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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, 2003

or

o **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE 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)	(I.R.S. Employer Identification No.)

2292 Faraday Avenue, Carlsbad, CA 92008
(Address of principal executive offices, including zip code)

(760) 931-9200
(Registrant's telephone number, including area code)

(Former name, former address and former fiscal year, if changed since last report)

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.

(1) Yes ☒ No o (2) 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

Indicate the number of shares outstanding of each of the issuer's classes of common stock, as of the latest practicable date.

Common stock $.001 par value	55,381,331 shares
(Class)	(Outstanding at May 8, 2003)

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

	March 31, 2003	December 31, 2002
	(Unaudited)	(Note)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 61,092	$ 101,856
Short-term investments	208,359	187,497
Contracts receivable	4,981	14,906
Inventory	14,463	11,090
Other current assets	5,768	4,831
Total current assets	294,663	320,180
Property, plant and equipment, net	60,797	59,094
Licenses, net	30,128	30,749
Patents, net	19,915	18,904
Deposits and other assets	9,022	9,186
Long-term investments	570	570
Total assets	$ 415,095	$ 438,683
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 2,889	$ 5,524
Accrued compensation	2,100	3,330
Accrued liabilities	10,971	6,794
Amount due to affiliates	—	5,193
Current portion of long-term obligations	20,602	21,435
Current portion of deferred contract revenues	30,597	33,674
Total current liabilities	67,159	75,950

5 1/2% convertible subordinated notes	125,000	125,000
Long-term obligations, less current portion	74,951	67,893
Long-term deferred contract revenue, less current portion	13,710	14,363
Stockholders' equity:		
Series B Convertible Exchangeable 5% Preferred stock, $.001 par value; 16,620 shares authorized, 12,015 shares issued and outstanding at March 31, 2003 and December 31, 2002	12,015	12,015
Accretion of Series B Preferred stock dividends	2,037	1,866
Common stock, $.001 par value; 100,000,000 shares authorized, 55,376,983 shares and 55,215,785 shares issued and outstanding at March 31, 2003 and December 31, 2002, respectively	55	55
Additional paid-in capital	602,974	602,101
Deferred compensation	(22)	(59)
Accumulated other comprehensive income (loss)	1,602	(608)
Accumulated deficit	(484,386)	(459,893)
Total stockholders' equity	134,275	155,477
Total liabilities and stockholders' equity	$ 415,095	$ 438,683

Note: The balance sheet at December 31, 2002 has been derived from the audited financial statements at that date.

See accompanying notes

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

	Three months ended March 31,	
	2003	**2002**
Revenue:		
Research and development revenue under collaborative agreements	$ 13,780	$ 14,714
Research and development revenue from affiliates	—	3,034
Licensing and royalty revenue	200	211
Total revenue	13,980	17,959
Expenses:		
Research and development	30,261	26,983
General and administrative	2,622	2,226
Compensation (benefit) related to stock options	9	(1,532)
Total operating expenses	32,892	27,677
Loss from operations	(18,912)	(9,718)
Other income (expenses):		
Equity in loss of affiliates	—	(5,767)
Investment income	1,636	2,144
Interest expense	(4,608)	(4,631)
Loss on investments	(2,438)	—
Net loss	(24,322)	(17,972)
Accretion of dividends on preferred stock	(171)	(335)
Net loss applicable to common stock	$ (24,493)	$ (18,307)

Basic and diluted net loss per share	$ (0.44)	$ (0.34)
Shares used in computing basic and diluted net loss per share	55,375	53,923

See accompanying notes

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

	Three months ended March 31,	
	2003	2002
Net cash used in operating activities	$ (18,005)	$ (15,730)
Investing activities:		
Short-term investments, net	(20,959)	(17,259)
Purchase of property, plant and equipment	(3,554)	(6,230)
Other assets	(1,365)	(1,485)
Investments in affiliates	(5,193)	(2,332)
Net cash used in investing activities	(31,071)	(27,306)
Financing activities:		
Net proceeds from issuance of equity	902	2,021
Proceeds from long-term borrowings	9,524	7,332
Principal payments on debt and capital lease obligations	(2,114)	(880)
Net cash provided from financing activities	8,312	8,473
Net decrease in cash and cash equivalents	(40,764)	(34,563)
Cash and cash equivalents at beginning of period	101,856	127,011
Cash and cash equivalents at end of period	$ 61,092	$ 92,448
Supplemental disclosures of cash flow information:		
Interest paid	$ 273	$ 207

See accompanying notes

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED FINANCIAL STATEMENTS
March 31, 2003
(Unaudited)

1. Basis of Presentation

The unaudited interim financial statements for the three-month periods ended March 31, 2003 and 2002 have been prepared on the same basis as the Company's audited financial statements for the year ended December 31, 2002. The financial statements include all adjustments (consisting only of normal recurring adjustments), which the Company 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, 2002 included in the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission.

2. Significant Accounting Policies

Revenue Recognition

The Company recognizes revenue when all contractual obligations have been satisfied and collection of the resulting receivable is reasonably assured.

Research and development revenue under collaborative agreements

The Company recognizes research and development revenue under collaborative agreements as it incurs the related expenses, up to contractual limits. The Company defers payments received under these agreements that are related to future performance and records revenue as it is earned over the specified future performance period. The Company recognizes revenue that relates to nonrefundable, upfront fees over the period of the contractual arrangements as it satisfies its performance obligations. The Company recognizes revenue that relates to milestones, under existing arrangements, upon completion of the milestone's performance requirement. The Company records revenue from federal research grants during the period in which it incurs the related expenditures. The Company recognizes revenue from product sales as it ships the products.

As part of the Company's alliance with Eli Lilly and Company, Lilly provided Isis a $100.0 million interest free loan to fund the research collaboration. As of March 31, 2003, the Company had drawn down $55.0 million on the $100.0 million loan. The Company discounted the $55.0 million 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. The Company accounts for this value as deferred revenue and recognizes it as revenue over the period of performance.

Research and development revenue from affiliates

The Company recognized research and development revenue from affiliates as it incurred the related expenses, up to contractual limits. The Company recognized revenue related to milestones upon completion of the milestone's performance requirement.

Licensing and royalty revenue

The Company recognizes licensing and royalty revenue immediately, if collectibility is reasonably assured, for arrangements in which the Company is not required to provide services in the future.

Concentration of Credit Risk

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

Cash, Cash Equivalents and Short-Term Investments

The Company considers all liquid investments with maturities of ninety days or less when purchased to be cash equivalents. The Company's short-term investments have initial maturities of greater than ninety days from date of purchase. The Company classifies its securities as "available-for-sale" in accordance with SFAS 115, *Accounting for Certain Investment in Debt and Equity Securities*. The Company 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. The cost of debt securities sold is based on the specific identification method. The Company includes gross realized gains and losses in investment income and these amounts have not been material. To date, the Company has not had any material losses related to its cash or cash equivalents. During the first quarter of 2003, the Company recorded a non-cash loss of $2.4 million related to the impairment of its equity investments in Antisense Therapeutics Limited and Hybridon, Inc. This charge reflects the current market climate and is associated with the decline in market value of the equity investments from their initial valuations and is determined to be other than temporary.

Inventory Valuation

The value at which the Company carries its inventory directly impacts the Company's results of operations. The Company's inventory primarily consists of drugs it manufactures for its partners under contractual terms. The Company states its inventories at the lower of cost or market, with cost determined under the first-in, first-out method. The Company reviews inventories periodically and reduces the carrying value of items considered to be slow moving or obsolete to its estimated net realizable value. Inventory includes the following categories as of March 31, 2003 and December 31, 2002, net of reserves (in thousands):

	March 31, 2003	December 31, 2002
Raw materials	$ 10,235	$ 10,186
Work-in-process	4,228	904
	$ 14,463	$ 11,090

Use of Estimates

The preparation of 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 financial statements and accompanying notes. Actual results could differ from those estimates.

Stock-Based Employee Compensation

The Company has adopted the disclosure-only provision of SFAS 123, *Accounting for Stock-Based Compensation*. Accordingly, no compensation expense has been recognized for the Company's stock option plans. Had compensation expense been determined consistent with SFAS 123, Isis' net loss and

basic and diluted net loss per share would have been changed to the following pro forma amounts (in thousands, except per share amounts):

	Three Months Ended March 31,	
	2003	2002
Net loss applicable to common stock	$ (24,493)	$ (18,307)
Stock based compensation	(3,028)	(6,057)
Pro forma net loss	$ (27,521)	$ (24,364)
Earnings per share:		
Basic and diluted	(0.44)	(0.34)
Basic and diluted, pro forma	(0.50)	(0.45)

The fair value of each option grant is estimated on the date of grant using the Black-Scholes option pricing model with the following assumptions for March 31, 2003 and 2002: 1) a risk-free interest rate of 3.8% each year; 2) a dividend yield of 0% each year; 3) a volatility factor of 82.1% and 78.7%, respectively, and 4) an option life of 5.5 and 5.4 years, respectively. The weighted average fair value of options granted was $6.72 and $20.38 for March 31, 2003 and 2002, respectively.

Impact of Recently Issued Accounting Standards

In November 2002, the Emerging Issues Task Force issued 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. EITF 00-21 will be effective for revenue arrangements entered into in fiscal quarters beginning after June 15, 2003. The Company is reviewing EITF 00-21 and has not yet determined the impact this issue will have on its operating results and financial position.

In December 2002, the Financial Accounting Standards Board issued SFAS 148, *Accounting for Stock-Based Compensation—Transition and Disclosure*, effective for fiscal years ending after December 15, 2002. The rule amends SFAS 123 to provide several alternatives for adopting the stock option expense provisions of SFAS 123, as well as additional required interim financial statement disclosures. SFAS 148 does not require companies to expense stock options in current earnings. The Company has not adopted the provisions of SFAS 123 for expensing stock based compensation; however, the Company has adopted the additional interim disclosure provisions of the statement (see *Stock-Based Employee Compensation above)*. The impact of the new standard is not expected to have a material impact on the results of operations or the financial position of the Company.

3. Strategic Alliances

Affiliates

Orasense

Due to the significant minority investor rights retained by Elan and its subsidiaries, the Company accounted for its investment in Orasense under the equity method of accounting. Through December 2002, Orasense incurred research and development expenses, performed by Elan and the Company on Orasense's behalf, in the course of its product development. In conjunction with its continuing restructuring efforts, Elan concluded its participation in the Orasense collaboration effective December 31, 2002, and the Company reacquired all rights to ISIS 104838, the compound being developed by the collaboration. The collaboration had no activity during the three months ended

March 31, 2003. The following table presents summary results of operations for the quarter ended March 31, 2002 for Orasense (in thousands):

	Three Months Ended March 31, 2002
Revenue	$ —
Research and development expense	3,231
Net loss	$ (3,231)

HepaSense

Due to the significant minority investor rights retained by Elan and its subsidiaries, the Company accounted for its investment in HepaSense under the equity method of accounting. At inception, Elan granted to HepaSense a license to its intellectual property for $15.0 million. Through December 2002, HepaSense incurred research and development expenses, performed by Elan and the Company on HepaSense's behalf, in the course of its product development. In conjunction with its continuing restructuring efforts, in 2002, Elan concluded its participation in the HepaSense collaboration and the Company reacquired all rights to ISIS 14803, the compound being developed by the collaboration. The collaboration had no activity during the three months ended March 31, 2003. The following table presents summary results of operations for the quarters ended March 31, 2002 for HepaSense (in thousands):

	Three Months Ended March 31, 2002
Revenue	$ —
Research and development expense	3,969
Net loss	$ (3,969)

Amgen

In February 2003, the Company earned a second research milestone in its drug discovery collaboration with Amgen, which was initiated in December 2001. Amgen and the Company collaborate to discover and develop new antisense drugs utilizing the Company's proprietary second-generation chemistry. Amgen has the right to develop and commercialize antisense drugs resulting from the collaboration.

4. Comprehensive Loss

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

	Statements of Comprehensive Loss (Unaudited) Three Months Ended March 31,	
	2003	2002
Comprehensive loss:		
Change in unrealized gains (losses) on available for sale securities	$ 2,210	$ (2,705)
Net loss	(24,493)	(18,307)
Comprehensive loss	$ (22,283)	$ (21,012)

5. Restructuring

In November 2002, the Company discontinued its GeneTrove database product offering and reorganized the GeneTrove division. As a result, the Company reduced its workforce by approximately 25 people. The restructuring plan also provided for the write-down of certain intellectual property. As a result of this plan, the Company recognized restructuring related charges of approximately $1.4 million as operating expenses in the fourth quarter of 2002. The Company did not recognize any additional restructuring related charges in the first quarter of 2003 and expects to complete utilization of the reserve related to this restructuring by October 2003.

The following table summarizes the balance of the accrued restructuring reserve, which has been included in accrued liabilities at March 31, 2003 (in thousands):

	Severance Cost For Involuntary Employee Terminations
Balance at December 31, 2002	$ 389
Reserve established	—
Utilization of reserve:	
Cash	(257)
Non-cash	—
Balance at March 31, 2003	$ 132

6. Subsequent Events

In April 2003, the Company initiated a restructuring in response to disappointing results from the first Phase III trial of Affinitak. As a result, the Company reduced its workforce by 9%, which primarily represented positions that were in support of the commercialization and manufacture of Affinitak. Consequently, the Company will incur a one-time restructuring charge of approximately $1.8 million during the second quarter of 2003 and expects to complete the utilization of the reserve related to this restructuring in the fourth quarter of 2003.

In April 2003, the Company implemented an employee stock option exchange program to ensure that Isis maintains one of its key assets, its employee base, in a manner that is sensitive to shareholder interests. The program allowed employees, during the offering period beginning on April 8, 2003 through May 8, 2003, to elect to surrender higher-priced options, granted prior to January 5, 2002, in exchange for a lesser number of lower priced options. Employees exchanged 2.2 million options with a weighted average exercise price of $14.89 for 1.0 million options with an exercise price of $5.15. The new options have a three-year vesting period that began on January 1, 2003. In addition, the new options expire on December 31, 2008. The Company will account for the affected options based on changes in the market value of the Company's common stock.

In April 2003, the Company earned a $1.5 million milestone from Lilly in the development of ISIS 23722, the antisense inhibitor of survivin, as part of its oncology expansion entered into in fiscal year 2002 with Lilly. ISIS 23722 is the first compound from the partnership to be selected for clinical development by Lilly, which resulted in the milestone.

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

In addition to historical information contained in this Report, this Report contains forward-looking statements regarding our business 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. Such statements are subject to certain risks and uncertainties, particularly those risks and uncertainties inherent in the process of discovering, developing and commercializing drugs that can be proven to be safe and effective for use as human therapeutics, in the process of conducting gene functionalization and target validation services, and in the endeavor of building a business around such products and services. Actual results could differ materially from those discussed in this Form 10-Q. 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, 2002, 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 18 of this Report. As a result, you are cautioned not to rely on these forward-looking statements.

Since our inception in 1989, we have pioneered the science of antisense for the development of a new class of drugs. We design 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 a broad pipeline of 13 antisense products currently in all phases of clinical development. Our drugs in development treat a variety of health conditions, including inflammatory, viral, metabolic and dermatological diseases, and cancer, and we are studying these drugs in intravenous, subcutaneous, topical cream, enema and oral formulations. We achieved marketing clearance for the world's first antisense drug Vitravene® (fomivirsen) in 1998.

Affinitak, formerly LY900003 or ISIS 3521, is our most advanced product in development. We recently announced the results of our Phase III clinical trial of Affinitak to treat patients with non-small cell lung cancer. In this 616-patient trial, we observed no difference in overall survival of those patients who received Affinitak plus the chemotherapy regimen of carboplatin and paclitaxel compared to those patients who received the chemotherapy alone. Survival was the primary endpoint. The median survival for the Affinitak treated patients was ten months, compared to 9.7 months for those patients treated with the chemotherapy alone. Additional analyses of the data, however, suggest that Affinitak was active in this trial. For example, using an alternative statistical analysis of all 616 patients, which considered predefined variables, including duration of treatment, survival of the Affinitak treated patients was greater than that of patients in the control group. This result was statistically significant. Lilly and we are performing an analysis of the data and expect to submit the complete findings from this trial for scientific presentation at an appropriate medical meeting later this year. In a second Phase III study, Lilly is continuing to follow patients currently enrolled, but has suspended further enrollment in this study and other studies of Affinitak. Pending a review upon completion of the second Phase III trial, Lilly and we will make a decision about the future development of Affinitak.

We currently have two on-going Phase III clinical trials for another product, ISIS 2302, or alicaforsen, in an inflammatory bowel disease known as Crohn's disease. These trials are being conducted in North America and Europe. We have five additional products undergoing Phase II clinical trials.

Our GeneTrove division uses our antisense technology as a tool to provide important information about the function of genes. We use this information to direct our own drug discovery research and that of our antisense drug discovery partners, such as Lilly and Amgen. We generate this information

rapidly and efficiently using the same proprietary methods and systems that we developed to create antisense drugs. We offer antisense-based gene function information and license our antisense based functional genomics patents to pharmaceutical company partners that are evaluating the genes as targets for their own drug discovery programs. We currently collaborate with 7 major pharmaceutical partners, including Amgen Inc.; Celera Genomics Group; Chiron Corporation; Eli Lilly and Company; GlaxoSmithKline plc; Merck & Co., Inc. and Pharmacia Corporation. We also license our technology to our partners to support their use of antisense, independent of a collaboration with us. Sequitur, Pfizer and atugen AG are examples of such licensees.

In November 2002, we announced the termination of GeneTrove's subscription database product originally added in August 2001. This resulted in a reorganization of the GeneTrove division. Our GeneTrove division continues to generate near-term revenue while enhancing our own antisense drug discovery efforts and our patent portfolio.

Our Ibis division has invented platform technology that has the potential to revolutionize the detection and treatment of infectious disease. We are creating a sensor that can detect known and unknown infectious agents, and are working to discover small molecule drugs that work by binding to RNA. Our scientists have invented methods of identifying common binding sites in RNA that facilitate the identification of organisms or serve as targets for drug binding. We have also invented mass spectrometry-based screening methods for both diagnostic and drug discovery applications.

In a program called Triangulation Identification for Genetic Evaluation of Risks, or TIGER, we apply our Ibis technology to develop a sensor to detect infectious agents that could be used in biological warfare attacks. We collaborate with San Diego-based Science Applications International Corporation, or SAIC, on this multi-year program funded by the Defense Advanced Research Projects Agency, or DARPA. Ibis expects to receive funding of up to $11.7 million for its efforts related to TIGER, which has been increased by $2.8 million over the original contract of October 2001.

Since the division's inception, Ibis has received significant financial support from various government agencies to use its technology to develop broad-spectrum anti-infective drugs that we believe will have usefulness in national defense. In early 2002, Ibis received a three-year contract to continue its drug discovery program with the U.S. Army Medical Research Institute of Infectious Diseases, or USAMRIID. The contract provides for funding of up to $2.4 million.

In addition to DARPA and USAMRIID, Ibis also has research relationships with several other government entities including the United States Navy, the Federal Bureau of Investigation and the Center for Disease Control and Prevention.

Critical Accounting Policies

We prepare our 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 estimates and assumptions affect the reported balances and amounts within our financial statements and supporting notes. The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, include the following:

Revenue Recognition

We generally recognize revenue when we have satisfied all contractual obligations and we are reasonably assured of collecting the resulting receivable. We often enter into collaborations where we receive nonrefundable up-front payments for prior or future expenditures. In compliance with current accounting rules, we recognize revenue related to up-front payments 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 obligation when the information is not clearly defined in the agreements we enter into. Should different estimates prevail, revenue recognized could be materially different. Agreements where we have made estimates of our continuing obligations include our collaborations with Antisense Therapeutics Limited, Amgen, Chiron, Lilly, Merck and Pfizer. As of March 31, 2003, we evaluated our estimates for the periods of contractual arrangements and determined that our estimates are appropriate.

We recognize revenue related to milestones upon completion of the milestone's performance requirement. During the first quarter 2003, we earned a milestone through our research collaboration with Amgen. In addition, in April 2003, we earned a $1.5 million milestone from Lilly in the development of ISIS 23722, the antisense inhibitor of survivin, as part of our oncology expansion entered into in 2002 with Lilly. ISIS 23722 is the first compound from the partnership to be selected for clinical development by Lilly, which resulted in the milestone.

In November 2002, the Emerging Issues Task Force issued 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. EITF 00-21 will be effective for revenue arrangements entered into in fiscal quarters beginning after June 15, 2003. We are reviewing EITF 00-21 and have not yet determined the impact this issue will have on our operating results and financial positions.

We generally recognize revenue related to the sale of our inventory as we ship or deliver drugs to our partners. Occasionally, we complete the manufacturing of drugs, but our partners ask us to deliver the drug on a later date. Under these circumstances, we ensure that our obligation is complete under the terms of the manufacturing agreement in place and title has transferred to the customer before we recognize the related revenue.

As part of our Lilly alliance, Lilly provided us a $100.0 million interest free loan to fund the research collaboration. As of March 31, 2003, we had drawn down $55.0 million on the $100.0 million loan. We discounted the $55.0 million that had been drawn on the loan as of March 31, 2003 to its 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. 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, and is accounted for as deferred revenue and is recognized as revenue over the period of performance.

Additionally, we recognize as revenue immediately those licensing and royalty agreements we enter into for which we have no future performance obligations and are reasonably assured of collecting the resulting receivable.

Inventory Valuation

The value at which we carry our inventory directly impacts our results of operations. Our inventories primarily consist of drugs we manufacture for our partners under contractual terms. Our inventories are stated at the lower of cost or market, cost being determined under the first-in, first-out method. We review inventories periodically and reduce our carrying value of items considered to be slow moving or obsolete to its estimated net realizable value.

Valuation of Intellectual Property

We evaluate our licenses and patent assets for impairment on a quarterly basis, and whenever indicators of impairment exist. During this process, we review our portfolio of 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 challenges or

potential challenges to our existing patents, the likelihood of applications being issued, the scope of our issued patents and our experience. In the event that we determine that an impairment exists where we had previously determined that one did not exist, it may result in a material adjustment to our financial statements.

Valuation of Short-Term Investments

We primarily invest our excess cash in U.S. Government securities and debt instruments of financial institutions and corporations with strong credit ratings. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. These guidelines are periodically reviewed and modified to take advantage of trends and interest rates. In determining if and when a decline in market value below amortized cost is other-than-temporary, we, together with our external portfolio managers, evaluate the market conditions, offering prices, trends of earnings, price multiples, and other key measures for our investments in debt instruments. To date, we have not had any material losses related to our cash or cash equivalents.

We also have equity investments in biotech companies where we have an ownership interest of less than 20%. In determining if and when a decrease in market value below our cost is other-than-temporary in our equity positions, we examine historical trends in stock price, the financial condition and near term

prospects of the issuer, and our current need for cash. When such a decline in value is deemed to be other-than-temporary, we recognize an impairment loss in the period operating results to the extent of the decline. During the first quarter of 2003, we recorded a non-cash loss of $2.4 million related to the impairment of our equity investments in ATL and Hybridon, Inc. This charge reflects the current market climate and is associated with the decline in market value of the equity investments from their initial valuations and is determined to be other than temporary.

Use of Estimates

In preparing our financial statements to conform with accounting principles generally accepted in the United States, we make estimates and assumptions that affect the amounts reported in our financial statements and accompanying notes. These estimates include useful lives for fixed assets for depreciation calculations, useful lives for intellectual property for amortization calculations, estimated lives for license agreements related to deferred revenue, valuation of inventory, and assumptions for valuing stock options. Actual results could differ from these estimates.

Results of Operations

Revenue

Our total revenue was $14.0 million for the three months ended March 31, 2003, compared with $18.0 million for the same period in 2002. In 2002, Isis reacquired product rights to ISIS 14803 for hepatitis C and an oral formulation of ISIS 104838 as a result of Elan Corporation's conclusion of its participation in the HepaSense and Orasense joint ventures. As a result, we did not earn revenue from these affiliates in the first quarter of 2003. This was the primary reason for the $4.0 million decrease in total revenue in the first quarter of 2003 compared to the same period of 2002.

Under the category of research and development revenue under collaborative agreements for the quarter ended March 31, 2003, we reported $13.8 million, compared to $14.7 million for the same period in 2002. The decrease of $0.9 million was primarily a result of drug shipments occurring in the first quarter of 2002 that were absent in the same quarter of 2003.

Research and development revenue from affiliates for the quarter ended March 31, 2002 consisted of revenue associated with our two joint ventures with Elan, Orasense and HepaSense. For the three months ended March 31, 2002, we recognized $1.6 million and $1.4 million from Orasense and

HepaSense, respectively, as revenue. During the same period in 2003, we did not earn revenue from these affiliates as Elan concluded its participation in the joint ventures in 2002.

Our revenue from licensing activities and royalties was $0.2 million for the periods ended March 31, 2003 and March 31, 2002.

Operating Expenses

Total operating expenses for the quarter ended March 31, 2003 totaled $32.9 million, compared to $27.7 million for the same period of 2002. The increase of $5.2 million was primarily the result of a $3.3 million increase in research and development expenses and a $0.4 million increase in general and administrative expenses. In addition, during the first quarter of 2003, we reported $9,000 in compensation expense related to stock options as a result of options granted to consultants, compared to a $1.5 million compensation benefit recorded for the same period of 2002 related to stock options accounted for as variable stock options.

Our research and development expenses consist of costs for antisense drug discovery, including GeneTrove, antisense drug development, our Ibis Therapeutics' division and R&D Support costs. For the quarter ended March 31, 2003, we reported total research and development expenditures of $30.3 million, compared to $27.0 million reported in 2002. The $3.3 million increase in 2003 over 2002 was primarily due to an increase in our antisense drug discovery costs and the investment in our 13 products in development, including costs for the Phase III trials for Affinitak and alicaforsen for Crohn's disease.

Antisense drug discovery costs for the quarter ended March 31, 2003 totaled $10.0 million compared to $8.8 million for the same period of 2002. The increase of $1.2 million was principally a result of increased gene functionalization and target validation activities to support our in-house drug discovery programs and our research collaborations with Lilly, including the expansion into oncology, and with Amgen.

Antisense drug development expenditures totaled $12.1 million and $11.5 million for the three months ended March 31, 2003 and 2002, respectively. The increase of $0.6 million consists of additional expenses resulting from the advancement of our pipeline, including the increased costs related to the Phase III trial of Affinitak for non-small cell lung cancer and two Phase III trials of alicaforsen for Crohn's disease, with the second trial initiated in June 2002. The increases resulting from our Phase III trials were partially offset by a decrease in expenditures related to our other products in development.

Expenditures related to Affinitak for the quarter ended March 31, 2003 were $2.9 million, compared to $2.5 million reported for the same period of 2002. The increase of $0.4 million was primarily a result of costs related to our Phase III trial entering its final stage, which included increased expenses related to data analysis. We recently announced the results of Affinitak for the treatment of non-small cell lung cancer. In this trial, we observed no difference in overall survival of those patients who received Affinitak plus a standard chemotherapy regimen compared to those patients who received the standard chemotherapy alone. Survival was the primary endpoint. The median survival for the Affinitak treated patients was ten months, compared to 9.7 months for those patients treated with the standard chemotherapy alone. Based on these results, we will not file an NDA for Affinitak in 2003.

In April 2003, we initiated a restructuring of the company in response to disappointing results from the first Phase III trial of Affinitak. As a result, we reduced our workforce by 9%, which primarily represented positions that were in support of the commercialization and manufacture of Affinitak. Consequently, we will incur a one-time restructuring charge of approximately $1.8 million during the second quarter of 2003 and we expect to complete the utilization of the reserve related to this restructuring in the fourth quarter of 2003. As a result of disappointing results from the first Phase III

trial of Affinitak and no NDA filing in 2003, we expect a decrease in total Affinitak related expenses for the 2003 year compared to 2002.

Our second drug in Phase III clinical trials, alicaforsen for Crohn's disease, had development expenditures totaling $1.8 million for the three months ended March 31, 2003, compared to $1.5 million for the same period of 2002. The increase of $0.3 million is a result of the initiation of our second Phase III trial in June 2002 in Europe, which resulted in additional expenses for the first quarter 2003 over the same period of 2002.

Expenditures related to our other products in development totaled $4.9 million in the first quarter of 2003, compared to $5.4 million for the same period of 2002. The decrease of $0.5 million was primarily attributed to decreased expenses on our early stage products, including ISIS 107248 and ISIS 112989, as our partners from our drug development collaborations agreed to perform continued development of certain drugs. This decrease was partially offset by increased expenses related to increased enrollment in Phase II trials associated with alicaforsen for ulcerative colitis and ISIS 104838 for rheumatoid arthritis.

Ibis expenditures for the three months ended March 31, 2003 totaled $2.6 million, compared to $2.0 million in 2002. The increase of $0.6 million was primarily related to Ibis' performance obligations under its multi-year government contracts with DARPA, awarded in October 2001, and USAMRIID, awarded in March 2002.

R&D Support costs for the three months ended March 31, 2003 totaled $5.6 million, compared to $4.7 million for 2002. The increase of $0.9 million is a direct result of increases in our research and development efforts to prepare for the manufacture and commercialization of Affinitak. While we work to control R&D Support costs, we expect that they will be directly related to fluctuations in our research and development expenses.

General and administration expenses for the three months ended March 31, 2003 totaled $2.6 million compared to $2.2 million for the same period of 2002. The increase of $0.4 million in 2003 over 2002 was primarily a result of an increase in employees and related benefits.

Compensation expense related to stock options for the quarter ended March 31, 2003 totaled $9,000. The expense relates to stock options granted to consultants. We account for these options in accordance with EITF 96-18. For the quarter ended March 31, 2002, we reported a benefit of $1.5 million, which represents a reversal of previously recorded compensation expense related to stock options accounted for as variable stock options. This benefit was associated with an option exchange program we offered to non-officer employees in January 2000. As of December 31, 2002, these variable stock options were either exercised or cancelled. These exchanged options were required to be accounted for as variable stock options in accordance with Accounting Principles Board Opinion No. 25 and Financial Accounting Standard Board Interpretation No. 44. Variable stock options can result in significant increases and decreases in compensation expense as a result of the variability in our stock price.

In April 2003, in response to disappointing results from the first Phase III trial of Affinitak and our subsequent restructuring, we implemented an employee stock option exchange program to ensure that we maintain one of our key assets, our employee base, in a manner that is sensitive to our shareholder interests. The program allowed employees, during the offering period beginning on April 8, 2003 through May 8, 2003, to elect to surrender higher-priced options, granted prior to January 5, 2002, in exchange for a lesser number of lower priced options. Employees exchanged 2.2 million options with a weighted average exercise price of $14.89 for 1.0 million options with an exercise price of $5.15. The new options have a three-year vesting period that began on January 1, 2003. In addition, the new options expire on December 31, 2008. We will account for affected options based on changes in the market value of our common stock.

Equity in Loss of Affiliates

We used the equity method of accounting for our investments in the Orasense and HepaSense joint ventures. As a result, we recognized 80.1% of the total loss reported by Orasense and HepaSense under equity loss of affiliates. For the quarter ended March 31, 2003, we did not recognize equity loss of affiliates. This compares to $5.8 million for the same period in 2002. The decrease was a result of Elan's conclusion of its participation in the HepaSense and Orasense joint ventures in 2002. As a result, we reacquired product rights to ISIS 14803 for hepatitis C and an oral formulation of ISIS 104838.

Investment Income

Investment income for the three months ended March 31, 2003 totaled $1.6 million, compared to $2.1 million for 2002. The decrease of $0.5 million is primarily due to our lower average cash balance in the first quarter of 2003 compared to the first quarter of 2002. In addition, our investment income was directly affected by the decline in interest rates as a result of current market conditions.

Interest Expense

Interest expense for the first quarter of 2003 remained unchanged from the same period of 2002. Interest expense was $4.6 million for each of the quarters ended March 31, 2003 and 2002. The effect of a higher debt balance as of March 31, 2003 compared to March 31, 2002 was offset by a decrease in the average interest rate on our debt. The decrease in the average interest rate, which resulted in a net interest savings, is primarily due to the retirement, in May 2002 and July 2002, of higher interest rate debt with the proceeds from the issuance, in May 2002, of our $5^{1}/_{2}$% convertible subordinated notes due 2009.

Net Loss Applicable to Common Stock

For the quarter ended March 31, 2003 and 2002, we reported a net loss of $24.3 million and $18.0 million, respectively. Our net loss applicable to common stock was $24.5 million for the quarter ended March 31, 2003, and $18.3 million in 2002, which included $0.2 million and $0.3 million of accreted dividends on preferred stock as of March 31, 2003 and 2002, respectively. The net loss applicable to common stock for the quarter ended March 31, 2003 included a non-cash loss on investments of $2.4 million related to the impairment of certain of our investments in ATL and Hybridon. This charge reflects the current market climate and is associated with the decline in market value of these equity investments from their initial valuations and is considered to be other than temporary.

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, 2003, we have earned approximately $364.5 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

$588.3 million from the sale of equity securities. We have borrowed approximately $300.1 million under long-term debt arrangements to finance a portion of our operations.

As of March 31, 2003, we had cash, cash equivalents and short-term investments totaling $269.5 million and working capital of $227.5 million. In comparison, we had cash, cash equivalents and short-term investments of $289.4 million and working capital of $244.2 million as of December 31, 2002. The decreases in our cash, cash equivalents and short-term investments and working capital are due primarily to cash used to fund our operations, to purchase property, plant, and equipment and to pay our debt and capital lease obligations.

As of March 31, 2003, our long-term obligations totaled $200.0 million, versus $192.9 million at December 31, 2002. The increase was primarily due to accrued interest on our convertible debt facility with Elan and an additional draw down from the $100.0 million interest-free loan from Lilly. We expect that capital lease obligations will increase over time to fund capital equipment acquisitions required for our growing business. We will continue to use lease financing as long as the terms remain commercially attractive. Based on our current operating plan, we believe that our available cash, cash equivalents and short-term investments at March 31, 2003 when combined with investment income and committed contractual cash payments from our partners, will be sufficient to meet our anticipated requirements for at least the next 36 months.

The following table summarizes our contractual obligations as of March 31, 2003. The table includes $55.0 million drawn down on our $100.0 million interest free loan to fund our Lilly research collaboration. As of March 31, 2003, $20.9 million of the $55.0 million drawn down is accounted for as deferred revenue. The table provides a breakdown of when obligations become due.

	Payments Due by Period (in thousands)				
Contractual Obligations	**Total**	**Less than 1 year**	**1-3 years**	**4-5 years**	**After 5 years**
Debt	$ 233,251	$ 16,926	$ 70,256	$ 5,715	$ 140,354
Capital Lease Obligations	$ 8,246	$ 3,676	$ 4,570	$ —	$ —
Operating Leases	$ 14,287	$ 2,687	$ 4,615	$ 3,670	$ 3,315

Prospective Information

In April 2003, we initiated a restructuring in response to disappointing results from the first Phase III trial of Affinitak. As a result, we reduced our workforce by 9%, which primarily represented positions that were in support of the commercialization and manufacture of Affinitak. Consequently, we will incur a one-time restructuring charge of approximately $1.8 million during the second quarter of 2003 and we expect to complete utilization of the reserve related to this restructuring charge in the fourth quarter of 2003.

In April 2003, we implemented an employee stock option exchange program to ensure that we maintain one of our key assets, our employee base, in a manner that is sensitive to our shareholder interests. The program allowed employees, during the offering period beginning on April 8, 2003 through May 8, 2003, to elect to surrender higher-priced options, granted prior to January 5, 2002, in exchange for a lesser number of lower priced options. Employees exchanged 2.2 million options with a weighted exercise price of $14.89 for 1.0 million options with an exercise price of $5.15. The new options have a three-year vesting period that began on January 1, 2003. In addition, the new options expire on December 31, 2008. We will account for the affected options based on changes in the market value of our common stock.

In April 2003, we earned a $1.5 million milestone from Lilly in the development of ISIS 23722, the antisense inhibitor of survivin, as part of our oncology expansion entered into in 2002 with Lilly. ISIS 23722 is the first compound from the partnership to be selected for clinical development by Lilly, which resulted in the milestone.

RISK FACTORS

Investing in our securities involves a high degree of risk. In addition to the other information in this 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.

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 U.S. 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 such receipt 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 could have a similar negative impact.

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, including Affinitak, are not suitable for commercial use, or if additional testing is required to demonstrate such 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, and the risk that a compound is not safe or effective for use in humans. 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, including some that remain in our pipeline, that have not resulted in proof of efficacy against targeted indications. In March 2003, we reported the results of our Phase III clinical trial of Affinitak in patients with late stage non-small cell lung cancer. In this trial, Affinitak, when added to carboplatin and paclitaxol, failed to demonstrate improved survival sufficient enough to support an NDA filing. A similar result could occur with the Affinitak trial Lilly is currently conducting as well as the trials for our other drugs.

If the market does not accept our products, we are not likely to generate significant 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 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 drug development programs.

We have entered into collaborative arrangements with third parties to develop certain 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 fail 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. Examples of terminated collaborations include the scheduled termination of our Hepatitis C research collaboration with Merck at the end of May 2003, the termination in 2002 of our HepaSense and Orasense collaborations with Elan and the termination of our collaboration with Merck to develop ISIS 113715.

We are collaborating with Lilly to develop Affinitak, our most advanced drug candidate, with Lilly funding Affinitak's development. Lilly could decide to discontinue its funding of Affinitak at any time. The results of our recently completed Phase III clinical trial for Affinitak, the market potential of Affinitak or negative results from Lilly's Phase III clinical trial for Affinitak could influence Lilly's decision to discontinue funding of future Affinitak activities.

Additional drug candidates in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics Limited and OncoGenex Technologies Inc. and Lilly with respect to ISIS 23722, the antisense inhibitor to survivin. If any of these pharmaceutical company partners were to stop funding and/or developing these drug candidates, our business would suffer.

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. Such competition may negatively impact the partners' focus on and commitment to our drug candidate and, as a result, could delay or otherwise negatively affect the commercialization of such drug candidate.

Historically, 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.

In addition, the disappointing results of our recently completed Affinitak Phase III trial could cause our existing partners to reevaluate their commitment to our drug discovery platforms or could impair our ability to attract new collaborative partners. If any of our collaborative partners withdraw their resources or if we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drug candidates could suffer.

If our GeneTrove business cannot market its products and services as planned, we could lose our investment in this technology.

Our business could suffer if pharmaceutical companies do not use our GeneTrove target validation or gene functionalization services. We have invested in the development of a gene target validation and gene functionalization service business for validation and functionalization of gene targets for drug discovery. If pharmaceutical companies fail to use these services due to competition or other factors, our GeneTrove business could fail to make the planned contribution to our financial performance.

For example, in November 2002, we terminated our GeneTrove database product offering and reorganized our GeneTrove division. Consequently, we incurred a one-time charge of approximately $1.4 million associated with the restructuring during the fourth quarter of 2002.

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

Because drug discovery and development and research services 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, 2003, our accumulated losses were approximately $484.4 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 derive our current product revenue solely from sales of Vitravene. 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 fail to obtain timely funding, we may need to curtail or abandon some of our programs.

Most 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, we believe that our available cash, cash equivalents and short-term investments as of March 31, 2003, combined with investment income and committed contractual cash payments will be sufficient to meet our anticipated requirements for at least the next 36 months. If we do not meet our goals to commercialize our drug products and research services or to license our proprietary technologies, we may 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 these 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 the marketing of our target validation service and licensing program; 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 or obtain funds through arrangements with collaborative partners or others. These arrangements may 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. Pharmaceutical products of the chemical class represented by our drug candidates, called oligonucleotides, have never been manufactured on a large scale, and to our knowledge there is no commercial scale oligonucleotide manufacturer in business today. We have a limited 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 cannot successfully operate our Affinitak manufacturing suite, the potential success of Affinitak, our revenues, and our relationship with Lilly could suffer.

Under a commercial supply agreement that we entered into with Lilly, we built a manufacturing suite to manufacture Affinitak. However, the FDA has not yet approved this manufacturing facility for the manufacture of Affinitak, and there is no guarantee that we will receive this approval. We have limited experience in operating these types of facilities on a commercial scale and may not be able to successfully operate the manufacturing suite. If we fail to successfully operate the manufacturing facility or if the FDA does not approve the facility, we may be unable to commercialize or meet the potential demands for Affinitak. This could harm the success of Affinitak, reduce our revenue and disrupt our relationship with Lilly.

Specific difficulties we may encounter related to our manufacturing facility include:

- Governmental regulation of our manufacturing facility, specifically FDA approvals required for the commercial manufacture of Affinitak;
- Cost overruns;
- Reduced yields;
- Delays in the delivery of, or inferior quality of, key components of Affinitak that are supplied by third parties; and

- Other unforeseeable factors inherent in the manufacturing process.

In addition, our manufacturing experience to date has been limited to production of preclinical and clinical quantities of our product candidates and to limited commercial production of Vitravene. As a result, we may not be able to effectively scale-up our production in this facility to meet the potential demand for Affinitak. Therefore, we cannot be certain that our manufacturing facilities or our ability to sustain ongoing production of Affinitak will be able to meet our or Lilly's expectations.

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. Our competitors may succeed in developing drug candidates that are more effective than any drug candidates that we are developing. These competitive developments could make our products obsolete or non-competitive.

Our GeneTrove division competes with other companies in the use of antisense technology, including siRNA, for gene target validation and gene functionalization, as well as with other technologies that are useful for target validation and gene functionalization. Our competition may provide services having more value to potential customers or may market their services more effectively to potential customers. In either case, our gene functionalization and target validation businesses may not contribute to our financial performance as planned.

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 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.

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 litigation or proceedings declared by the U.S. Patent and Trademark Office or the International Trade Commission. 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, such as when a certain product candidate will enter the clinic, when a clinical trial will be completed or when an application for marketing approval will be filed. Our estimates are based on present facts and a variety of assumptions. Many of the underlying assumptions are outside of our control. If milestones are not achieved when we expect them to be, investors could be disappointed and the price of our securities would likely decrease.

For example, since the data from our Phase III trial for Affinitak were not sufficiently positive to support a single study NDA, we now must wait for the results of Lilly's ongoing Phase III Affinitak trial before we reevaluate whether the data are sufficiently positive to support filing an NDA for Affinitak. We expect results from this second Phase III trial in 2004.

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 management. 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 specific clinical trials, including the recently announced Phase III Affinitak results, may make it more challenging to recruit and retain qualified scientific personnel.

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 convertible notes. During the 12 months preceding March 31, 2003, the market price of our common stock has ranged from $2.80 to $18.00 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 $66^{2}/_{3}\%$ 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 Elan International Services, Ltd., Eli Lilly and Company, and Reliance Insurance Company. In the aggregate, these registration rights cover approximately 4,166,667 shares of our common stock, which are currently outstanding and additional shares of our common stock, which may become outstanding upon the conversion of outstanding convertible securities. If these holders exercise their 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.

If the private placement of our $5^{1}/_{2}\%$ convertible subordinated notes violated securities laws, purchasers in the private placement would have the right to seek refunds or damages.

On May 1, 2002, we issued and sold $125 million of $5^{1}/_{2}\%$ convertible subordinated notes due 2009 in a private placement transaction. The initial purchasers of the notes in that offering resold the notes to persons reasonably believed to be qualified institutional buyers (as defined in Rule 144A under the Securities Act) and non-U.S. persons (as defined in Regulation S under the Securities Act). On April 24, 2002, an article appeared in a San Diego newspaper regarding this offering in which one of our officers was interviewed. The newspaper article could form the basis for a claim that we have engaged in an unregistered public offering of the convertible notes in violation of the securities laws. We would dispute any such claim. However, if such a claim were made and it prevailed, the initial purchasers and persons who purchase the convertible notes from the initial purchasers in the private offering would have the right, for a period of one year, to obtain recovery of the consideration paid in connection with their purchase of the convertible notes or, if they have already sold the convertible notes, to recover any losses resulting from their purchase of the convertible notes.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES OF 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

For the period ended March 31, 2003, an evaluation was performed under the supervision and with the participation of our management, including the Chief Executive Officer (CEO) and the Chief Financial Officer (CFO), of the effectiveness of the design and operation of our disclosure controls and procedures. Based on that evaluation, our management, including the CEO and CFO, concluded that our disclosure controls and procedures were effective as of March 31, 2003. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 2003.

PART II—OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

Not applicable

ITEM 2. CHANGES IN SECURITIES

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 AND REPORTS ON FORM 8-K

a. Exhibits

Exhibit Number	Description of Document
99.1-	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.

b. Reports on Form 8-K

On March 17, 2003, the Registrant filed a report on Form 8-K for the announcement of the results of its 600 patient Phase III clinical trial for Affinitak (formerly LY900003 or ISIS 3521) and the related press release dated March 17, 2003.

On May 8, 2003, the Registrant filed a report on Form 8-K for the announcement of its first quarter results and the related press release dated May 8, 2003.

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, M.D., PH.D. Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	May 15, 2003

/s/ B. LYNNE PARSHALL B. Lynne Parshall, Esq.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	May 15, 2003

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 financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officers and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-14 and 15d-14) for the registrant and have:

   a) designed such disclosure controls and procedures 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 quarterly report is being prepared;

   b) evaluated the effectiveness of the registrant's disclosure controls and procedures as of a date within 90 days prior to the filing date of this quarterly report (the "Evaluation Date"); and

   c) presented in this quarterly report our conclusions about the effectiveness of the disclosure controls and procedures based on our evaluation as of the Evaluation Date;

5. The registrant's other certifying officers and I have disclosed, based on our most recent evaluation, 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 in the design or operation of internal controls which could adversely affect the registrant's ability to record, process, summarize and report financial data and have identified for the registrant's auditors any material weaknesses in internal controls; and

   b) any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal controls; and

6. The registrant's other certifying officers and I have indicated in this quarterly report whether there were significant changes in internal controls or in other factors that could significantly affect internal controls subsequent to the date of our most recent evaluation, including any corrective actions with regard to significant deficiencies and material weakness.

Dated: May 15, 2003

/s/ Stanley T. Crooke

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

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 financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4.

The registrant's other certifying officers and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-14 and 15d-14) for the registrant and have:

a) designed such disclosure controls and procedures 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 quarterly report is being prepared;

b) evaluated the effectiveness of the registrant's disclosure controls and procedures as of a date within 90 days prior to the filing date of this quarterly report (the "Evaluation Date"); and

c) presented in this quarterly report our conclusions about the effectiveness of the disclosure controls and procedures based on our evaluation as of the Evaluation Date;

5. The registrant's other certifying officers and I have disclosed, based on our most recent evaluation, 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 in the design or operation of internal controls which could adversely affect the registrant's ability to record, process, summarize and report financial data and have identified for the registrant's auditors any material weaknesses in internal controls; and

b) any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal controls; and

6. The registrant's other certifying officers and I have indicated in this quarterly report whether there were significant changes in internal controls or in other factors that could significantly affect internal controls subsequent to the date of our most recent evaluation, including any corrective actions with regard to significant deficiencies and material weakness.

Dated: May 15, 2003

/s/ B. Lynne Parshall

B. Lynne Parshall, Esq.
Chief Financial Officer

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ISIS PHARMACEUTICALS, INC. FORM 10-Q INDEX
ISIS PHARMACEUTICALS, INC. CONDENSED BALANCE SHEETS (in thousands, except share data)
ISIS PHARMACEUTICALS, INC. CONDENSED STATEMENTS OF OPERATIONS (in thousands, except for per share amounts) (Unaudited)
ISIS PHARMACEUTICALS, INC. CONDENSED STATEMENTS OF CASH FLOWS (in thousands) (Unaudited)
ISIS PHARMACEUTICALS, INC. NOTES TO CONDENSED FINANCIAL STATEMENTS March 31, 2003 (Unaudited)
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Exhibit 99.1

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, 2003, to which this Certification is attached as Exhibit 99.1 (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 15, 2003

/s/ Stanley T. Crooke	/s/ B. Lynne Parshall
Stanley T. Crooke, M.D., Ph.D. Chief Executive Officer	B. Lynne Parshall, Esq. 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.

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CERTIFICATION