through licenses we grant them. Licensing partnerships may include traditionally structured antisense drug discovery and development collaborations with large pharmaceutical companies like Lilly and Amgen.

In addition, we have extended our licensing partnerships to include our satellite company strategy in which we provide our expertise and intellectual property position in RNA-based therapeutics to industry partners that are interested in developing RNA-based therapeutics. We are able to pursue this partnering strategy because antisense allows us to produce more drug candidates than we can afford to develop on our own. We have implemented this integral component of our strategy through our partnerships with Alnylam Pharmaceuticals, Inc., Antisense Therapeutics, Ltd., or ATL, Ercole, OncoGenex, Santaris Pharma A/S, and most recently, Sarissa.

Further, we have an active intellectual property licensing program in which we license aspects of our intellectual property to companies like Hybridon, Inc., Integrated DNA Technologies, Inc., Roche Molecular Systems, atugen A/S, and Dharmacon, Inc. Through this program, we also license our non-antisense patents as we did with Eyetech Pharmaceuticals, Inc. In December 2001, we licensed several chemistry patents to Eyetech for the development of Macugen, a drug for the treatment of wet age-related macular degeneration, or AMD, that Eyetech is co-developing and commercializing with Pfizer, Inc.

In 2004, we earned $4.0 million in milestone payments from Eyetech associated with their filing of a New Drug Application, for Macugen with the FDA and Eyetech's receipt of marketing clearance for the drug. In December 2004, we sold a portion of our royalty rights in Macugen to Drug Royalty USA., Inc., in exchange for aggregate payments of $24 million over the next three years.

We are pursuing early-stage antisense mechanisms, including RNA interference, or RNAi, micro-RNA, and alternative splicing through research collaborations and partnerships, like our strategic alliances with Alnylam and Ercole.

Business Segments

We focus our business on two principal segments:

Drug Discovery and Development. Our proprietary technology to discover and characterize novel antisense inhibitors has enabled our scientists to modify the properties of our antisense drug candidates for optimal use with particular targets and thus, to produce a broad proprietary portfolio of compounds applicable to many disease targets. Further, over the past decade, our scientists have made great advances in chemistries, which we call our second-generation antisense drugs. Second-generation drugs may have increased potency, stability, oral bioavailability and an improved side effect profile. We have also made significant progress in developing new formulations of antisense drugs, like oral, topical cream, subcutaneous, intravitreal, aerosol and enema that further expand the potential for antisense technology.

We and our partners currently have 11 drugs in development, of which three are in Phase II clinical development, four are in Phase I clinical development and four are in preclinical development. Our partners are developing, with our support, five of these 11 drugs, which substantially reduce our development costs.

Ibis Division. Within our Ibis division, we have invented a technology that has the potential to revolutionize the identification of infectious diseases. This technology is called Triangulation Identification for Genetic Evaluation of Risks, or TIGER. TIGER is the product of core technology development and small molecule drug discovery research conducted within our Ibis division in its early years. Ibis' central focus now is to develop and commercialize our TIGER technology.

Recent Events

In December 2004, we made a strategic decision to reorganize and refocus our resources to advance our most promising second-generation drugs and to continue the development of antisense technology. We announced this decision in January 2005. In the fourth quarter of 2004 we recorded a $32.4 million charge for restructuring activities resulting from this decision, which consisted of non-cash write-downs of tangible and intangible assets that were non-essential to our current focus, including excess or idle equipment, inventories, patent costs, and certain prepaid expenses. We incurred additional charges relating to our restructuring activities of $7.1 million during the first quarter of 2005, including those associated with employee termination costs, termination of certain contractual

obligations, the consolidation of our United States facilities, and the closure of our research and development laboratory in Singapore.

Critical Accounting Policies

We prepare our consolidated financial statements in conformity with accounting principles generally accepted in the United States of America. As such, we are required to make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. We discuss the development, selection and disclosure of such estimates with our audit committee each quarter. There are specific risks associated with these critical accounting policies that we describe in the following paragraphs. For all of these policies, we caution that future events rarely develop exactly as expected, and that best estimates routinely require adjustment. The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, require the following:

- Assessment of the propriety of revenue recognition and associated deferred revenue;
- Determination of the proper valuation of investments in marketable securities and other equity investments;
- Estimations to assess the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determination of the proper valuation of inventory;
- Determination of the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimation of our net deferred income tax asset valuation allowance;
- Determine appropriateness of the judgments and estimates used in allocating revenue and expenses to operating segments; and
- Estimations to determine the fair value of stock-based compensation, including the expected life of the option and the expected stock price volatility over the term of the expected life.

Descriptions of these critical accounting policies follow.

Revenue Recognition

We follow the provisions as set forth by current accounting rules, which primarily include Staff Accounting Bulletin No. 101, or SAB 101, *"Revenue Recognition in Financial Statements,"* SAB 104, *"Revenue Recognition,"* and Financial Accounting Standards Board Emerging Issue Task Force No. 00-21,

or EITF 00-21, "*Accounting for Revenue Arrangements with Multiple Deliverables*."

We generally recognize revenue when we have satisfied all contractual obligations and we are reasonably assured of collecting the resulting receivable. We are often entitled to bill our customers and receive payment from our customers in advance of recognizing the revenue under current accounting rules. In those instances where we have billed our customers or received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on the balance sheet.

We often enter into collaborations where we receive non-refundable up-front payments for prior or future expenditures. We recognize revenue related to up-front payments ratably over the period of the contractual arrangements as we satisfy our performance obligations. Occasionally, we are required to estimate the period of a

contractual arrangement or our performance obligations when the agreements we enter into do not clearly define such information. Should different estimates prevail, revenue recognized could be materially different. We have made estimates of our continuing obligations on several agreements, including our collaborations with ATL, Lilly and OncoGenex.

As part of our Lilly alliance, in 2001 Lilly provided us a $100.0 million interest free loan to fund the research collaboration. We take quarterly draw downs against this loan and discount the amounts to their net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time we entered into the loan. As of March 31, 2005, we had drawn down the entire $100.0 million on this loan. We are accreting 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 represents value Lilly gave to us to help fund the research collaboration. We account for this difference as deferred revenue and recognize it as revenue over the period of contractual performance.

Our collaborations often include contractual milestones. When we achieve these milestones, we are entitled to payment, as defined by the underlying agreements. We generally recognize revenue related to milestones upon completion of the milestone's performance requirement, as long as we are reasonably assured of collecting the resulting receivable and we are not obligated to future performance related to the achievement of the milestone. We recognized revenue during 2004 related to milestones achieved under our agreements with Eyetech, Lilly and Singapore EDB.

We often enter into agreements to license our proprietary patent rights on an exclusive or non-exclusive basis in exchange for license and/or royalty fees. We generally recognize as revenue immediately those licensing and royalty fees for which we have no future performance obligations and are reasonably assured of collecting the resulting receivable.

We often enter into revenue arrangements that contain multiple deliverables. In these cases, we recognize revenue from each element of the arrangement as long as we are able to determine a separate value for each element, we have completed our obligation to deliver or perform on that element and we are reasonably assured of collecting the resulting receivable.

Valuation of Investments in Marketable Securities

We account for our investments in marketable securities in accordance with current accounting rules as set forth by SFAS 115, "*Accounting for Certain Investments in Debt and Equity Securities."* We carry these investments at fair market value based upon market prices quoted on the last day of the fiscal quarter. We record unrealized gains and losses as a separate component of stockholders' equity, and include gross realized gains and losses in investment income.

In addition to our investments in marketable securities, we also have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20% in each of the respective entities. In determining if and when a decrease in market value below our cost in our equity positions is other-than-temporary, we examine historical trends in the stock price, the financial condition of the issuer, near term prospects of the issuer, and our current need for cash. When we determine that a decline in value is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs.

Valuation of Long-Lived Assets

We assess the value of our long-lived assets, which include property and equipment, patent costs, and licenses acquired from third parties, under the provisions set forth by SFAS 144, *Accounting for the Impairment or Disposal of Long-Lived Assets*, or SFAS 144. We evaluate our long-lived assets for impairment on at least a quarterly basis. During this process, we review our property and equipment listings, pending domestic and international patent applications, domestic and international issued patents, and licenses we have acquired from other parties. To determine if any impairment is present, we consider the following, among other factors:

- Evidence of decreases in market value;
- Changes in the extent or manner in which we use an asset;
- Adverse changes in legal factors or in the business climate that would affect the value of an asset;
- An adverse action or assessment by a regulator;
- An accumulation of costs significantly in excess of amounts originally expected to acquire or construct an asset;

- Current period operating or cash flow loss combined with a history of operating or cash flow losses associated with an asset used for the purpose of producing revenue; and

- Challenges or potential challenges to our existing patents, the likelihood of applications being issued and the scope of our issued patents.

In December 2004, we made a strategic decision to reorganize and refocus our resources to advance our most promising second-generation drugs and to continue the development of antisense technology. As a result, during the fourth quarter of 2004 we recorded charges of approximately $11.5 million related to the write-down of tangible and intangible assets, including equipment and patent costs that were non-essential to our current focus.

Valuation of Inventory

We include 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. We expense these costs when we deliver our drugs to partners, or as we use these drugs in our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce our carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf lives of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. In the fourth quarter of 2004, we recorded a charge of approximately $21.0 million for the write-down of inventory to its estimated net realizable value related to our strategic decision to re-organize and re-focus our resources to advance our most promising second-generation drugs.

Estimated Liability for Clinical Development Costs

We maintain accrued liabilities related to unbilled costs for ongoing preclinical studies and clinical trials. These costs primarily relate to third-party clinical management costs, laboratory costs and analysis, toxicology studies and investigator grants, among other costs. We have multiple drugs in concurrent preclinical studies and clinical trials at several clinical sites throughout the world. We expect that at any given time we will have liabilities outstanding for our preclinical and clinical development costs related to products or services for which our service providers have not yet billed us. In order to ensure that we have adequately provided for ongoing preclinical and clinical development costs during the period in which we incur such costs, we maintain an accrual to cover these costs. We update our estimate for this accrual on at least a quarterly basis. The assessment of these costs is a subjective process that requires judgment. The ultimate settlement of these costs may differ materially from the amounts we have accrued in our consolidated financial statements.

Valuation Allowance for Net Deferred Tax Assets

We recorded a valuation allowance to offset our net deferred tax assets because we are uncertain that we will realize these net tax assets. When and if circumstances warrant, we will assess the likelihood that our net deferred tax assets will more likely than not be recovered from future taxable income and record an appropriate reversal to the

valuation allowance. Because we have had net operating losses since inception, we have established a 100% valuation allowance for our net deferred tax asset.

Segment Information

We provide segment financial information and results for our Drug Discovery and Development segment and our Ibis division based on the segregation of revenue 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.

Proforma Stock-Based Compensation

We provide proforma net income and loss per share amounts in accordance with the disclosure only provision of Statement of Financial Accounting Standards No. 123, *"Accounting for Stock-Based Compensation."* or SFAS No. 123. The stock-based compensation expense used in these proforma amounts is based on the fair value of the option at the grant date, which uses the fair value pricing method described in SFAS No. 123. This method requires us to use several assumptions to estimate the fair value, including the expected life of the option and the expected stock price volatility over the term of the expected life. Should any of these assumptions change or differ from the actual life or actual stock price volatility, our pro forma results could differ substantially.

Effective in January 1, 2006, pursuant to the provisions of SFAS No. 123(R), *"Share-Based Payment,"* we will be required to recognize as a charge to our statement of operations the fair value of all share-based payments to employees, including stock option grants. We cannot currently predict the impact that this new accounting treatment will have on our statement of operations because it will depend on levels of share-based payments we grant in the future. However, accounting for share-based payments to employees using the fair value method will have no impact on our overall financial position.

Results of Operations

Total revenue for the three months ended March 31, 2005 was $7.4 million, compared to $12.3 million for the same period in 2004. Our revenue fluctuates from period-to-period based on the nature and timing of license fees and milestones earned, and other deliverables under agreements with partners. Our ability to maintain revenue at current levels will depend on new revenue sources and the expansion of existing revenue sources for the remainder of 2005.

The following table sets forth information on our revenue by segment (in thousands):

	Three Months Ended

	March 31, 2005	March 31, 2004
Drug Discovery and Development:		
Research and development revenue	$ 4,810	$ 4,201
Licensing and royalty revenue	307	5,305
	$ 5,117	$ 9,506
Ibis Division:		
Research and development revenue	$ 2,325	$ 2,797
Licensing and royalty revenue	—	—
	$ 2,325	$ 2,797
Total revenue:		
Research and development revenue	$ 7,135	$ 6,998
Licensing and royalty revenue	307	5,305
	$ 7,442	$ 12,303

Revenue for our drug discovery and development segment includes revenue from research and development under collaborative agreements and licensing and royalty revenue. Research and development revenue under collaborative agreements for the three months ended March 31, 2005 was $4.8 million, compared to $4.2 million for the same period in 2004. The net increase of $609,000 primarily reflects an increase in revenue related to additional drawdowns on our loan from Lilly. This increase was offset in part by a decrease in revenue from our Amgen research collaboration that ended in 2004 in accordance with its terms and from OncoGenex for whom we manufactured and sold clinical trial materials in the first quarter of 2004. Our revenue from licensing activities and royalties for the three months ended March 31, 2005 was $307,000, compared to $5.3 million for the same period in 2004. In the first quarter of 2004 we earned a $5 million license fee related to our strategic alliance with Alnylam, which was the primary reason for the decrease.

Our Ibis division generates research and development revenue from grants and contracts from United States government agencies, including DARPA, CDC, FBI, DHS, and NIAID, a part of the NIH. Our Ibis division generated revenue of $2.3 million for the quarter ended March 31, 2005 compared to revenue of $2.8 million for the same period in 2004. Ibis' revenue may fluctuate on a quarter to quarter basis due primarily to the timing of equipment purchased in support of its government contracts. In general, when Ibis purchases equipment, it records expenses associated with the purchase and corresponding revenue. During 2004, Ibis was acquiring the necessary equipment components to build the TIGER systems that Ibis expects to deploy to its government partners this year. As a result, revenue in the first quarter of 2004 included $1.0 million in revenue and associated expense related to these equipment purchases, compared to $283,000 for the same period in 2005. This variance in revenue related to equipment purchases was the primary reason for the decrease in revenue from first quarter 2004 to first quarter 2005.

We receive our DARPA funding through a subcontract with San Diego-based Science Applications International Corporation or SAIC. Historically, we have generated the majority of our government-funded revenue through our collaboration with SAIC. This collaboration accounted for approximately 9% and 18% of our total revenue in 2005 and 2004, respectively, which represents 30% and 81% of our 2005 and 2004 Ibis division revenue, respectively. During 2004 and early 2005, we entered into several new government contracts, expanding our reach to multiple government agencies. Consequently, our government-funded revenues are subject to greater period-to-period fluctuations than in the past, depending on the timing of when we enter into and commence work under various contracts with these agencies.

From inception through March 31, 2005, Ibis has earned $38.5 million in revenue from various government agencies to further the development of our TIGER program. An additional $9.0 million is committed under existing contracts and grants. We may receive additional funding under these contracts based upon a variety of factors, including the accomplishment of program objectives and the exercise of contract options by the contracting agencies. In addition, these agencies may terminate these contracts and grants at their convenience at any time, even if we have fully performed our obligations. Consequently, we may never receive the full amount of the potential value of these awards.

Operating Expenses

Total operating expenses for the three months ended March 31, 2005 were $30.9 million, compared to $34.6 million for the same period in 2004. The change was primarily due to cost savings we achieved as a result of our recent strategic decision to reorganize and refocus our resources to advance our most promising second-generation drugs and to continue our development of antisense technology, and, to a lesser extent, non-cash compensation benefit due to variable accounting for stock options. This decrease in operating expenses was offset in part by $7.1 million in additional charges we incurred during the first quarter of 2005 related to our restructuring activities. We expect to achieve additional cost savings during the remainder of 2005 as a result of these restructuring activities. In order to analyze and compare our results of operations to other similar companies, we believe that it is important to exclude compensation related to stock options from operating expenses because it is based on the variability of our stock price rather than operations, and to exclude restructuring activities because the costs are directly related to isolated events.

Our research and development expenses consist of costs for antisense drug discovery, antisense drug development, our Ibis division, and R&D Support costs. As part of our corporate restructuring earlier this year, we consolidated our research manufacturing functions and our drug manufacturing functions into a combined manufacturing group that can serve the needs of both Antisense Research and Antisense Drug Development. We call this new function Manufacturing and Operations, and include the costs related to this new function in our research and development expenses. We expect that the consolidation will result in overall efficiencies and related cost savings. For the three months ended March 31, 2005, we incurred total research and development expenses of $22.4 million, compared to $28.9 million for the same period in 2004. The $6.5 million decrease is attributed to cost savings achieved as a result of our recent restructuring activities, including significant reductions in personnel costs, as well as a reduction in third party clinical development costs attributed to our decision to focus our research and development resources on our second-generation drugs and the resulting decision to discontinue development of ISIS 104838, ISIS 14803 and alicaforsen for Crohn's disease.

Our research and development expenses by segment were as follows (in thousands):

	Three Months Ended March 31, 2005	Three Months Ended March 31, 2004
Drug Discovery and Development	$ 19,216	$ 25,266

Ibis Division	3,145	3,681
Total research and development expenses	$ 22,361	$ 28,947

Antisense drug discovery costs for the three months ended March 31, 2005 were $5.1 million, compared to $9.0 million for the same period in 2004. The decrease of $3.9 million was principally the result of cost savings achieved as a result of our recent restructuring activities. These cost savings were primarily attributed to a decrease in personnel costs. We anticipate that our existing relationships and collaborations, as well as prospective new partners, will continue to help fund our research programs, as well as contribute to the advancement of the science by funding core antisense technology research.

Antisense drug development expenditures were $7.7 million for the three months ended March 31, 2005, compared to $10.3 million for the same period in 2004. The decrease of $2.6 million was primarily due to cost savings achieved as a result of our recent restructuring activities. These cost savings were primarily attributed to a decrease in personnel costs and third party clinical development costs resulting from our decision to focus resources on our most

promising second generation drug candidates. We expect our drug development expenses to fluctuate based on the timing and size of our clinical trials. We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. For example, during 2004, we decided not to initiate additional studies of ISIS 14803 and ISIS 104838. In addition we decided to discontinue further investment in the development of alicaforsen for Crohn's disease following disappointing results in Phase III trials for this drug. Generally, Phase III clinical trials are the longest, largest and most expensive component of the drug development process. Further, products in Phase III trials represent the most near term possibility of commercial success. In addition, because Phase III trials typically involve a well-defined protocol and require dedicated resources, it is easier for us to separately capture costs associated with these projects. Our Phase I and Phase II programs are really research programs that fuel our Phase III pipeline. When our products are in Phase I or Phase II clinical trials, they are in a dynamic state where we continually adjust the development strategy for each product. Although we may characterize a product as "in Phase I" or "in Phase II," it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product's particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous products in preclinical and early stage clinical research, the fluctuations in expenses from product-to-product, in large part, offset one another. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related cost. For example, during 2003, Lilly reimbursed us for our costs to develop Affinitak for the treatment of non small cell lung cancer. Our partners are developing, with our support, five of our 11 drug candidates, which substantially reduces our development costs.

The following table sets forth research and development expenses for our major antisense drug development projects (in thousands):

	Three Months Ended March 31,	
	2005	2004
Alicaforsen for Crohn's disease	$ 246	$ 1,457
Other antisense development products	5,811	7,083
Development overhead costs	1,620	1,771
Total antisense drug development	$ 7,677	$ 10,311

We incurred development expenditures related to alicaforsen for Crohn's disease of $246,000 for the three months ended March 31, 2005, compared to $1.5 million for the same period in 2004. The decrease of $1.3 million was primarily due to the completion of our Phase III trials in December 2004. In December 2004, we reported the results of our Phase III clinical trials of alicaforsen in patients with Crohn's disease. In these trials alicaforsen did not demonstrate statistically significant induction of clinical remission compared to placebo. As a result of these data, we decided not to invest further in the development of alicaforsen for Crohn's disease.

We incurred expenses related to our other products in development of $5.8 million for the three months ended March 31, 2005, compared to $7.1 million for the same period in 2004. The decrease of $1.3 million was primarily the result of a decrease in development activity related to our first-generation drugs, offset in part by increased expenditures related to our most promising second-generation drug candidates, specifically ISIS 113715 for the treatment of diabetes and ISIS 301012 for the treatment of high cholesterol.

Expenditures in our manufacturing and operations function consist primarily of personnel costs, specialized chemicals for oligonucleotide manufacturing, laboratory supplies and outside services. These costs for the three months ended March 31, 2005 were $1.5 million. As discussed above, manufacturing and operations is a new function that was created in 2005 to provide manufacturing efficiencies and related cost savings. This function is

responsible for providing drug supplies to antisense research and antisense drug development, including the analytical testing to satisfy good laboratory and good manufacturing practices requirements. We believe that it would be impractical to obtain comparative information for prior periods for this new function, and that such comparisons between any period in 2004 would be meaningless; therefore, we do not discuss these comparisons.

Research and development expenditures in our Ibis division include costs for scientists, pass-through equipment costs, laboratory supplies, chemicals and highly specialized information technology consultants to advance the research and development of our TIGER program. In addition, we allocate a portion of R & D support costs and general and administrative costs to our Ibis division. Our Ibis division R & D expenses for the three months ended March 31, 2005 were $3.1 million, compared to $3.7 million for the same period in 2004. During 2004, Ibis was acquiring the necessary equipment components to build the TIGER systems that Ibis expects to deploy to its government partners this year. As a result, the first quarter of 2004 included $1.0 million in expense related to these equipment purchases, compared to $283,000 for the same period in 2005. This was the primary reason for the decrease in

Ibis' operating expenses from first quarter 2004 to first quarter 2005. Our Ibis research and development expenses are the result of our performance under our contracts with DARPA, the FBI, the NIAID, a part of the NIH, and the CDC, in support of our ongoing development of our TIGER program. We include in our Ibis division expenses all contract-related costs we incur on behalf of government agencies in connection with the performance of our obligations under the respective contracts, including costs for equipment to which the government retains title. We expect our costs for our Ibis division to increase as we continue to expand this business.

In our research and development expenses, we include support costs such as rent, repair and maintenance for buildings and equipment, utilities, depreciation of laboratory equipment and facilities, amortization of our intellectual property, information technology costs, procurement costs and waste disposal costs. We call these costs R&D Support costs.

The following table sets forth information on R&D Support costs (in thousands):

	Three Months Ended March 31,	
	2005	2004
Personnel costs	$ 1,502	$ 2,662
Occupancy	2,076	1,667
Depreciation and amortization	1,293	1,466
Insurance	299	272
Other	431	534
Total R&D Support costs	$ 5,601	$ 6,601

R&D Support costs for the three months ended March 31, 2005 were $5.6 million, compared to $6.6 million for the same period in 2004. The decrease of $1.0 million was primarily due to decreased personnel, facilities and equipment depreciation and patent amortization costs resulting from our recent restructuring activities, which included employee terminations, consolidation and closure of facilities, and the write-down of equipment and patent costs.

Our R&D Support costs by segment were as follows (in thousands):

	Three Months Ended March 31,	
	2005	2004
Drug Discovery and Development	$ 4,973	$ 5,861
Ibis Division	1,217	724
Total R&D Support costs	$ 6,190	$ 6,585

General and administrative expenses for the three months ended March 31, 2005 were $2.1 million, compared to $2.5 million for the same period in 2004. The decrease of $400,000 was primarily related to a reduction in personnel and outside services costs resulting from our recent restructuring activities.

Our general and administrative expenses by segment were as follows (in thousands):

	Three Months Ended March 31,	
	2005	2004
Drug Discovery and Development	$ 1,845	$ 2,179
Ibis Division	292	274
Total general and administrative expenses	$ 2,137	$ 2,453

Compensation benefit related to stock options for the three months ended March 31, 2005 was $633,000, compared to compensation expense of $3.2 million for the same period in 2004. The changes in compensation expense (benefit) were primarily related to the effects of using variable accounting to account for stock options associated with the employee stock option exchange program initiated in April 2003. We accounted for options affected by the employee stock option exchange program as variable stock options in accordance with Accounting Principles Board, or APB, Opinion No. 25 and Financial Accounting Standards Board Interpretation, or FIN, No. 44.

During the three months ended March 31, 2005, we recorded a $7.1 million charge for restructuring activities resulting from our strategic decision to reorganize and refocus our resources to advance our most promising second-generation drugs and to continue our development of antisense technology. The 2005 charge for restructuring activities consists of costs associated with employee terminations, the consolidation of our facilities, termination of certain contractual obligations, and the closure of our research and development laboratory in Singapore. We expect that our cost containment measures will continue to decrease our cash use in 2005 as compared to 2004.

Investment Income

Investment income for the three months ended March 31, 2005 totaled $504,000, compared to $1.1 million for the same period in 2004. The decrease in investment income for the first three months of 2005 over 2004 was primarily due to our lower average cash and investments balances for the first three months of 2005 compared to the first three months of 2004.

Interest Expense

Interest expense for the three months ended March 31, 2005 totaled $6.7 million, compared to $5.1 million for the same period in 2004. This increase was due to the effect of a higher debt balance during 2005 than during 2004 related to an increase in the loan to fund our Lilly research collaboration offset in part by a decrease in the carrying value of our term loan from Silicon Valley Bank.

Net Loss Applicable to Common Stock

For the three months ended March 31, 2005, we reported a net loss applicable to common stock of $29.7 million, compared to a net loss applicable to common stock of $26.5 million for the same period in 2004. Our net loss applicable to common stock for the first quarter of 2004 included $181,000 of accreted dividends on preferred stock. The increase in net loss applicable to common stock for the three months ended March 31, 2005 compared to the same period in 2004 was primarily the result of $7.1 million in costs related to restructuring activities, an increase in interest expense due to the effect of a higher debt balance in 2005 as compared to 2004, and a decrease in investment income due to our lower average cash and investments balance in 2005 as compared to 2004. The net impact of these changes was offset in part by a decrease in operating expenses as a result of cost savings achieved by our recent restructuring activities.

Liquidity and Capital Resources

We have financed our operations with revenue from research and development under collaborative agreements and from affiliates. Additionally, we have earned licensing and royalty revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through March 31, 2005, we have earned approximately $450.5 million in revenue from contract research and development and the sale and licensing of our intellectual property. Since we were founded, we have raised net proceeds of approximately $593.6 million from the sale of equity securities. We have borrowed approximately $387.1 million under long-term debt arrangements to finance a portion of our operations.

At March 31, 2005, we had cash, cash equivalents and short-term investments of $82.7 million, working capital of $60.9 million and a stockholders' deficit of $104.2 million. In comparison, we had cash, cash equivalents and short-term investments of $103.9 million, working capital of $82.2 million and a stockholders' deficit of $72.1 million as of December 31, 2004. Our $100.0 million Lilly research collaboration loan, of which $100.0 million was outstanding as of March 31, 2005, is due in August 2005. We can repay this loan at our option in either cash or our common stock at a fixed conversion price of $40 per share, which equals 2.5 million shares of our common stock. Accordingly, the outstanding balance on this loan has been classified as a long-term obligation in the current quarter. The decreases in our cash, cash equivalents and short-term investments and working capital were due primarily to cash used to fund our operations, pursue patents, and to pay our debt and capital lease obligations.

As of March 31, 2005, our debt and other obligations totaled $261.0 million, compared to $258.9 million at December 31, 2004. Our debt and other obligations at March 31, 2005 included current and long-term deferred contract revenue of approximately $10.8 million and other contractual obligations. The increase in our debt and other obligations was primarily due to additional draw downs from the $100.0 million interest-free loan from Lilly, which we discounted to their present value by imputing interest on the amounts at 20% and accreting to their face value over their term by recording interest expense.

We will continue to use lease financing as long as the terms remain commercially attractive. Based on our current operating plan with reasonable assumptions for new sources of revenue and cash, we believe our resources will be sufficient to meet our anticipated requirements through at least mid 2007. The following table summarizes our contractual obligations as of March 31, 2005. The table provides a breakdown of when obligations become due. A more detailed description of the major components of our debt is provided in the paragraphs following the table:

	Payments Due by Period (in millions)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
Lilly Research Collaboration Loan	$ 100.0	$ 100.0	$ —	$ —	$ —
5 ½% Convertible Subordinated Notes	125.0	—	—	125.0	—
Standard Operating Debt	30.6	6.4	18.9	5.3	—
Capital Lease and Other Obligations	5.4	3.3	2.1	—	—
Operating Leases	9.0	2.8	4.1	1.9	0.2

Our contractual obligations consist primarily of our publicly traded convertible debt and Lilly research collaboration loan. We can repay our Lilly research collaboration loan at our option in either cash or our common stock at a fixed conversion price of $40 per share, which equals 2.5 million shares of our common stock. In addition, we also have standard operating debt, capital leases and other obligations. Our standard operating debt includes a term loan from Silicon Valley Bank, and our mortgage loan payable to another bank.

In December 2003, we secured a $32.0 million term loan from Silicon Valley Bank to retire our existing debt to Boehringer Ingelheim, and Elan Corporation. We amortize the term loan over sixty months. The term loan requires equal monthly payments of principal plus accrued interest, and bears interest at the prime interest rate, which was 5.5% at March 31, 2005. The loan is secured by substantially all of our operating assets, excluding intellectual property, real estate, and certain equity investments. The loan is subject to certain liquidity requirements,

including a requirement that we maintain a minimum balance in an account at Silicon Valley Bank at all times equal to the outstanding balance of the loan. The loan is convertible to a fixed interest rate at our option at any time at the then-applicable prime rate plus 1.25%. The carrying value of the term loan at March 31, 2005 was $24.6 million.

In May 2002, we completed a $125.0 million convertible debt offering, which raised proceeds of approximately $120.9 million, net of $4.1 million in issuance costs. The subordinated notes bear interest at 5.5%, which is payable semi-annually, and mature in May 2009. Holders of the subordinated notes can, at any time, convert the notes into shares of common stock at a conversion price of $16.625 per share. At March 31, 2005, the principal outstanding on the notes was $125.0 million.

In August 2001, Lilly made available to us a $100.0 million interest-free loan to fund the joint research collaboration between the two companies. The loan is interest-free and is repayable, at our option, in cash or common stock at $40 per share at the end of four years. The term of the loan provides for quarterly draw downs by us. As of March 31, 2005, we had drawn down the entire $100.0 million of the loan. We discounted the loan to its present value by imputing interest on the amount at 20%, which represented market conditions in place at the time we entered into the loan. We are accreting 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 represents value given to us

by Lilly to help fund the research collaboration. We account for this difference as deferred revenue and recognize it as revenue over the period of contractual performance. As of March 31, 2005, the balance in long-term obligations was $92.1 million and the balance in deferred revenue was $7.9 million.

In addition to contractual obligations, we had outstanding purchase orders as of March 31, 2005 for the purchase of services, capital equipment and materials as part of our normal course of business.

We plan to continue to enter into more collaborations with partners to provide for additional revenue and cash to us and we may be required to incur additional cash expenditures related to our obligations under any of the new agreements we may enter into. We currently intend to use our cash and short-term equivalents to finance our activities. However, we may also pursue other financing alternatives, like issuing additional shares of our common stock, issuing debt instruments, refinancing our existing debt, or securing lines of credit. Whether we use our existing capital resources or choose to obtain financing will depend on various factors, including the future success of our business, the prevailing interest rate environment and the condition of financial markets generally.

RISK FACTORS

Investing in our securities involves a high degree of risk. In addition to the other information in this report on Form 10-Q, you should carefully consider the risks described below before purchasing our securities. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment.

We have incurred losses, and our business will suffer if we fail to achieve profitability in the future.

Because drug discovery and development require substantial lead-time and money prior to commercialization, our expenses have exceeded our revenue since we were founded in January 1989. As of March 31, 2005, we had accumulated losses of approximately $728.1 million and a stockholders' deficit of approximately $104.2 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from interest income and research grants and the sale or licensing of patents. We currently have only one product, Vitravene, approved for commercial use. This product has limited sales potential. We expect to incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or services, or achieve or sustain future profitability.

If we or our partners fail to obtain regulatory approval for our products, we will not be able to sell them.

We and our partners must conduct time-consuming, extensive and costly clinical trials to show the safety and efficacy of each of our drug candidates before a drug candidate can be approved for sale. We must conduct these trials in compliance with United States Food and Drug Administration regulations and with comparable regulations in other countries. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of our drug candidates, it will not approve them or will require additional studies, which can be time consuming and expensive and which will delay commercialization of a drug candidate. We and our partners may not be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our drug candidates. Failure to receive these approvals or delays in these approvals could prevent or delay commercial introduction of a product and, as a result, could negatively impact our ability to generate revenue from product sales. In addition, following approval of a drug candidate, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute products. If we fail to comply with these regulations, regulators could force us to withdraw a drug candidate from the market or impose other penalties or requirements that also could have a negative impact on our financial results.

We have only introduced one commercial product, Vitravene. We cannot guarantee that any of our other drug candidates will be safe and effective, will be approved for commercialization or that our partners or we can successfully commercialize these drug candidates.

If the results of clinical testing indicate that any of our drugs under development are not suitable for commercial use, or if additional testing is required to demonstrate suitability, we may need to abandon one or more of our drug development programs.

Drug discovery and development has inherent risks, including the risk that molecular targets prove not to be important in a particular disease, the risk that compounds that demonstrate attractive activity in preclinical studies do not demonstrate similar activity in human beings, the risk that a compound is not safe or effective for use in humans, and the risk that successful results in early human clinical trials may not be indicative of results in late-stage clinical trials. Antisense technology in particular is relatively new and unproven. We are applying most of our resources to create safe and effective drugs for human use. Any of the risks described above could prevent us from meeting this goal. In the past, we have invested in clinical studies of drug candidates that have not met the primary clinical end points in their initial Phase III studies.

In March 2003, we reported the results of a Phase III clinical trial of Affinitak in patients with late stage non-small cell lung cancer and in October 2004, we reported the results of a second similar Phase III clinical trial. In each case, Affinitak failed to demonstrate improved survival sufficient enough to support an NDA filing. In December 2004, we reported the results of our Phase III clinical trials of alicaforsen in patients with active Crohn's disease, in which alicaforsen did not demonstrate statistically significant induction of clinical remissions compared to placebo. Similar results could occur with the trials for our other drugs. If any of our drugs in clinical studies do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for this and other drugs and our stock price could decline.

If the market does not accept our products, we are not likely to generate revenues or become profitable.

Our success will depend upon the medical community, patients and third-party payors accepting our products as medically useful, cost-effective and safe. We cannot guarantee that, if approved for commercialization, doctors will use our products to treat patients. We currently have one commercially available product, Vitravene, a treatment for cytomegalovirus, or CMV, retinitis in AIDS patients, which addresses a small market. Our partners and we may not successfully commercialize additional products.

The degree of market acceptance for any of our products depends upon a number of factors, including:

- The receipt and scope of regulatory approvals;
- The establishment and demonstration in the medical and patient community of the efficacy and safety of our drug candidates and their potential advantages over competing products;

- The cost and effectiveness of our drug candidates compared to other available therapies;
- The patient convenience of the dosing regimen for our drug candidates; and
- Reimbursement policies of government and third party payors.

Based on the profile of our drug candidates, physicians, patients, patient advocates, payors or the medical community in general may not accept and use any products that we may develop.

If any of our collaborative partners fail to fund our collaborative programs or develop or sell any of our products under development, or if we cannot obtain additional partners, we may have to delay or stop progress on our product development programs.

To date, corporate partnering has played a key role in our strategy to fund our development programs and to add key development resources. We plan to continue to rely on additional collaborative arrangements to develop and commercialize our products. However, we may not be able to negotiate additional attractive collaborative arrangements, and, even if negotiated, the collaborative arrangements may not be successful.

We have entered into collaborative arrangements with third parties to develop many of our product candidates. We enter into these collaborations in order to:

- Fund our research and development activities;
- Access manufacturing by third parties;
- Seek and obtain regulatory approvals;
- Conduct clinical trials; and
- Successfully commercialize existing and future product candidates.

If any of our partners fails to develop or sell any drug in which we have retained a financial interest, our business may suffer. These collaborations may not continue or result in commercialized drugs. Our collaborators can terminate their relationships with us under certain circumstances, some of which are outside of our control. For example, in November 2004 based on the outcome of both Phase III trials, Lilly discontinued its investment in Affinitak.

Other drug candidates in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics Limited, OncoGenex Technologies Inc. and Lilly. We have received significant financial support from United States Government-funded grants and contracts for our Ibis division and the development of our TIGER system. The United States Government can unilaterally terminate these contracts and grants at its convenience at any time, even if we have fully performed our obligations. If any of these pharmaceutical company or government partners stopped funding and/or developing these products, our business could suffer and we may not have the resources available to develop these products on our own.

Certain of our partners are pursuing other technologies or developing other drug candidates either on their own or in collaboration with others, including our competitors, to develop treatments for the same diseases targeted by our own collaborative programs. Competition may negatively impact a partner's focus on and commitment to our drug candidate and, as a result, could delay or otherwise negatively affect the commercialization of a drug candidate.

In addition, the disappointing results of the two Affinitak trials, our Phase III clinical trials of alicaforsen in patients with active Crohn's disease or any future clinical trial failures could impair our ability to attract new collaborative partners. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drug candidates could suffer.

We may not successfully develop or derive revenues from our business based on our TIGER system to identify infectious organisms.

Our TIGER system is subject to the risks inherent in developing tools based on innovative technologies. Our product is at an early stage of development and requires additional research and development prior to marketing. If our potential customers fail to purchase our TIGER system due to competition or other factors, or if we fail to develop applications that lead to market acceptance, we could lose our investment in this technology and our TIGER business could fail to meet our business and financial objectives.

If we fail to obtain timely funding, we may need to curtail or abandon some of our programs.

All of our product candidates are still undergoing clinical trials or are in the early stages of research and development. All of our products under development will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and a commitment of significant additional resources prior to their commercialization. Based on our current operating plan with reasonable assumptions for new sources of revenue and cash, we believe our resources will be sufficient to meet our anticipated requirements through at least mid 2007. If we do not meet our goals to commercialize our

products, or to license our drugs and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- the profile and launch timing of our drugs;
- continued scientific progress in our research, drug discovery and development programs;
- the size of our programs and progress with preclinical and clinical trials;
- the time and costs involved in obtaining regulatory approvals;
- competing technological and market developments, including the introduction by others of new therapies that address our markets;
- success in developing and commercializing a business based on our TIGER system to identify infectious organisms; and
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and their price, as well as the price of our other securities, may decline. If adequate funds are not available, we may have to cut back on one or more of our research, drug discovery or development programs. For example, in January 2005 we decided to terminate the development of two lower priority drugs, ISIS 14803 and ISIS 104838. Alternatively, we may obtain funds through arrangements with collaborative partners or others, which could require us to give up rights to certain of our technologies, product candidates or products.

If we cannot manufacture our products or contract with a third party to manufacture our products at costs that allow us to charge competitive prices to buyers, we will not be able to market products profitably.

If we successfully commercialize any of our drug candidates, we may be required to establish large-scale commercial manufacturing capabilities. In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. We have limited experience manufacturing pharmaceutical products of the chemical class represented by our drug candidates, called oligonucleotides, on a commercial scale for the systemic administration of a drug. There are a small number of suppliers for certain capital equipment and raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our product costs. We may not be able to manufacture at a cost or in quantities necessary to make commercially successful products.

Also, manufacturers, including us, must adhere to the FDA's current Good Manufacturing Practices regulations which the FDA enforces through its facilities inspection program. We and our contract manufacturers may not be able to comply or maintain compliance with Good Manufacturing Practices regulations. Non-compliance could significantly delay our receipt of marketing approval for potential products or result in FDA enforcement action after approval that could limit the commercial success of our potential product.

If we fail to compete effectively, our products will not contribute significant revenues.

Our competitors are engaged in all areas of drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. Other companies are engaged in developing antisense technology or unique methods of identifying infectious organisms. Our competitors may succeed in developing drug candidates or technologies that are more effective than any drug candidates or technologies that we are developing. These competitive developments could make our products obsolete or non-competitive.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical trials of new pharmaceutical products and in obtaining FDA and other regulatory approvals of products for use in health care. Accordingly, our competitors may succeed in obtaining regulatory approval for products earlier than we do. We will also compete with respect to marketing and sales capabilities, areas in which we have limited or no experience.

If we cannot protect our patents or our proprietary rights, others may compete more directly against us.

Our success depends to a significant degree upon our ability to continue to develop and secure intellectual property rights to proprietary products and services. However, we may not receive issued patents on any of our pending patent applications in the United States or in other countries. In addition, the scope of any of our issued patents may not be sufficiently broad to provide us with a competitive advantage. Furthermore, our issued patents or patents licensed to us may be successfully challenged, invalidated or circumvented so that our patent rights would not create an effective competitive barrier or revenue source.

Intellectual property litigation could be expensive and prevent us from pursuing our programs.

It is possible that in the future we may have to defend our intellectual property rights. In the event of an intellectual property dispute, we may be forced to litigate to defend our rights or assert them against others. Disputes could involve arbitration, litigation or proceedings declared by the United States Patent and Trademark Office or the International Trade Commission or foreign patent authorities. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business.

If a third party claims that our products or technology infringe their patents or other intellectual property rights, we may have to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to such intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of

patents or applications held by others that relate to our business. This is especially true since patent applications in the United States are filed confidentially. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain unresolved.

If we do not progress in our programs as anticipated, the price of our securities could decrease.

For planning purposes, we estimate the timing of a variety of clinical, regulatory and other milestones, like when a certain product candidate will enter the clinic, when we will complete a clinical trial, or when we will file an application for marketing approval. We base our estimates on present facts and a variety of assumptions. Many of the underlying assumptions are outside of our control. If we do not achieve milestones when we expect to, investors could be disappointed and the price of our securities would likely decrease.

The loss of key personnel, or the inability to attract and retain highly skilled personnel, could make it more difficult to run our business and reduce our likelihood of success.

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our executive officers. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. Failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel.

We depend on third parties in the conduct of our clinical trials for our product candidates and any failure of those parties to fulfill their obligations could adversely affect our development and commercialization plans.

We depend on independent clinical investigators, contract research organizations and other third party service providers in the conduct of our clinical trials for our product candidates and expect to continue to do so in the future. We rely heavily on these parties for successful execution of our clinical trials, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Third parties may not complete activities on schedule, or may not conduct our clinical trials in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations could delay or prevent the development, approval and commercialization of our product candidates.

If the price of our securities continues to be highly volatile, this could make it harder for you to liquidate your investment and could increase your risk of suffering a loss.

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding March 31, 2005, the market price of our common stock has ranged from $3.86 to $8.79 per share. On May 4, 2005 the closing price of our common stock on the Nasdaq National Market was $2.84 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial results, technological innovations or new drug products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

Provisions in our certificate of incorporation, other agreements and Delaware law may prevent stockholders from receiving a premium for their shares.

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66% of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15% or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. We also have implemented a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. These provisions, as well as Delaware law and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests. In addition, our board of directors has the authority to fix the rights and preferences of and issue shares of preferred stock, which

may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

If registration rights that we have previously granted are exercised, then the price of our securities may be negatively affected.

We have granted registration rights in connection with the issuance of our securities to Eli Lilly and Company. These registration rights cover approximately 2.5 million shares of our common stock which may become outstanding upon the conversion of outstanding convertible securities. If these securities are converted and the holder exercises its registration rights, it will bring additional shares of our common stock into the market, which may have an adverse effect on the price of our securities.

Our business is subject to changing regulations for corporate governance and public disclosure that has increased both our costs and the risk of noncompliance.

Each year we are required to evaluate our internal controls systems in order to allow management to report on, and our Registered Independent Public Accounting Firm to attest to, our internal controls as required by Section 404 of the Sarbanes-Oxley Act. As a result, we will incur additional expenses and will suffer a diversion of management's time. In addition, if we cannot continue to comply with the requirements of Section 404 in a timely manner, we might be subject to sanctions or investigation by regulatory authorities, such as the Securities and Exchange Commission, the Public Company Accounting Oversight Board, or PCAOB, or the NASDAQ Stock Exchange. Any such action could adversely affect our financial results and the market price of our common stock.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to changes in interest rates primarily from our long-term debt arrangements and, secondarily, investments in certain short-term investments. We invest our excess cash in highly liquid short-term investments that are typically held for the duration of the term of the respective instrument. We do not utilize derivative financial instruments, derivative commodity instruments or other market risk sensitive instruments, positions or transactions to manage exposure to interest rate changes. Accordingly, we believe that, while the securities we hold are subject to changes in the financial standing of the issuer of such securities, we are not subject to any material risks arising from changes in interest rates, foreign currency exchange rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments.

ITEM 4. CONTROLS AND PROCEDURES

As of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of March 31, 2005. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 2005.

An evaluation was also performed under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of any change in our internal control over financial reporting that occurred during our last fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting. That evaluation did not identify any change in our internal control over financial reporting that occurred during our latest fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

We maintain disclosure controls and procedures that are designed to ensure that information required to be disclosed in our Exchange Act reports is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely

decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable and not absolute assurance of achieving the desired control objectives.

PART II – OTHER INFORMATION

ITEM 1. 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, which 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. Ajinomoto also seeks a determination that the license is still in force. We have not yet filed an answer, and a hearing has not yet been set. We believe that Ajinomoto's claims are without merit, and we intend to vigorously defend our position in arbitration.

ITEM 2. UNREGISTERED SALES OF EQUITY SECURITIES AND USE OF PROCEEDS

Not applicable

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

ITEM 4. SUBMISSION OF MATTERS TO A VOTE OF SECURITY HOLDERS

Not applicable

ITEM 5. OTHER INFORMATION

Not applicable

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
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.

Isis Pharmaceuticals, Inc.

(Registrant)

SIGNATURES

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)	May 9, 2005
/s/ B. Lynne Parshall B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	May 9, 2005

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly 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 quarterly report;

3. Based on my knowledge, the consolidated financial statements, and other financial information included in this quarterly 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 quarterly 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: May 9, 2005

/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 Quarterly Report on Form 10-Q of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly 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 quarterly report;

3. Based on my knowledge, the consolidated financial statements, and other financial information included in this quarterly 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 quarterly 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: May 9, 2005

/s/ B. Lynne Parshall

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

Exhibit 32.1

CERTIFICATION

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, 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 Quarterly Report on Form 10-Q for the period ended March 31, 2005, to which this Certification is attached as Exhibit 32.1 (the "Periodic 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 Periodic Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Periodic Report and the results of operations of the Company for the period covered by the Periodic Report.

Dated: May 9, 2005

/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.