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 June 30, 2004

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.)

2292 Faraday Ave., 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 August 3, 2004 was 57,272,534

ISIS PHARMACEUTICALS, INC.
FORM 10-Q

INDEX

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

	June 30, 2004 (Unaudited)	December 31, 2003 (Note)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 30,371	$ 33,117
Short-term investments	116,973	182,387
Contracts receivable	9,593	2,657
Inventory	16,074	13,995
Other current assets	9,281	7,405
Total current assets	182,292	239,561
Property, plant and equipment, net	32,172	34,790
Licenses, net	27,200	28,363
Patents, net	24,691	22,374
Deposits and other assets	8,253	8,479
Long-term investments	5,354	1,375
Total assets	$ 279,962	$ 334,942
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 3,416	$ 3,720
Accrued compensation	3,033	4,149
Accrued liabilities	7,900	6,527
Current portion of long-term obligations	10,260	16,477
Current portion of deferred contract revenue	17,523	14,684
Total current liabilities	42,132	45,557
5 ½% convertible subordinated notes	125,000	125,000
Long-term obligations, less current portion	99,033	88,397
Long-term deferred contract revenue, less current portion	2,186	8,810

Stockholders' equity:		
Series B Convertible Exchangeable 5% Preferred stock, $0.001 par value; 4,605 shares authorized, no shares issued or outstanding at June 30, 2004; 16,620 shares authorized, 12,015 shares issued and outstanding at December 31, 2003	—	12,015
Accretion of Series B Preferred stock dividends	—	2,560
Common stock, $0.001 par value; 100,000,000 shares authorized, 57,119,852 shares and 55,557,253 shares issued and outstanding at June 30, 2004 and December 31, 2003, respectively	57	56
Additional paid-in capital	622,106	604,948
Deferred compensation	(127)	(294)
Accumulated other comprehensive income (loss)	(2,226)	3,476
Accumulated deficit	(608,199)	(555,583)
Total stockholders' equity	11,611	67,178
Total liabilities and stockholders' equity	$ 279,962	$ 334,942

Note: The balance sheet at December 31, 2003 has been derived from the audited consolidated financial statements at that date.

See accompanying notes

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2004	2003	2004	2003
Revenue:				
Research and development revenue under collaborative agreements	$ 8,217	$ 14,900	$ 15,215	$ 28,681
Licensing and royalty revenue	1,626	116	6,931	316
Total revenue	9,843	15,016	22,146	28,997
Operating expenses:				
Research and development	32,036	30,179	60,983	60,439
General and administrative	2,568	2,431	5,021	5,054
Compensation expense (benefit) related to stock options	(3,421)	123	(183)	132
Restructuring activities	—	1,803	—	1,803
Total operating expenses	31,183	34,536	65,821	67,428
Loss from operations	(21,340)	(19,520)	(43,675)	(38,431)
Other income (expenses):				
Investment income	842	1,167	1,975	2,803
Interest expense	(5,451)	(4,745)	(10,555)	(9,352)
Loss on investments	—	—	—	(2,438)
Net loss	(25,949)	(23,098)	(52,255)	(47,418)
Accretion of dividends on preferred stock	(180)	(172)	(361)	(343)
Net loss applicable to common stock	$ (26,129)	$ (23,270)	$ (52,616)	$ (47,761)
Basic and diluted net loss per share	$ (0.47)	$ (0.42)	$ (0.94)	$ (0.86)
Shares used in computing basic and diluted net loss per share	56,111	55,380	55,984	55,378

See accompanying notes

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

	Six Months Ended June 30,	
	2004	2003
Net cash used in operating activities	$ (54,885)	$ (40,308)

Investing activities:		
Purchase of short-term investments	(45,213)	(93,594)
Proceeds from the sale of short-term investments	108,747	110,578
Purchase of property, plant and equipment	(1,637)	(5,343)
Other assets	(3,549)	(2,481)
Strategic investments	(10,000)	—
Investments in affiliates	—	(5,193)
Net cash provided by investing activities	48,348	3,967
Financing activities:		
Net proceeds from issuance of equity	2,573	962
Proceeds from long-term borrowings	12,573	22,116
Principal payments on debt and capital lease obligations	(11,355)	(3,275)
Net cash provided by financing activities	3,791	19,803
Net decrease in cash and cash equivalents	(2,746)	(16,538)
Cash and cash equivalents at beginning of period	33,117	101,856
Cash and cash equivalents at end of period	$ 30,371	$ 85,318
Supplemental disclosures of cash flow information:		
Interest paid	$ 4,525	$ 4,931
Supplemental disclosures of non-cash investing and financing activities:		
Conversion of preferred stock into common stock	$ 14,934	$ —
Decrease in property, plant and equipment and notes payable	$ —	$ 21,200
Decrease in inventory and deferred revenue	$ —	$ 8,750

See accompanying notes

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
June 30, 2004
(Unaudited)

1. Basis of Presentation

The unaudited interim consolidated financial statements for the three and six-month periods ended June 30, 2004 and 2003 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2003. The financial statements include all adjustments (consisting only of normal recurring 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, 2003 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 ("the Company") 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 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. Isis recognizes revenue that relates to milestones upon completion of the milestone's performance requirement, and recognizes revenue from arrangements containing multiple deliverables in accordance with Emerging Issues Task Force ("EITF") Issue No. 00-21, *Accounting for Revenue Arrangements with Multiple Deliverables*. In these cases, the Company recognizes revenue from each element of the arrangement as long as it can determine a separate value for each element, it has completed its obligation to deliver or perform on that element, and is reasonably assured of collecting the resulting receivable. Isis records revenue from federal research grants and contracts 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 ("SAB") No. 104, which was issued in December 2003. SAB No. 104 updates portions of the interpretive guidance included in Topic 13 of the codification of SAB No. 101 in order to make this interpretive guidance consistent with current authoritative accounting and auditing guidance and SEC rules and regulations. SAB No. 104 provides interpretation on selected revenue recognition issues. Under SAB No. 104, revenue should be recognized when it is realized or realizable and earned, and has met 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.

In August 2001, as part of Isis' alliance with Eli Lilly and Company ("Lilly"), Lilly provided Isis a $100.0 million interest free loan to fund the research collaboration. As of June 30, 2004, Isis had drawn down $85.0 million on the $100.0 million loan. Isis discounted the $85.0 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 Statement of Financial Accounting Standards ("SFAS") No. 115, *Accounting for Certain Investments in Debt and Equity Securities*, and carries these investments at fair market value with any unrealized gains and losses recorded as a separate component of stockholders' equity. Isis determines fair value based upon market prices quoted on the last day of the fiscal quarter, and 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. During the first quarter of 2003, Isis recorded a non-cash loss of $2.4 million related to the impairment of its equity investments in Antisense Therapeutics Limited ("ATL") and Hybridon, Inc. ("Hybridon"). This charge reflected the then-current market climate and was associated with the decline in market value of the equity investments from their initial valuations and Isis determined the decline in value to be other-than-temporary. Isis determined that there were no other-than-temporary declines in value for its equity investments during the six months ended June 30, 2004.

Inventory valuation

Isis' inventory includes drugs with alternative uses that are used primarily for its clinical development activities and drug products it manufactures for its partners under contractual terms. Isis states its inventory at the lower of cost or market, with cost determined under the first-in, first-out method. Isis reviews inventory periodically and reduces the carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. For example, in the second quarter of 2003, Isis reduced the carrying value of its raw materials related to Affinitak to zero.

Inventory includes the following categories as of June 30, 2004 and December 31, 2003 (net realizable value in thousands):

	June 30, 2004	December 31, 2003
Raw materials	$ 1,976	$ 1,526
Work in process	11,699	9,920
Finished goods	2,399	2,549
	$ 16,074	$ 13,995

The composition of inventory among raw materials, work-in-process and finished goods fluctuates from period-to-period based on the nature and timing of Isis' manufacturing activities in response to product requirements to support Isis' and its partners' clinical trials.

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 nine years and 15 years.

Patents

Isis capitalizes costs consisting principally of outside legal costs and filing fees related to obtaining patents. Isis reviews costs regularly to determine that they include costs for patent applications Isis is pursuing. Isis evaluates costs related to patents that Isis is not actively pursuing for impairment and writes off the related 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.

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.

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 June 30, 2004, Isis had a collaborative arrangement with Ercole Biotech, Inc. ("Ercole"), a development stage biopharmaceutical company developing drugs based on RNA splicing technology. Isis considers Ercole to be a Variable Interest Entity ("VIE") under the provisions of FIN No. 46. Pursuant to the terms of a Note and Warrant Purchase Agreement (the "Agreement"), during 2003 and early 2004, Isis made cash payments to Ercole of $500,000 and $250,000 respectively; in exchange for a convertible promissory note (the "Note"). Isis expensed the payments when made. The Note is secured by all of Ercole's assets, including intellectual property and licenses, and will convert into securities that Ercole issues in a qualified financing, as defined by the Agreement. Isis is not required to consolidate Ercole's results of operations under FIN No. 46.

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 $3.4 million and $183,000 during the three and six months ended June 30, 2004, respectively.

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 June 30,		Six Months Ended June 30,	
	2004	2003	2004	2003
Net loss applicable to common stock—as reported	$ (26,129)	$ (23,270)	$ (52,616)	$ (47,761)
Net loss applicable to common stock—pro forma	$ (31,425)	$ (21,245)	$ (56,525)	$ (48,751)
Basic and diluted net loss per share—as reported	$ (0.47)	$ (0.42)	$ (0.94)	$ (0.86)
Basic and diluted net loss per share—pro forma	$ (0.56)	$ (0.38)	$ (1.01)	$ (0.88)

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:

	June 30,	
	2004	2003
Risk-free interest rate	4.6%	3.53%
Dividend yield	0%	0%
Volatility	67.8%	85.6%
Expected Life	6.3 years	5.1 years

The weighted average fair values of options granted were $6.94 and $6.92 for the three and six months ended June 30, 2004, respectively. The weighted average fair values of options granted were $5.11 and $5.79 for the three and six months ended June 30, 2003, respectively.

Comprehensive income

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 June 30,		Six Months Ended June 30,	
	2004	2003	2004	2003
Comprehensive loss:				
Change in unrealized gains (losses)	$ (6,973)	$ 1,474	$ (5,702)	$ 3,684
Net loss applicable to common stock	(26,129)	(23,270)	(52,616)	(47,761)
Comprehensive loss	$ (33,102)	$ (21,796)	$ (58,318)	$ (44,077)

Included in comprehensive loss at June 30, 2004 is an unrealized loss of approximately $4.0 million related to Isis' equity investment in Alnylam Pharmaceuticals, Inc. which was part of a strategic alliance between the two companies. Isis does not consider the investment to be other-than-temporarily impaired.

Impact of recently issued accounting standards

In March 2004, the Financial Accounting Standards Board ("FASB") issued EITF 03-01, *The Meaning of Other-Than-Temporary Impairment and Its Application to Certain Investments.* EITF 03-01 requires a three-step model to determine other-than-temporary impairments for all current and future investments in marketable securities, and will be effective for interim and annual reporting periods beginning after June 15, 2004. Isis does not expect that the adoption of EITF 03-01 will have a material impact on its operating results and financial position.

3. Stockholders' Equity

Elan Corporation, plc

In June 2004, Isis entered into an agreement with a subsidiary of Elan Corporation, plc, ("Elan") to acquire Elan's minority interest in Orasense™ and HepaSense™. Through this agreement, Isis eliminated all future royalties to Elan related to the oral delivery platform developed within the Orasense collaboration and to ISIS 14803, Isis' antisense drug for the treatment of the hepatitis C virus, which is currently in Phase 2 clinical trials for the treatment of hepatitis C and was the focus of the HepaSense collaboration. In connection with this agreement, Elan transferred its shares of Isis Series B preferred stock to a third party. Immediately upon transfer, these shares converted into 1,055,502 shares of Isis common stock, eliminating the 5% in-kind dividend, thereby reducing future dilution of approximately 86,000 shares of Isis common stock. Isis also cancelled a warrant Elan held to purchase 14,881 shares of Isis common stock. In addition, a warrant Elan held to purchase 215,000 shares of Isis common stock expired unexercised in April 2004.

4. Strategic Alliances

Eyetech Pharmaceuticals, Inc.

In June 2004, Isis recorded $1.0 million in licensing revenue from Eyetech Pharmaceuticals, Inc. ("Eyetech") related to a milestone associated with the filing of a New Drug Application with the U.S. Food and Drug Administration ("FDA") for Macugen™ for the treatment of wet age-related macular degeneration. Macugen is a non-antisense oligonucleotide (aptamer). In 2002, Eyetech licensed from Isis specific patents necessary to develop, manufacture and commercialize Macugen. Under the terms of the agreement, Isis may earn additional milestone and royalty payments from Eyetech.

Science Applications International Corporation

In March 2004, Isis entered into a two-year contract with Science Applications International Corporation ("SAIC") to further the development of Isis' TIGER biosensor to identify infectious agents in biological warfare attacks. The contract provides for up to $19.5 million in funding by the Defense Advanced Research Projects Agency ("DARPA").

Alnylam Pharmaceuticals, Inc.

In March 2004, Isis entered into a strategic alliance with Alnylam Pharmaceuticals, Inc. ("Alnylam") to develop and commercialize RNAi therapeutics. Under the terms of the agreement, Isis exclusively licensed to Alnylam its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5.0 million license fee, participation in fees for Alnylam's partnering programs, as well as future milestone and royalty payments. In turn, Alnylam nonexclusively licensed Isis its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for single-stranded RNAi therapeutics and to a limited extent for double-stranded RNAi therapeutics. If Isis develops or commercializes an RNAi based drug using Alnylam's technology, Isis will pay Alnylam milestones and royalties.

In March 2004, Isis recorded $5.0 million in licensing revenue from this strategic alliance. As of June 30, 2004, Alnylam had paid $3.0 million of this fee to Isis. The remaining $2.0 million is due and payable to Isis in January 2005, and is reflected in contracts receivable on the accompanying condensed consolidated balance sheet as of June 30, 2004.

In June 2004, Isis recorded $500,000 in licensing revenue from Alnylam related to Alnylam's recently established alliance with Merck to develop and commercialize RNAi therapeutics for ocular diseases.

As part of its strategic alliance with Alnylam, Isis also made a $10.0 million equity investment in Alnylam.

5. Significant Partners and Concentration 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 June 30,		Six Months Ended June 30,	
	2004	2003	2004	2003
Partner A	33%	70%	27%	69%
Partner B	29%	14%	23%	13%
Partner C	12%	—	7%	—
Partner D	10%	—	5%	—
Partner E	5%	—	25%	—

For the three and six months ended June 30, 2004, Isis derived approximately 43% and 32%, respectively, of its revenue directly or indirectly from agencies of the U.S. Government. For the three and six months ended June 30, 2003, Isis derived approximately 17% and 16%, respectively, of its revenue directly or indirectly from agencies of the U.S. Government.

Contract receivables from four significant partners comprised approximately 39%, 26%, 11% and 10% of contract receivables at June 30, 2004. Contract receivables from a single partner comprised approximately 49% of contract receivables at December 31, 2003.

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, 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 developing technology and systems used to identify infectious agents, in discovering and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such products and services. Actual results could differ materially from those discussed in this Report on 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, 2003, 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 21 of this Report. 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 10 antisense drugs currently in all phases of clinical development. Our drugs in development treat a variety of health conditions, including metabolic, cardiovascular, inflammatory and viral diseases, and cancer. We are studying these drugs in intravenous, subcutaneous, enema, aerosol, and oral formulations, and we are advancing antisense drugs using second-generation chemistry. We achieved marketing clearance for the world's first antisense drug, Vitravene (fomivirsen) in 1998.

Affinitak™, formerly LY900003 or ISIS 3521, which we licensed to Lilly in 2001, is our most advanced product in development. In March 2003, we announced the results of our Phase III clinical trial of Affinitak to treat patients with non-small cell lung cancer, which were not sufficient to support a single study new drug application. Lilly and we completed an analysis of the data from this trial and presented a summary of the findings at the 39th Annual Meeting of the American Society of Clinical Oncology in June 2003. In a second Phase III study, Lilly is continuing to follow enrolled patients. Lilly and we will make a decision about the future development of Affinitak pending a review upon completion of the second Phase III trial, which is planned to occur in the second half of 2004.

We are conducting two Phase III clinical trials for another product, alicaforsen, or ISIS 2302, in an inflammatory bowel disease known as Crohn's disease. These trials are being conducted in North America, Europe, and Israel. In addition, we are conducting two Phase II studies of alicaforsen in patients with ulcerative colitis. We plan to report data from these clinical trials by the end of 2004.

We recently announced that we are accelerating development of the oral formulation of ISIS 104838 for the treatment of rheumatoid arthritis (RA) and that we plan to initiate a Phase II trial comparing the oral and subcutaneous formulations of ISIS 104838 in patients with RA. In the planned study, which will be conducted outside the U.S., ISIS 104838 will be dosed in combination with methotrexate, a commonly used treatment for RA. We expect to initiate this trial in mid-2005. To support oral dosing in the new trial, we plan to complete ongoing oral delivery trials and conduct an additional preclinical safety study of oral ISIS 104838. In addition, to provide the U.S. Food and Drug Administration with additional information on the safety profile of ISIS 104838, we will conduct a preclinical safety study to reevaluate high dose toxicities and recovery from them. We will also conduct an additional preclinical study to evaluate nine months of dosing with ISIS 104838 to support longer dosing. Both studies are required to support further clinical trials in the U.S. In order to move the oral formulation of ISIS 104838 forward aggressively and due to the

number of promising drugs in development for psoriasis, we decided not to initiate additional studies of ISIS 104838 for the treatment of psoriasis.

In addition to our Phase III trials for Affinitak and alicaforsen for Crohn's, and our Phase II trials for ISIS 104838 and alicaforsen for ulcerative colitis, we also have two drugs in Phase II clinical development and four drugs in Phase I clinical or preclinical development.

Our Ibis program has invented a platform technology that has the potential to revolutionize the identification of infectious diseases. Through a project called Triangulation Identification for Genetic Evaluation of Risks, or TIGER, we have applied our proprietary technologies to develop a biological sensor to identify a broad range of infectious organisms in a sample, including organisms that are newly-emerging, genetically altered and unculturable. We have successfully demonstrated proof-of-principle of the TIGER biosensor with the identification of a variety of bacteria and viruses in both environmental and human clinical samples. To date, our Ibis program has received awards and contracts worth up to $55.0 million through our collaborations with agencies of the U.S. Government, including DARPA, the Centers for Disease Control, or CDC, the U.S. Army Medical Research Institute of Infectious Diseases, or USAMRIID, the US Navy, and the Federal Bureau of Investigation, or FBI, among others.

We have a broad patent portfolio covering our technologies. We own or exclusively license more than 1,400 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 more than $42.0 million in license and royalty fees related to our patent portfolio.

The principal purpose of our intellectual property portfolio is to protect our inventions in RNA-based drug discovery. Our intellectual property estate also enables us to expand our pipeline by granting partners limited access to antisense technology, through licenses we grant them. Licensing partnerships may include antisense drug discovery collaborations like those we have with Lilly, Amgen, Antisense Therapeutics, Ltd., and OncoGenex Technologies, Inc., and functional genomics agreements, like our licenses to Chiron, Amgen, Sequitur and atugen AG. We also license our non-antisense patents, as we did to Eyetech Pharmaceuticals, Inc.

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, the Singapore Economic Development Board, or Singapore EDB, and Ercole Biotech, Inc.

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 may periodically 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 propriety of revenue recognition and associated deferred revenue;
- Determination of proper valuation of investments in marketable securities;
- Estimations to assess the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determination of proper valuation of inventory;

- Determination of appropriate cost estimates for unbilled preclinical studies and clinical development activities; and
- Estimation of our net deferred income tax asset valuation allowance.

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, or SAB No. 101, *Revenue Recognition in Financial Statements*, SAB 104, *Revenue Recognition*, and Emerging Issue Task Force, or EITF, No. 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, Amgen, Chiron, Lilly and the Singapore EDB.

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 drawdowns 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 June 30, 2004, we had drawn down $85.0 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 generally recognize revenue related to the sale of our inventory as we ship or deliver drugs to our partners. To date, in two instances, we completed the manufacturing of drugs, but our partners asked us to deliver the drug on a later date. Under these circumstances, we ensured that our obligation was complete under the terms of the manufacturing agreement in place and title had transferred to the customer before we recognized the related revenue.

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 Statement of Financial Accounting Standards, or SFAS, No.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. 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. We recorded these charges based on declines in market value of the equity investments, as compared to their initial valuations, which we determined to be other-than-temporary.

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 No. 144, *Accounting for the Impairment or Disposal of Long-Lived Assets*, or SFAS No. 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 the event that we determine that impairment exists where we had previously determined that it did not exist, we may need to make a material adjustment to our condensed consolidated financial statements. To date, we have experienced no significant impairment of our long-lived assets.

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 second quarter of 2003, we reduced the carrying value of our raw materials related to Affinitak to zero.

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 condensed consolidated financial statements.

Valuation Allowance for Net Deferred Tax Asset

Isis recorded a valuation allowance to offset the 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.

Results of Operations

Revenue

Our total revenue for the three and six months ended June 30, 2004 was $9.8 million and $22.1 million, respectively, compared to $15.0 million and $29.0 million for the same periods in 2003. 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 our partners. Our ability to maintain revenue at current levels will depend on new revenue sources and expansion of existing revenue sources for the remainder of 2004.

Under the category research and development revenue under collaborative agreements, we earned revenue of $8.2 million and $15.2 million for the three and six months ended June 30, 2004, respectively, compared to $14.9 million and $28.7 million for the same periods in 2003. The decrease reflects the completion of Isis' Phase III clinical trial of Affinitak™ and an associated reduction in revenue, which was partially offset by increased revenue from our TIGER biosensor program.

Our revenue from licensing activities and royalties was $1.6 million and $6.9 million, respectively for the three and six months ended June 30, 2004, respectively, compared with $116,000 and $316,000 for the same periods in 2003. The increase for the six months ended June 30, 2004 reflects $5.5 million we earned under our strategic alliance with Alnylam, and a $1 million milestone earned from Eyetech Pharmaceuticals, Inc. associated with Eyetech's filing of a New Drug Application, or NDA, with the U.S. Food and Drug Administration, or FDA, for Macugen™ for the treatment of wet age-related macular degeneration, or AMD.

Operating Expenses

Total operating expenses for the three and six months ended June 30, 2004 of $31.2 million and $65.8 million, respectively, decreased $3.3 million and $1.6 million, respectively, compared to $34.5 million and $67.4 million for the same periods in 2003. The decreases were primarily due to non-cash compensation benefit due to variable accounting for stock options, and by changes in research and development and general and administration expenses as we describe in the following paragraphs. In addition, we incurred restructuring costs of $1.8 million in 2003, and incurred no such charges in 2004. 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 program, and R&D Support costs. For the three and six months ended June 30, 2004, we incurred total research and development expenses of $32.0 million and $61.0 million, respectively, compared to $30.2 million and $60.4 million for the same periods in 2003. The increases were due primarily to increased spending to support our TIGER biosensor program, partially offset by planned expense reductions in other parts of the company that began in the second quarter of 2003.

Antisense drug discovery costs for the three and six months ended June 30, 2004 were $9.3 million and $18.3, respectively, compared to $9.1 million and $19.2 million for the same periods in 2003. The decrease of $900,000 for the six months ended June 30, 2004 was principally the result of our planned expense reductions, which began in the second quarter of 2003. We anticipate that our existing relationships and collaborations, as well as prospective new partners, will continue to help fund our many research programs, as well as contribute to the advancement of the science by funding core antisense technology research.

Antisense drug development expenditures were $12.3 million and $22.7 million for the three and six months ended June 30, 2004, respectively, compared to $13.5 million and $25.6 million for the same periods in 2003. The decrease of $2.9 million for the six months ended June 30, 2004 was primarily due to the completion in 2003 of our Phase III trial of Affinitak, offset in part by increased clinical development expenses for other products in development. 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 variety of 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, we recently decided not to initiate additional studies of ISIS 104838 for the treatment of psoriasis. Generally, a late stage Phase III trial is substantially more expensive than early stage trials, such as Phase I or Phase II. Currently we have 10 drug candidates in various stages of development, including two drugs in Phase III clinical trials, Affinitak and alicaforsen for Crohn's disease.

Expenditures related to Affinitak for the three and six months ended June 30, 2004 were zero and $42,000, respectively, compared to $4.3 million and $7.2 million for the same periods in 2003. The decrease was primarily due to a reduction in costs associated with the development of Affinitak following the disappointing results from the first Phase III trial of Affinitak and the decision not to file an NDA in 2003. Our partner, Lilly, is continuing to follow enrolled patients in a second Phase III trial for Affinitak. Lilly and we will make a decision about the future development of Affinitak pending a review upon completion of this second Phase III trial, which is planned to occur in the second half of 2004.

We incurred development expenditures related to our second drug in Phase III trials, alicaforsen for Crohn's disease of $1.6 million and $3.3 million for the three and six months ended June 30, 2004, respectively, compared to $1.8 million and $3.6 million for the same periods in 2003. This is consistent with our ongoing development efforts for alicaforsen. We plan to report data on our Phase III trials of alicaforsen for Crohn's disease by the end of 2004.

We incurred expenses related to our other products in development of $8.6 million and $15.3 million for the three and six months ended June 30, 2004, respectively, compared to $8.7 million and $13.6 million for the same period in 2003. The increase in the six months ended June 30, 2003, compared to the same period in 2003, is primarily the result of an increase in development activity related to Phase I and Phase II trials for our ulcerative colitis, diabetes, cancer and cardiovascular drugs, as well as expenses related to other products in the early stages of development.

Our Ibis program expenses for the three and six months ended June 30, 2004 were $3.5 million and $6.6 million, respectively, compared to $2.3 million and $4.9 million for the same periods in 2003. The increases were the result of our performance under our contracts with SAIC, USAMRIID, the CDC, and with various other government agencies, primarily in support of our TIGER biosensor program. We include in Ibis 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 Ibis to increase as we continue to expand this business.

R&D Support costs for the three and six months ended June 30, 2004 were $6.9 million and $13.5 million, respectively, compared to $5.1 million and $10.7 million for the same periods in 2003. While we experienced decreases in direct research and development costs during the first three and six months of 2004 as compared to 2003 related to decreased costs for Affinitak and our cost reduction efforts, we did not experience similar reductions in R&D Support costs. A significant portion of R&D Support costs include fixed occupancy and facility costs, patent costs, and personnel costs that support the entire research and development organization. While we work to control our R&D Support costs, we expect that they will increase as we advance the clinical and preclinical development of our products. Specifically, we expect our depreciation and amortization expense to increase as we continue to make investments in capital equipment and patents to support our development activities.

General and administrative expenses for the three and six months ended June 30, 2004 were $2.6 million and $5.0 million, respectively, compared to $2.4 million and $5.1 million for the same periods in 2003. The $200,000 increase for the second quarter of 2004 was primarily related to consulting and outside services for finance, investor relations and business development activities as compared to the second quarter of 2003.

Compensation benefit related to stock options for the three and six months ended June 30, 2004 was $3.4 million and $183,000, respectively, compared to compensation expense of $123,000 and $132,000 for the same periods in 2003. 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.

Investment Income

Investment income for the three and six months ended June 30, 2004 totaled $842,000 and $2.0 million, respectively, compared to $1.2 million and $2.8 million for the same periods in 2003. The decrease in investment income for the first three and six months of 2004 over 2003 was primarily due to our lower average cash balance for the first three and six months of 2004 compared to the first three and six months of 2003. In addition, our investment income was affected by the decline in interest rates as a result of current market conditions.

Interest Expense

Interest expense for the three and six months ended June 30, 2004 totaled $5.5 million and $10.6 million, respectively, compared to $4.7 million and $9.4 million for the same periods in 2003. This increase was due to the effect of a higher debt balance related to the loan to fund our Lilly research collaboration as of June 30, 2004, compared to June 30, 2003. We will continue to make quarterly draw-downs on our $100.0 million loan from Lilly of approximately $5.0 million per quarter through March 2005. As a result, we expect our interest expense to increase throughout 2004.

Net Loss Applicable to Common Stock

For the three and six months ended June 30, 2004, we reported a net loss applicable to common stock of $26.1 million and $52.6 million, respectively, compared to a net loss applicable to common stock of $23.3 million and $47.8 million for the same periods in 2003. Our net loss applicable to common stock included approximately $180,000 and $361,000 of accreted dividends on preferred stock for the three and six months ended June 30, 2004, respectively, compared to $172,000 and $343,000 for the same periods in 2003.

The increases in net loss applicable to common stock for the three and six months ended June 30, 2004 compared to the same period in 2003 were primarily the result of a decrease in revenue, decrease in interest income, and increase in interest expense as described previously. The net effect of these changes was offset in part by compensation benefit related to stock options. In addition, during each of the three and six months ended June 30, 2003, we incurred a charge of $1.8 million related to restructuring activities, and for the six months ended June 30, 2003 we incurred a non-cash loss on investments of $2.4 million related to the other-than-temporary impairment of our investments in ATL and Hybridon. There were no restructuring or impairment charges incurred during the same periods in 2004.

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 June 30, 2004, we have earned approximately $422.6 million in revenue from contract research and development and from the sale and licensing of our intellectual property. Since we were founded, we have raised net proceeds of approximately $591.7 million from the sale of equity securities. We have borrowed approximately $370.0 million under long-term debt arrangements to finance a portion of our operations.

As of June 30, 2004, we had cash, cash equivalents and short-term investments totaling $147.3 million and working capital of $140.2 million. In comparison, we had cash, cash equivalents and short-term investments of $215.5 million and working capital of $194.0 million as of December 31, 2003. Our $100.0 million Lilly research collaboration loan, of which $85.0 million was outstanding as of June 30, 2004, comes due in August 2005. Accordingly, the outstanding balance on this loan will be classified as a current obligation beginning in the third quarter of 2004, which will have a negative impact on our working capital. We can repay this loan at our option in either cash or our common stock at a fixed conversion price of $40 per share. If we draw down the remaining amount available under the loan, we could repay the loan for 2.5 million shares of our common stock. The decreases in our cash, cash equivalents and short-term investments and working capital were due primarily to cash used to fund our operations, to purchase property, plant, and equipment, and to pay our debt and capital lease obligations. In addition, we made a $10.0 million cash investment in Alnylam as part of our strategic alliance with them.

As of June 30, 2004, our debt and other obligations totaled $251.9 million, compared to $250.6 million at December 31, 2003. Our debt and other obligations at June 30, 2004 included current and long-term deferred contract revenue of approximately $19.7 million and contractual obligations that represent our payment obligations. The increase in our debt and other obligations is 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. The increase in debt was partially offset by the repayment in January of convertible partner debt from Boehringer Ingleheim International BmbH, or BI, of approximately $6.4 million, the payment of principal and interest related to our standard operating debt, and payments related to our capital leases. We also financed $1.3 million in capital additions under our existing capital lease financing arrangement. We expect that capital lease obligations will increase over time to fund capital equipment acquisitions required to support our business. 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 that our available cash, cash equivalents and short-term investments as of June 30, 2004, when combined with investment income and committed contractual cash payments from our partners, will be sufficient to meet our anticipated requirements through at least the end of 2006. The following table summarizes our contractual obligations as of June 30, 2004. 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:

Contractual Obligations (selected balances described below)	Payments Due by Period (in thousands)				
	Total	Less than 1 year	1-3 years	3-5 years	After 5 years
Lilly Research Collaboration Loan	$ 85.0	$ —	$ 85.0	$ —	$ —
5 ½% Convertible Subordinated Notes	$ 125.0	$ —	$ —	$ 125.0	$ —
Standard Operating Debt	$ 35.3	$ 6.3	$ 18.7	$ 10.3	$ —
Capital Lease Obligations	$ 6.6	$ 3.9	$ 2.7	$ —	$ —
Operating Leases	$ 10.9	$ 2.7	$ 5.3	$ 2.0	$ 0.9

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. If we draw down the remaining amount available under the loan, we could repay the loan for 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 BI and Elan. 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 4.25% at June 30, 2004. 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%. We used the proceeds from the loan to pay off existing debt to Elan of $5.1 million plus accrued interest and to BI of $22.6 million plus accrued interest, of which $6.4 million plus accrued interest we paid during January 2004. The carrying value of the term loan at June 30, 2004 and December 31, 2003 was $29.1 million and $32.0 million, respectively.

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 5½%, 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 June 30, 2004 and December 31, 2003, 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 June 30, 2004, we had drawn down $85.0 million of the $100.0 million available. We are accounting for this loan using an imputed interest rate of 20%, consistent with market conditions in place at the time the loan was agreed to. We carry the net present value of the drawdowns as a long-term obligation and record interest expense over the term of the loan. 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, and we are accounting for the difference as deferred revenue related to the collaboration, which is recognized as revenue over the period of performance. As of June 30, 2004, the balance in long-term obligations was $67.4 million and the balance in deferred revenue was $17.6 million.

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 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, including Affinitak and alicaforsen, 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, 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 that have not met the primary clinical end points in their initial Phase III studies.

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. In 2004, we expect to report the results of our Phase III clinical trials of alicaforsen in patients with active Crohn's disease. 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 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 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 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.

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 U.S. Government-funded grants and contracts for our Ibis program and the development of our TIGER biosensor. The U.S. 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.

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.

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 first Affinitak Phase III trial or Lilly's ongoing Phase III trial, 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 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 June 30, 2004, our accumulated losses were approximately $608.2 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.

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

Our TIGER biosensor 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 biosensor 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 that our available cash, cash equivalents and short-term investments as of June 30, 2004, combined with investment income and committed contractual cash payments will be sufficient to meet our anticipated requirements through at least the end of 2006. If we do not meet our goals to commercialize our products, or to license our drugs and 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 developing and commercializing a business based on our TIGER biosensor 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 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. 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 the results of our Phase III trials for alicaforsen are positive and we fail to secure a marketing and distribution partner for this product, our commercialization efforts for alicaforsen may be harmed or delayed.

We have limited personnel with experience in marketing, selling and distributing products. We expect to depend on third parties to commercialize alicaforsen if our Phase III trials for alicaforsen are positive and we receive marketing approval. If we are unable to reach agreements with suitable third parties, we may fail to meet our business objectives for alicaforsen. We may not successfully establish a collaboration or be able to make alternative arrangements. Moreover, a collaboration or other arrangement we secure may not succeed.

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.

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 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 U.S. 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. 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 the second half of 2004.

If Macugen does not achieve marketing approval or its commercial success does not meet our expectations, we will not receive milestone and royalty payments.

As part of our license agreement with Eyetech, we are entitled to receive milestones and royalty payments. However, if Eyetech does not achieve these milestones or receive marketing approval for Macugen, or if Eyetech receives marketing approval for Macugen but fails to commercialize Macugen as expected, we may not receive these payments, or derive the expected value.

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 June 30, 2004, the market price of our common stock has ranged from $4.72 to $9.50 per share. On August 3, 2004, the closing price of our common stock on the Nasdaq National Market was $4.60 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 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.

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 June 30, 2004. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to June 30, 2004.

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

Not applicable

ITEM 2. CHANGES IN SECURITIES AND USE OF PROCEEDS

In April 2004, a warrant held by Elan to purchase 215,000 shares of Isis' common stock expired unexercised.

In June 2004, Elan transferred it shares of Isis Series B preferred stock to a third party. Immediately upon transfer, these shares converted into 1,055,502 shares of Isis common stock. Isis also cancelled a warrant Elan held to purchase 14,881 shares of Isis common stock.

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

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

On May 26, 2004, we held our Annual Meeting of Stockholders in Carlsbad, California for the following purposes:

(1) To elect three (3) directors to serve as Class I directors of the company. For Director number one, Stanley T. Crooke, the number of votes for and withheld was 48,402,507 and 472,839, respectively. For Director number two, John C. Reed, the number of votes for and withheld was 48,525,804 and 349,542, respectively. For Director number three, Mark B. Skaletsky, the number of votes for and withheld was 48,371,532 and 503,814, respectively.

(2) To approve the amendment and restatement of the 1989 Stock Option Plan. The number of votes for, against and abstaining was 25,245,523; 4,072,469 and 486,754, respectively.

(3) To ratify the appointment of Ernst & Young LLP as the Company's independent auditors for the fiscal year ending December 31, 2004. The number of votes for, against and abstaining was 47,855,042; 944,941 and 75,362, respectively.

ITEM 5. OTHER INFORMATION

Not applicable

ITEM 6. EXHIBITS AND REPORTS ON FORM 8-K

a. Exhibits

Exhibit Number	Description of Document
10.4	Securities Purchase Agreement dated June 4, 2004 between Isis Pharmaceuticals, Inc. and Elan Pharmaceutical Investments II, Ltd.
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.

b. Reports on Form 8-K

On May 6, 2004, the Registrant filed a report on Form 8-K for the announcement of its first quarter results and the related press release dated May 6, 2004. We furnished this information under Item 12 of Form 8-K, “Results of Operations and Financial Condition.”

On August 5, 2004, the Registrant filed a report on Form 8-K for the announcement of its second quarter results and the related press release dated August 5, 2004. We furnished this information under Item 12 of Form 8-K, “Results of Operations and Financial Condition.”

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)	August 5, 2004
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	August 5, 2004

SECURITIES PURCHASE AGREEMENT

THIS SECURITIES PURCHASE AGREEMENT (the "Agreement"), dated as of June 4, 2004, is made and entered into by and between Elan Pharmaceutical Investments II, Ltd., a Bermuda exempted company limited by shares (the "Seller"), and Isis Pharmaceuticals, Inc., a Delaware corporation (the "Purchaser").

WHEREAS, the Seller is the owner of certain securities identified on Schedule A (the "Securities");

WHEREAS, the Seller desires to sell to the Purchaser and the Purchaser desires to purchase from the Seller the Securities.

NOW, THEREFORE, in consideration of the premises and of the respective representations, warranties, covenants, agreements and conditions contained herein, the Purchaser and the Seller agree as follows:

1. Definitions. As used in this Agreement, the following terms shall have the meanings set forth below:

"Securities" has the meaning set forth in the recitals hereto.

"Purchase Price" means $500.

"SEC" means the United States Securities and Exchange Commission.

"Securities Act" means the United States Securities Act of 1933, as amended, and the rules and regulations in effect from time to time thereunder.

2. Purchase and Sale of the Securities; Closing. The Purchaser and the Seller agree as follows:

(a) Purchase and Sale of the Securities. On the basis of the representations and warranties, and subject to the terms and conditions, set forth herein, (i) the Seller agrees to sell to the Purchaser the Securities set forth on Schedule A, and (ii) the Purchaser agrees to purchase from the Seller the Securities set forth on Schedule A.

(b) Closing. The closing (the "Closing") of the purchase and sale of the Securities shall take place at 10:00 a.m. on June 4, 2004 (the "Closing Date") at the offices of Cahill Gordon & Reindel LLP, 80 Pine Street, New York, New York, or at such other place as the parties hereto shall mutually agree. At the Closing, (i) the Seller shall deliver to the Purchaser certificates representing the Securities and such other appropriate instruments of transfer and assignment (including blank stock powers), as the Purchaser shall reasonably request prior to the Closing Date, in order to

---

vest in the Purchaser, as of the Closing Date, all of the Seller's right, title and interest in, to and under the Securities, and (ii) the Purchaser shall deliver or cause to be delivered to the Seller, or its agent, the Purchase Price in immediately available funds.

3. Conditions to the Purchaser's Obligation. The obligation of the Purchaser to purchase and pay for the Securities is subject to the satisfaction (or waiver by Purchaser) of the following conditions as of the Closing Date:

(a) the representations and warranties of the Seller made in this Agreement shall be true and correct in all respects, as of the date hereof and as of the Closing Date as though then made; and

(b) the Seller shall have delivered to the Purchaser the documents or instruments contemplated by Section 2(b) above.

4. Conditions to the Seller's Obligation. The obligation of the Seller to sell and deliver the Securities to the Purchaser is subject to the satisfaction (or waiver by the Seller) of the following conditions as of the Closing Date:

(a) the representations and warranties of the Purchaser made in this Agreement shall be true and correct in all respects, as of the date hereof and as of the Closing Date as though then made; and

(b) the Purchaser shall have delivered to the Seller the Purchase Price.

5. Representations and Warranties of Purchaser. The Purchaser represents and warrants to the Seller that:

(a) The Purchaser has all requisite corporate power and authority to enter into and perform this Agreement and to consummate the transactions contemplated hereby. The Purchaser has duly and validly authorized, executed and delivered this Agreement.

(b) This Agreement constitutes a valid and binding agreement of the Purchaser, enforceable against the Purchaser in accordance with its terms, except as enforceability may be limited by (i) applicable bankruptcy, insolvency, reorganization, moratorium, fraudulent conveyance or other similar laws relating to or affecting creditors' rights generally and (ii) general principles of equity (regardless of whether such enforceability is considered in a proceeding in equity or at law).

(c) The Securities being acquired by the Purchaser hereunder are being acquired for the Purchaser's own account and not with the view to, or for resale in connection with, any distribution in violation of applicable securities laws.

(d) The Purchaser acknowledges that neither the offer nor sale of the Securities has been registered under the Securities Act or any state or foreign securities or "blue sky" laws and that the sale of the Securities is being made pursuant to an exemption from registration under the Securities Act. In furtherance thereof, the Purchaser represents and warrants that it is an accredited investor within the meaning of Rule 501 of Regulation D under the Securities Act.

(e) The Purchaser consents to the sale, transfer or other disposition of the Series B Convertible Exchangeable Preferred Stock of the Purchaser contingent upon the successful completion of the transactions contemplated in this Agreement and Seller's continued compliance with the provisions of Section 6(e) of this Agreement. This consent is only effective if, when and so long as the purchaser of the Series B Convertible Exchangeable Preferred Stock has agreed in writing to the following covenant:

"The Purchaser will immediately upon effectiveness of the Closing convert the 12,015 shares of Series B Convertible Exchangeable Preferred Stock of Isis Pharmaceuticals, Inc., included in the Securities purchased under this Agreement, into 1,055,502 shares of Common Stock of Isis Pharmaceuticals, Inc. Isis Pharmaceuticals, Inc. is a third party beneficiary to this Section and will be entitled to enforce this Section against Purchaser, including through specific performance."

6. Representations and Warranties of the Seller. The Seller represents and warrants to the Purchaser that:

(a) The Seller has all requisite corporate power and authority to enter into and perform this Agreement and to consummate the transactions contemplated hereby. The Seller has duly and validly authorized, executed and delivered this Agreement.

(b) This Agreement constitutes a valid and binding agreement of the Seller, enforceable against the Seller in accordance with its terms, except as enforceability may be limited by (i) applicable bankruptcy, insolvency, reorganization, moratorium, fraudulent conveyance or other similar laws relating to or affecting creditors' rights generally and (ii) general principles of equity (regardless of whether such enforceability is considered in a proceeding in equity or at law).

(c) No consent, approval, qualification, order or authorization of, or filing with, any local, state or federal governmental authority is required for the consummation by the Seller of the transactions contemplated hereby, other than the permission of the Bermuda Monetary Authority for the sale of the Bermuda Securities to the Purchaser as detailed herein, which permission has been obtained.

(d) The Seller has good and marketable title to the Securities that it is transferring hereunder, free and clear of any liens, claims, encumbrances, charges or restrictions of any kind (collectively, "Liens"). Upon consummation of the transactions contemplated hereby, the Purchaser will have acquired good and marketable title in and to the Securities, free and clear of any Liens.

(e) If and when the Seller sells, transfers or otherwise disposes of the 12,015 shares of Series B Convertible Exchangeable Preferred Stock of the Purchaser which are owned by the Seller, a condition to such sale, transfer or disposition shall be that the acquiror of such shares will immediately convert such shares into shares of Common Stock of the Purchaser.

7. Applicable Law. THIS AGREEMENT SHALL BE GOVERNED BY AND CONSTRUED IN ACCORDANCE WITH THE LAWS OF THE STATE OF CALIFORNIA.

8. Invalidity of Provisions. The invalidity or unenforceability of any provision of this Agreement in any jurisdiction shall not affect the validity or enforceability of the remainder of this Agreement in that jurisdiction or the validity or enforceability of this Agreement, including that provision, in any other jurisdiction.

9. Survival of Representations and Warranties. The representations and warranties contained herein shall survive the Closing or any termination of this Agreement for a period of six months.

10. Headings; Execution in Counterparts. The headings and captions contained herein are for convenience of reference only and shall not control or affect the meaning or construction of any provision hereof. This Agreement may be executed in counterparts, each of which shall be deemed to be an original and which together shall constitute but one and the same instrument.

11. Notices. All notices and other communications relating to this Agreement shall be dated and in writing and shall be deemed to have been duly given when delivered, if delivered personally or sent by registered or certified mail, return receipt requested, postage prepaid, and when received if delivered otherwise, to the party to whom it is directed;

(a) If to the Seller, to the Seller at the following address:

Elan Pharmaceutical Investments II, Ltd.
Clarendon House
Church Street
Hamilton, Bermuda
Attn: President

Fax: (441) 292-2224

(b) If to the Purchaser, to the Purchaser at the following address:

Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008-7298
Attn: Grant Bryce, V.P. and General Counsel
Fax: 760-931-9639

12. Integration. The parties agree that this Agreement contains the entire understanding between the parties hereto relating to the subject matter hereof.

13. Third Party Beneficiaries. Nothing expressed or implied in this Agreement is intended or shall be construed to confer upon or give to any third party any rights or remedies against any party hereto.

14. Further Assurances. Each of the parties hereto covenants and agrees upon the request of the other, to do, execute, acknowledge and deliver or cause to be done, executed, acknowledged and delivered all such further acts, deeds, documents, assignments, transfers, conveyances, powers of attorney and assurances as may be reasonably necessary or desirable to give full effect to this Agreement.

[Signature Page Follows]

IN WITNESS WHEREOF, the Purchaser and the Seller have executed this Agreement as of the date first above written.

ELAN PHARMACEUTICAL INVESTMENTS II, LTD.

By: /s/ Kevin Insley
Name: Kevin Insley
Title: Vice President

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshal
Name: B. Lynne Parshall
Title: EVP & CFO

Schedule A

2,388 Shares of common stock of Orasense Ltd.

2,388 shares of non-voting preferred stock of Hepasense Ltd.

Warrant to purchase 14,881 shares of common stock of Isis Pharmaceuticals, Inc. at the price of $50.40 per share on or before April 11, 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 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-15(e) and 15d-15(e)) 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) 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

   c) 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 officers and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: August 5, 2004

/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 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-15(e) and 15d-15(e)) 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) 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

   c) 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 officers and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: August 5, 2004

/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 June 30, 2004, 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: August 5, 2004

/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.