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SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 10-Q

(Mark One)

☒ **QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(D) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the quarterly period ended September 30, 2003

OR

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

For the transition period from to

Commission file number 0-19125

Isis Pharmaceuticals, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**33-0336973**
(State or other jurisdiction of incorporations or organization)	(I.R.S. Employer Identification No.)

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

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

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

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(D) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days.

(1) Yes ☒ No (2) Yes ☒ No

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

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

Common stock $.001 par value	**55,557,601 shares**
(Class)	(Outstanding at November 6, 2003)

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

ASSETS

	September 30, 2003 (Unaudited)	December 31, 2002 (Note)
Current assets:		
Cash and cash equivalents	$ 55,792	$ 101,856
Short-term investments	179,028	187,497
Contracts receivable	2,749	14,906
Inventory	9,293	11,090
Other current assets	8,380	4,831
Total current assets	255,242	320,180
Property, plant and equipment, net	37,880	59,094
Licenses, net	28,887	30,749
Patents, net	21,497	18,904
Deposits and other assets	8,664	9,186
Long-term investments	1,376	570
Total assets	$ 353,546	$ 438,683

LIABILITIES AND STOCKHOLDERS' EQUITY

Current liabilities:		
Accounts payable	$ 2,171	$ 5,524
Accrued compensation	3,784	3,330
Accrued liabilities	10,902	6,794
Amount due to affiliates	—	5,193
Current portion of long-term obligations	26,699	21,435
Current portion of deferred contract revenue	16,083	33,674
Total current liabilities	59,639	75,950

5 1/2% convertible subordinated notes	125,000	125,000
Long-term obligations, less current portion	64,390	67,893
Long-term deferred contract revenue, less current portion	11,003	14,363
Stockholders' equity:		
Series B Convertible Exchangeable 5% Preferred stock, $.001 par value; 16,620 shares authorized, 12,015 shares issued and outstanding at September 30, 2003 and December 31, 2002	12,015	12,015
Accretion of Series B Preferred stock dividends	2,384	1,866
Common stock, $.001 par value; 100,000,000 shares authorized, 55,552,244 shares and 55,215,785 shares issued and outstanding at September 30, 2003 and December 31, 2002, respectively	56	55
Additional paid-in capital	604,978	602,101
Deferred compensation	(321)	(59)
Accumulated other comprehensive income (loss)	4,434	(608)
Accumulated deficit	(530,032)	(459,893)
Total stockholders' equity	93,514	155,477
Total liabilities and stockholders' equity	$ 353,546	$ 438,683

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

See accompanying notes

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2003	2002	2003	2002
Revenue:				
Research and development revenue under collaborative agreements	$ 11,263	$ 16,977	$ 39,944	$ 49,580
Research and development revenue from affiliates	—	3,313	—	8,434
Licensing and royalty revenue	31	10	347	306
Total revenue	11,294	20,300	40,291	58,320
Operating expenses:				
Research and development	27,410	35,470	87,849	93,983
General and administrative	2,147	2,244	7,201	6,915
Compensation (benefit) related to stock options	804	95	936	(3,011)
Restructuring activities	—	—	1,803	—
Total operating expenses	30,361	37,809	97,789	97,887
Loss from operations	(19,067)	(17,509)	(57,498)	(39,567)
Other income (expenses):				
Equity in loss of affiliates	—	(3,454)	—	(13,180)
Investment income	1,177	2,207	3,980	6,243
Interest expense	(4,313)	(3,796)	(13,665)	(12,591)
Loss on investments	—	—	(2,438)	—
Loss on prepayment of 14% Notes	—	—	—	(2,294)
Gain on prepayment of 12% Notes	—	4,976	—	4,976
Net loss	(22,203)	(17,576)	(69,621)	(56,413)
Accretion of dividends on preferred stock	(175)	(222)	(518)	(892)
Net loss applicable to common stock	$ (22,378)	$ (17,798)	$ (70,139)	$ (57,305)

Basic and diluted net loss per share	$ (0.40)	$ (0.33)	$ (1.27)	$ (1.06)
Shares used in computing basic and diluted net loss per share	55,540	54,708	55,418	54,253

See accompanying notes

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

	Nine Months Ended September 30,	
	2003	2002
Net cash used in operating activities	$ (63,065)	$ (84,364)
Investing activities:		
Purchase of short-term investments	(137,593)	(153,714)
Proceeds from the sale of short-term investments	144,499	139,105
Purchase of property, plant and equipment	(6,138)	(22,978)
Other assets	(4,396)	(4,114)
Investments in affiliates	(5,193)	(8,949)
Net cash used in investing activities	(8,821)	(50,650)
Financing activities:		
Net proceeds from issuance of equity	1,680	7,563
Proceeds from long-term borrowings	28,366	28,245
Net proceeds from issuance of convertible debt	—	120,921
Principal payments on debt and capital lease obligations	(4,224)	(2,942)
Principal payment on prepayment of debt	—	(52,705)
Net cash provided from financing activities	25,822	101,082
Net decrease in cash and cash equivalents	(46,064)	(33,932)
Cash and cash equivalents at beginning of period	101,856	127,011
Cash and cash equivalents at end of period	$ 55,792	$ 93,079
Supplemental disclosures of cash flow information:		
Interest paid	$ 5,168	$ 34,578
Supplemental disclosures of non-cash investing and financing activities:		
Decrease in property, plant and equipment and notes payable	$ 21,200	$ —
Decrease in inventory and deferred revenue	$ 8,750	$ —
Conversion of preferred stock into common stock	$ —	$ 14,142
Additions to long-term investments for acquired corporation securities	$ 750	$ —
Additions to debt for licensing costs	$ —	$ 1,400

See accompanying notes

1. Basis of Presentation

The unaudited interim financial statements for the nine-month periods ended September 30, 2003 and 2002 have been prepared on the same basis as the Company's audited financial statements for the year ended December 31, 2002. The financial statements include all adjustments (consisting only of normal recurring adjustments), which the Company considers necessary for a fair presentation of the financial position at such dates and the operating results and cash flows for those periods. Results for the interim periods are not necessarily indicative of the results for the entire year. For more complete financial information, these financial statements, and notes thereto, should be read in conjunction with the audited financial statements for the year ended December 31, 2002 included in the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission.

2. Significant Accounting Policies

Revenue Recognition

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

Research and development revenue under collaborative agreements

The Company recognizes research and development revenue under collaborative agreements as it incurs the related expenses, up to contractual limits. The Company defers payments received under these agreements that are related to future performance and records revenue as it is earned over the specified future performance period. The Company recognizes revenue that relates to nonrefundable, upfront fees over the period of the contractual arrangements as it satisfies its performance obligations. The Company recognizes revenue that relates to milestones, under existing arrangements, upon completion of the milestone's performance requirement. The Company recognizes revenue related to milestones that are part of arrangements entered into subsequent to June 30, 2003 in accordance with *Emerging Issues Task Force Issue No. 00-21* (EITF 00-21) *Accounting for Revenue Arrangements with Multiple Deliverables*. EITF 00-21 requires the Company to recognize revenue related to milestones over the period of obligation, if any. The Company records revenue from federal research grants during the period in which it incurs the related expenditures. The Company recognizes revenue from product sales as it ships the products.

As part of the Company's alliance with Eli Lilly and Company (Lilly) in August 2001, Lilly provided Isis a $100.0 million interest free loan to fund the research collaboration. As of September 30, 2003, the Company had drawn down $67.5 million on the $100.0 million loan. The Company discounted the $67.5 million loan to its net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time the Company entered into the loan. The Company accretes the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan represents value Lilly gave to Isis to help fund the research collaboration. The Company accounts for this value as deferred revenue and recognizes it as revenue over the period of performance.

Research and development revenue from affiliates

In late 2002, the Company terminated its HepaSense and Orasense collaborations with Elan Corporation plc (Elan) and as a result, the Company no longer earns revenue from these collaborations.

Licensing and royalty revenue

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

Concentration of credit risk

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

The Company considers all liquid investments with maturities of ninety days or less when purchased to be cash equivalents. The Company's short-term investments have initial maturities of greater than ninety days from date of purchase. The Company classifies its securities as "available-for-sale" in accordance with SFAS 115, *Accounting for Certain Investments in Debt and Equity Securities.* The Company carries these investments at fair market value with any unrealized gains and losses recorded as a separate component of stockholders' equity. Fair value is based upon market prices quoted on the last day of the fiscal quarter. The cost of debt securities sold is based on the specific identification method. The Company includes gross realized gains and losses in investment income and these amounts have not been material. To date, the Company has not had any material losses related to its cash or cash equivalents. During the first quarter of 2003, the Company recorded a non-cash loss of $2.4 million related to the impairment of its equity investments in Antisense Therapeutics Limited (ATL) and Hybridon, Inc. 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 was determined to be other-than-temporary. In the second and third quarters of 2003, the Company recorded unrealized gains related to its equity investments in ATL and Hybridon as a separate component of stockholders' equity, which reflected the increase in the market value of the investments since the first quarter of 2003.

Inventory Valuation

The Company's inventory includes drugs with alternative uses that are used primarily for its development activities and drugs it manufactures for its partners under contractual terms. The Company states its inventories at the lower of cost or market, with cost determined under the first-in, first-out method. The Company reviews inventories periodically and reduces the carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. In the second quarter of 2003, the Company reduced the carrying value of its raw materials related to Affinitak to zero. No reduction in the carrying value of inventory occurred in the third quarter of 2003. Inventory includes

the following categories as of September 30, 2003 and December 31, 2002, net of reserves (in thousands):

	September 30, 2003	December 31, 2002
Raw materials	$ 3,000	$ 10,186
Work-in-process	4,739	904
Finished goods	1,554	—
	$ 9,293	$ 11,090

Use of Estimates

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

Stock-Based Employee Compensation

In April 2003, the Company implemented an employee stock option exchange program to maintain one of the Company's key assets, its employee base, in a manner that was sensitive to shareholder interests. The 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. The Company accounts for the affected options, until all these options have been exercised or cancelled, using variable accounting consistent with the provisions of *Accounting Principles Board Opinion No. 25* and *Financial Accounting Standard Board Interpretation No. 44*. As a result, the Company has recorded compensation expense of approximately $912,000 to date in 2003 and will continue to account for the affected options using variable accounting.

The Company has adopted the disclosure-only provision of SFAS 123, *Accounting for Stock-Based Compensation*. Accordingly, no compensation expense, except for compensation expense primarily related to the affected options from the 2000 and 2003 exchange programs, has been recognized for the Company's stock option plans. Had compensation expense been determined consistent with SFAS 123,

the Company's net loss and basic and diluted net loss per share would have been changed to the following proforma amounts (in thousands, except per share amounts):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2003	2002	2003	2002
Net loss applicable to common stock	$ (22,378)	$ (17,798)	$ (70,139)	$ (57,305)
Stock based compensation	(1,600)	(4,796)	(2,589)	(17,097)
Proforma net loss applicable to common stock	$ (23,978)	$ (22,594)	$ (72,728)	$ (74,402)
Earnings per share:				
Basic and diluted	$ (0.40)	$ (0.33)	$ (1.27)	$ (1.06)
Basic and diluted, proforma	$ (0.43)	$ (0.41)	$ (1.31)	$ (1.37)

For the purpose of this proforma calculation, the Company estimates the fair value of each option grant on the date of grant using the Black-Scholes option pricing model with the following assumptions for September 30, 2003 and 2002: 1) a risk free rate of 3.9% and 3.6%, respectively; 2) a dividend yield of 0% each year; 3) a volatility factor of 76.0% and 80.5%, respectively; and 4) an option life of 5.8 years each year. The weighted average fair value of options granted was $5.36 and $5.74 for the three and nine months ended September 30, 2003, respectively. The weighted average fair value of options granted was $9.09 and $15.99 for the three and nine months ended September 30, 2002, respectively.

Reclassification

Certain prior period amounts have been reclassified to conform to current presentation.

Impact of Recently Issued Accounting Standards

In November 2002, the Emerging Issues Task Force issued Issue No. 00-21 (EITF 00-21), *Accounting for Revenue Arrangements with Multiple Deliverables.* This issue addresses the timing and method of revenue recognition for revenue arrangements that include the delivery of more than one product or service. EITF 00-21 is effective for revenue arrangements entered into in fiscal quarters beginning after June 15, 2003. The Company has adopted EITF 00-21 and this issue is not expected to have a material impact on its operating results and financial position.

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

3. Strategic Alliances

Affiliates

Orasense

Due to the significant minority investor rights retained by Elan and its subsidiaries, the Company accounted for its investment in Orasense under the equity method of accounting. Through December 2002, Orasense incurred research and development expenses, performed by Elan and the Company on Orasense's behalf, in the course of its product development. In conjunction with its continuing restructuring efforts, Elan concluded its participation in the Orasense collaboration effective December 31, 2002, and the Company reacquired all rights to ISIS 104838, the compound that the collaboration had been developing. However, the Company has continued to develop its oral delivery technology within Orasense. The following table presents summary results of operations for the three and nine months ended September 30, 2003 and 2002 for Orasense (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2003	2002	2003	2002
Revenue	$ —	$ —	$ —	$ —
Research and development expense	546	4,039	3,291	8,350
Net loss	$ (546)	$ (4,039)	$ (3,291)	$ (8,350)

HepaSense

Due to the significant minority investor rights retained by Elan and its subsidiaries, the Company accounted for its investment in HepaSense under the equity method of accounting. Through December 2002, HepaSense incurred research and development expenses, performed by Elan and the Company on HepaSense's behalf, in the course of its product development. In conjunction with its continuing restructuring efforts, Elan concluded its participation in the HepaSense collaboration in 2002 and the Company reacquired all rights to ISIS 14803, the compound that the collaboration had been developing. As a result of the collaboration termination, there was no activity during the nine months ended September 30, 2003. The following table presents summary results of operations for the three and nine months ended September 30, 2003 and 2002 for HepaSense (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2003	2002	2003	2002
Revenue	$ —	$ —	$ —	$ —
Research and development expense	—	271	—	8,104
Net loss	$ —	$ (271)	$ —	$ (8,104)

Amgen

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

Lilly Oncology Collaboration

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

Santaris Pharma A/S (formerly Pantheco A/S)

In May 2003, the Company entered into an amended and restated license agreement with Pantheco A/S. The amended and restated license agreement replaces the nonexclusive license agreement the Company entered into with Pantheco in September 2000 and the exclusive license agreement the Company entered into with Pantheco in November 1998. Under the terms of the amended and restated license agreement, the Company licensed its novel antisense chemistry, Peptide Nucleic Acid, or PNA, to Pantheco on a limited exclusive basis to develop products. The license is restricted to a limited number of molecular targets that are subject to the Company's approval. In consideration for the license, Pantheco agreed to pay the Company royalties and milestones on any products developed under the license.

In addition, in May 2003, Pantheco A/S and Cureon A/S merged to form Santaris Pharma A/S. Prior to the merger, the Company purchased additional shares of Pantheco for $55,000 as a result of antidilution provisions related to Pantheco's stock. After the merger and as of September 30, 2003, the Company's ownership interest in Santaris is 7.4%.

Ercole

In May 2003, the Company and Ercole Biotech, Inc. (Ercole) initiated a multi-year collaboration to discover antisense drugs that regulate alternative RNA splicing. As part of the collaboration, the parties cross-licensed their respective splicing-related intellectual property. Ercole also received a license to some of the Company's chemistry patents. The Company has taken an equity ownership in Ercole, with the initial funding in the form of convertible debt, which the companies anticipate will convert into securities Ercole issues in its next venture capital financing. The Company also has the option to make an additional equity investment in Ercole.

Lilly

In June 2003, the Company and Lilly reached a mutually beneficial renegotiation of their manufacturing relationship. Lilly waived repayment of the $21.2 million manufacturing loan it provided the Company to build the Affinitak manufacturing facility. Lilly agreed to allow the Company to use the facility to manufacture other drugs. In exchange, the Company released Lilly from its obligations contained in the supply agreement for Affinitak, including the obligation to purchase additional product from the Company and the obligation to pay for the costs of maintaining an idle manufacturing suite.

Industrial and Technology Research Institutes of Taiwan

In June 2003, Isis initiated a collaboration with the Industrial and Technology Research Institutes (ITRI) of Taiwan to identify antisense candidates targeting the coronavirus associated with Severe Acute Respiratory Syndrome (SARS). The Company is conducting the antisense drug discovery research and ITRI will provide up to $2.0 million in funding to support the collaboration, with the potential for further funding.

OncoGenex Technologies Inc.

In September 2003, the Company and OncoGenex Technologies Inc. (OncoGenex) expanded their antisense drug development partnership to include the development of the second generation antisense anti-cancer drug candidate, OGX-225. OncoGenex has responsibility for the preclinical and clinical development of the drug. OncoGenex issued the Company OncoGenex securities as payment for an upfront fee. In addition, OncoGenex will provide to the Company milestone payments for key clinical and regulatory achievements and royalties on product sales.

The Centers for Disease Control and Prevention

In September 2003, the Company's Ibis program received a three-year grant for up to $6.0 million from the Centers for Disease Control and Prevention (CDC) to develop and apply its diagnostic technology to the surveillance of human infectious disease in the U.S. Using the grant from the CDC, Ibis will develop and provide diagnostic technology for CDC projects focused on human emerging infectious disease and biodefense.

4. Comprehensive Loss

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2003	2002	2003	2002
Comprehensive loss:				
Change in unrealized gains (losses)	$ 1,358	$ 648	$ 5,042	$ (672)
Net loss applicable to common stock	(22,378)	(17,798)	(70,139)	(57,305)
Comprehensive loss	$ (21,020)	$ (17,150)	$ (65,097)	$ (57,977)

5. Restructuring

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

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

The following table summarizes the balance of the accrued restructuring reserve related to GeneTrove and Affinitak, which has been included in accrued liabilities at September 30, 2003 (in thousands):

	GeneTrove Severance Cost For Involuntary Employee Terminations	Affinitak Severance Cost For Involuntary Employee Terminations	Total
Balance at June 30, 2003	$ 81	$ 701	$ 782
Reserve additions	—	—	—
Utilization of reserve:			
Cash	(51)	(485)	(536)
Balance at September 30, 2003	$ 30	$ 216	$ 246

6. Subsequent Events

In November 2003, the Company received a grant of up to $8.0 million over three years from the Singapore Economic Development Board which will fund, in part, the broadening of two of Isis' RNA-based drug discovery and development programs: micro-RNA drug discovery and antisense drug discovery targeting the coronavirus associated with SARS.

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

In addition to historical information contained in this Report, this Report contains forward-looking statements regarding our business and the therapeutic and commercial potential of our technologies and products in development. Any statement describing our goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those risks and uncertainties inherent in the process of discovering, developing and commercializing drugs that can be proven to be safe and effective for use as human therapeutics, in the process of conducting gene functionalization and target validation services, and in the endeavor of building a business around such products and services. Actual results could differ materially from those discussed in this Form 10-Q. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in our Annual Report on Form 10-K for the year ended December 31, 2002, which is on file with the U.S. Securities and Exchange Commission and those identified in the section of Item 2 entitled "Risk Factors" beginning on page 23 of this Report. As a result, you are cautioned not to rely on these forward-looking statements.

Since our inception in 1989, we have pioneered the science of antisense for the development of a new class of drugs. We design antisense drugs to treat a wide variety of diseases. We are applying our expertise in RNA-based drug discovery to understand and develop drugs based on numerous antisense mechanisms, including RNase H, the mechanism that is used by the drugs in our pipeline, as well as siRNA, microRNAs and splicing mechanisms. 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 diseases. We have developed new chemistries and novel formulations to enhance the potency and utility of antisense drugs, and we have successfully turned our expertise into a broad pipeline of antisense products currently in all phases of clinical development. Our drugs in development treat a variety of health conditions, including inflammatory, viral, metabolic, cardiovascular and dermatological diseases, and cancer, and we are studying these drugs in intravenous, subcutaneous, topical cream, enema and oral formulations. We achieved marketing clearance for the world's first antisense drug Vitravene® (fomivirsen) in 1998.

Affinitak™, formerly LY900003 or ISIS 3521, is our most advanced product in development. 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 patients currently enrolled. 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 most likely will occur in the second half of 2004. In June 2003, Lilly and we reached a mutually beneficial renegotiation of our manufacturing relationship. Lilly waived repayment of the $21.2 million manufacturing loan it provided us to build the Affinitak manufacturing facility. Lilly agreed to allow us to use the facility to manufacture other drugs. In exchange, we released Lilly from its obligations contained in the supply agreement for Affinitak, including the obligation to purchase additional product from us and the obligation to pay for the costs of maintaining an idle manufacturing suite.

We are currently 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 and Europe and we expect to complete enrollment of these trials in the first half of 2004. Alicaforsen is an antisense inhibitor of ICAM-1 (Intercellular Adhesion Molecule-1), a molecule that plays a key role in the recruitment and activation of the immune cells associated with the inflammatory response in a wide range of inflammatory and autoimmune conditions such as Crohn's disease. We are also studying alicaforsen in an enema formulation for patients with ulcerative colitis in

Phase II trials. We expect results in the second half of 2004. We also have several products in Phase II and earlier stages of development.

Our GeneTrove program uses our antisense technology as a tool to provide important information about the function of genes and has automated the initial steps in our antisense drug discovery process. Our current focus is to use GeneTrove information to direct our own drug discovery research and that of our antisense drug discovery partners, such as Lilly and Amgen. We also offer antisense-based gene function information and license our antisense based functional genomics patents to pharmaceutical company partners that are evaluating the genes as targets for their own drug discovery programs. In November 2002, we announced the termination of GeneTrove's subscription database product originally added in August 2001. This resulted in a reorganization of the GeneTrove program.

Our Ibis program has invented a platform technology that has the potential to revolutionize the detection and treatment of infectious diseases. We are creating a sensor that can detect known and unknown infectious agents, and are working to discover small molecule drugs that work by binding to RNA. Our scientists have invented methods of identifying common binding sites in RNA that facilitate the identification of organisms or serve as targets for drug binding. We have also invented mass spectrometry-based screening methods for both diagnostic and drug discovery applications. In a project called Triangulation Identification for Genetic Evaluation of Risks, or TIGER, we are applying our Ibis technology to develop a sensor to detect infectious agents that could be used in biological warfare attacks. We collaborate with San Diego-based Science Applications International Corporation, or SAIC, on this multi-year project funded by the Defense Advanced Research Projects Agency, or DARPA. Ibis expects to receive funding of up to $11.7 million for its efforts related to this collaboration with SAIC, of which $11.4 million has been billed and $10.8 million has been collected as of September 30, 2003. In September 2003, our Ibis program received a three-year grant for up to $6.0 million from the Centers for Disease Control and Prevention, or the CDC, to develop and apply its diagnostic technology to the surveillance of human infectious disease in the U.S. Using the grant from the CDC, Ibis expects to develop and provide diagnostic technology for CDC projects focused on human emerging infectious disease and biodefense. In early 2002, Ibis received a three-year contract from the U.S. Army Medical Research Institute of Infectious Diseases, or USAMRIID, to use its technology to develop broad-spectrum anti-infective drugs that we believe will be useful in national defense. The contract provides for funding of up to $2.4 million. In addition to DARPA, USAMRIID and the CDC, Ibis also has research relationships with other government entities including the United States Navy and the Federal Bureau of Investigation.

Critical Accounting Policies

We prepare our financial statements in conformity with accounting principles generally accepted in the United States of America. As such, we are required to make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These estimates and assumptions affect the reported balances and amounts within our financial statements and supporting notes. The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, include the following:

Revenue Recognition

We generally recognize revenue when we have satisfied all contractual obligations and we are reasonably assured of collecting the resulting receivable. We often enter into collaborations where we receive nonrefundable up-front payments for prior or future expenditures. In compliance with current accounting rules, we recognize revenue related to up-front payments over the period of the contractual arrangements as we satisfy our performance obligations. Occasionally, we are required to estimate the period of a contractual arrangement or our performance obligations when the information is not clearly defined in the agreements we enter into. Should different estimates prevail, revenue recognized could

be materially different. Agreements where we have made estimates of our continuing obligations include our collaborations with Antisense Therapeutics Limited, or ATL, Amgen, Chiron, Industrial Technology Research Institutes of Taiwan and Lilly. As of September 30, 2003, we evaluated our estimates for the periods of contractual arrangements and determined that our estimates are appropriate.

In November 2002, the Emerging Issues Task Force issued Issue No. 00-21, or EITF 00-21, *Accounting for Revenue Arrangements with Multiple Deliverables.* This issue addresses the timing and method of revenue recognition for revenue arrangements that include the delivery of more than one product or service. EITF 00-21 is effective for revenue arrangements entered into in fiscal quarters beginning after June 15, 2003. We adopted EITF 00-21 for all revenue arrangements entered into after June 30, 2003 and have determined that this issue will not have a material impact on our operating results and financial positions.

Prior to the adoption of EITF 00-21, we recognized revenue related to milestones upon completion of the milestone's performance requirement. During the first quarter of 2003, we earned a milestone through our research collaboration with Amgen. In addition, during the second quarter of 2003, we earned a $1.5 million milestone from Lilly in the development of ISIS 23722, the antisense inhibitor of survivin. We adopted EITF 00-21 for revenue associated with all milestones earned under agreements entered into after June 30, 2003.

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

As part of our Lilly alliance, Lilly provided us a $100.0 million interest free loan to fund the research collaboration. As of September 30, 2003, we had drawn down $67.5 million on the $100.0 million loan. We discounted the $67.5 million loan to its net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time we entered into the loan. We are accreting the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan represents value Lilly gave to us to help fund the research collaboration, and is accounted for as deferred revenue and is recognized as revenue over the period of performance.

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

Inventory Valuation

Our inventories include drugs with alternative uses that are used primarily in our development activities and drugs we manufacture for our partners under contractual terms. Our inventories are stated at the lower of cost or market, cost being determined under the first-in, first-out method. We review inventories periodically and reduce our carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. In the second quarter of 2003, we reduced the carrying value of our raw materials related to Affinitak to zero. No reduction in the carrying value of inventory occurred in the third quarter of 2003.

Valuation of Intellectual Property

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

international patent applications, domestic and international issued patents, and licenses we have acquired from other parties. To determine if any impairment is present, we consider challenges or potential challenges to our existing patents, the likelihood of applications being issued, the scope of our issued patents and our experience. In the event that we determine that an impairment exists where we had previously determined that one did not exist, it may result in a material adjustment to our financial statements.

Valuation of Investments

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

We also have equity investments in biotech companies where we have an ownership interest of less than 20%. In determining if and when a decrease in market value below our cost is other-than-temporary in our equity positions, we examine historical trends in stock price, the financial condition and near term prospects of the issuer, and our current need for cash. When such a decline in value is deemed to be other-than-temporary, we recognize an impairment loss in the period operating results to the extent of the decline. During the first quarter of 2003, we recorded a non-cash loss of $2.4 million related to the impairment of our equity investments in ATL and Hybridon, Inc. This charge reflected the then-current market climate and was associated with the decline in market value of the equity investments from their initial valuations and was determined to be other-than-temporary. In the second and third quarters of 2003, we recorded unrealized gains related to our equity investments in ATL and Hybridon as a separate component of stockholders' equity, which reflected the increase in the market value of the investments since the first quarter of 2003.

Use of Estimates

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

Results of Operations

Revenue

Our total revenue was $11.3 million and $40.3 million for the three and nine months ended September 30, 2003, respectively, compared with $20.3 million and $58.3 million for the same periods in 2002. The decrease in revenue was primarily due to the reduction in revenue associated with the clinical development of Affinitak and the conclusion of Elan's participation in the Orasense and HepaSense collaborations. In late 2002, we reacquired product rights to ISIS 14803 for hepatitis C and an oral formulation of ISIS 104838 as a result of Elan's conclusion of its participation in the HepaSense and Orasense joint ventures, respectively. As a result, we did not earn revenue from these affiliates in 2003. The decrease in revenue was offset in part by new sources of revenue not present in

the same nine-month period of 2002, including the achievement of milestones in the discovery and development of drugs for our partners Lilly and Amgen.

Under the category of research and development revenue under collaborative agreements for the three and nine months ended September 30, 2003, we reported $11.3 million and $39.9 million, respectively, compared to $17.0 million and $49.6 million for the same periods in 2002. The decrease was primarily a result of drug shipments occurring in the first nine months of 2002 that were absent in the same period of 2003 and the reduction in revenue associated with the clinical development of Affinitak.

Research and development revenue from affiliates for the three and nine months ended September 30, 2002 consisted of revenue associated with our two joint ventures with Elan, Orasense and HepaSense. For the three and nine months ended September 30, 2002, we recognized $3.3 million and $8.4 million, respectively, from these collaborations as revenue. During the same periods in 2003, we did not earn revenue from these collaborations as Elan concluded its participation in the joint ventures in 2002.

Our revenue from licensing activities and royalties was $31,000 and $347,000 for the three and nine months ended September 30, 2003, respectively, compared to $10,000 and $306,000 for the same periods in 2002.

Operating Expenses

Total operating expenses for the three and nine months ended September 30, 2003 were $30.4 million and $97.8 million, respectively, compared to $37.8 million and $97.9 million for the same periods in 2002. On a proforma basis, operating expenses, for the three and nine months ended September 30, 2003 were $29.6 million and $95.1 million, respectively, compared to $37.7 million and $100.9 million for the same periods in 2002. The decrease in the proforma basis operating expenses for the three and nine months ended September 30, 2003 compared to the same periods in 2002 was primarily due to our implementation of an expense reduction plan in the second quarter of 2003 and the substantial completion of our development activities for Affinitak compared to the same periods last year. The decrease was offset in part by increased clinical development expenses for many of our other products. Proforma operating expenses, which include research and development and general and administrative expenses, but exclude compensation expense or benefit related to stock options and restructuring activities expense, provide a supplemental comparison of results of operating expenses and represent the costs of key activities and cost drivers for us. We believe that it is important to exclude compensation expense or benefit related to stock options from proforma operating expenses because it is based on the variability of our stock price rather than operations. We believe that it is important to exclude restructuring activities because these costs are directly related to a first quarter event, which was an isolated event, and should be excluded for comparability purposes and analysis of results of operations. We have provided a reconciliation of GAAP operating expenses to proforma operating expenses. Proforma operating expenses for the three and nine months ended September 30, 2003 and 2002, respectively, were the following (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2003	2002	2003	2002
	(unaudited)		(unaudited)	
As reported operating expenses according to GAAP	$ 30,361	$ 37,809	$ 97,789	$ 97,887
Excluding compensation expense (benefit) related to stock options	804	95	936	(3,011)
Excluding restructuring activities	—	—	1,803	—
Proforma operating expenses	$ 29,557	$ 37,714	$ 95,050	$ 100,898

Our research and development expenses consist of costs for antisense drug discovery, antisense drug development, our Ibis Therapeutics program and R&D Support costs. For the three and nine months ended September 30, 2003, we reported total research and development expenditures of $27.4 million and $87.8 million, respectively, compared to $35.5 million and $94.0 million for the same periods in 2002. The $6.2 million decrease for the first nine months in 2003 over 2002 was primarily due to our implementation of an expense reduction plan and a decrease in our total Affinitak related expenses. The decrease was offset in part by increased clinical development expenses for many of our other products.

Antisense drug discovery costs for the three and nine months ended September 30, 2003 totaled $8.7 million and $27.9 million, respectively, compared to $11.7 million and $31.2 million for the same periods in 2002. The decrease of $3.3 million for the nine months of 2003 over 2002 was principally a result of our planned expense reductions starting in the second quarter of 2003. This decrease was offset in part by the increase in expenses to support our research collaborations with Lilly and with Amgen.

Antisense drug development expenditures totaled $11.1 million and $36.7 million for the three and nine months ended September 30, 2003, respectively, compared to $16.1 million and $40.6 million for the same periods in 2002. The decrease of $3.9 million for the nine months in 2003 over 2002 is primarily due to the planned expense reductions started in the second quarter of 2003, offset in part by increased clinical development expenses for our other products.

Expenditures related to Affinitak for the three and nine months ended September 30, 2003 were $143,000 and $7.3 million, respectively, compared to $7.7 million and $14.2 million for the same periods of 2002. The decrease of $6.9 million for the first nine months of 2003 over 2002 was primarily due to a reduction in Affinitak related expenses as a result of the disappointing results from the first Phase III trial of Affinitak and the decision not to file a 2003 NDA. Costs related to the final phases of our Phase III trial primarily occurred in the first and second quarters of 2003 with minimal amounts incurred in the third quarter of 2003. In March 2003, we announced the results of Affinitak for the treatment of non-small cell lung cancer. In this trial, we observed no difference in overall survival of those patients who received Affinitak plus a standard chemotherapy regimen compared to those patients who received the standard chemotherapy alone. Based on these results, we will not file an NDA for Affinitak in 2003 and in April 2003, we initiated a small reduction in our workforce, which primarily represented positions that were in support of the commercialization and manufacture of Affinitak. Consequently, we incurred a one-time restructuring charge of approximately $1.8 million during the second quarter of 2003 and we expect to complete the utilization of the reserve related to this restructuring in the fourth quarter of 2003.

Our second drug in Phase III clinical trials, alicaforsen for Crohn's disease, had development expenditures totaling $1.9 million and $5.5 million for the three and nine months ended September 30, 2003, respectively, compared to $2.0 million and $5.3 million for the same periods of 2002. The increase of $200,000 for the nine months of 2003 over 2002 is a result of an increase in the number of patients undergoing treatment in our two Phase III trials. The trials initiated in November 2001 and June 2002.

Expenditures related to our other products in development totaled $8.4 million and $22.1 million for the three and nine months ended September 30, 2003, respectively, compared to $5.5 million and $19.2 million for the same periods of 2002. For the first nine months of 2003 and 2002, the $2.9 million increase is primarily due to an increase in the number of patients undergoing treatment in our Phase II trials and expenses related to products in the early stages of development.

Ibis expenditures for the three and nine months ended September 30, 2003 were $1.8 million and $6.8 million, respectively, compared to $2.1 million and $6.3 million for the same periods in 2002. The $500,000 increase for the nine months of 2003 over 2002 was primarily related to Ibis' performance

obligations under its multi-year government contracts with DARPA, awarded in October 2001, and USAMRIID, awarded in March 2002.

R&D Support costs for the three and nine months ended September 30, 2003 were $5.8 million and $16.5 million, respectively, compared to $5.7 million and $16.0 million for the same periods in 2002. The $500,000 increase for the nine months ended September 30, 2003 over the same period of 2002 is primarily due to increases in our research and development efforts to prepare for the manufacture and commercialization of Affinitak in the first quarter of 2003. This increase was partially offset by our planned expense reductions. While we work to control R&D Support costs, we expect that they will be directly related to fluctuations in our research and development expenses.

General and administration expenses for the three and nine months ended September 30, 2003 were $2.1 million and $7.2 million, respectively, compared to $2.2 million and $6.9 million for the same periods in 2002. The $300,000 increase for the nine months of 2003 over 2002 was primarily a result of an increase in employees and related benefits in the first quarter of 2003. As a result of the restructuring in April 2003, we reduced the number of employees to levels comparable to the first nine months of 2002.

Compensation expense related to stock options for the three and nine months ended September 30, 2003 was $804,000 and $936,000, respectively, which primarily consisted of compensation expense related to stock options associated with the employee stock option exchange program initiated in April 2003 and stock options granted to consultants, which we accounted for in accordance with EITF 96-18. We accounted for options affected by the employee stock option exchange program as variable stock options in accordance with *Accounting Principles Board Opinion No. 25* and *Financial Accounting Standard Board Interpretation No. 44*. In the same periods in 2002, we reported compensation expense of $95,000 and compensation benefit of $3.0 million, respectively. The compensation benefit represented the reversal of previously recorded compensation expense related to stock options accounted for as variable stock options. This benefit was associated with the option exchange program we offered to non-officer employees in January 2000. These variable stock options were either exercised or cancelled by December 31, 2002.

In the second quarter of 2003, we recorded a one-time restructuring charge of $1.8 million related to our expense reduction plan, which included a small reduction in our workforce. There were no restructuring charges in the same period of 2002.

Equity in Loss of Affiliates

We used the equity method of accounting for our investments in the Orasense and HepaSense joint ventures in which we own 80.1% and Elan owns 19.9%. As a result, we recognized 80.1% of the total loss reported by Orasense and HepaSense under equity in loss of affiliates. In 2002, Elan concluded its participation in the associated collaborations and as a result, we did not recognize any equity in loss of affiliates for the three and nine months ended September 30, 2003. This compares to $3.5 million and $13.2 million for the respective periods in 2002.

Investment Income

Investment income for the three and nine months ended September 30, 2003 totaled $1.2 million and $4.0 million, respectively, compared to $2.2 million and $6.2 million for the same periods in 2002. The $2.2 million decrease in investment income for the first nine months of 2003 over 2002 is primarily due to our lower average cash balance for the first nine months of 2003 compared to the first nine months of 2002. 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 nine months ended September 30, 2003 totaled $4.3 million and $13.7 million, respectively, compared to $3.8 million and $12.6 million for the same periods in 2002. The effect of a higher debt balance as of September 30, 2003, compared to September 30, 2002, was primarily offset by a decrease in the average interest rate on our debt. The decrease in the average interest rate was primarily due to the retirement, in May 2002 and July 2002, of higher interest rate debt with the proceeds from the issuance, in May 2002, of our $5^1/_2$% convertible subordinated notes due in 2009.

Net Loss Applicable to Common Stock

For the three and nine months ended September 30, 2003, we reported a net loss applicable to common stock of $22.4 million and $70.1 million, respectively, which included $175,000 and $518,000 of accreted dividends on preferred stock, respectively. Our net loss applicable to common stock was $17.8 million and $57.3 million for the three and nine months ended September 30, 2002, respectively, which included $222,000 and $892,000 of accreted dividends on preferred stock, respectively. The net loss applicable to common stock for the nine months ended September 30, 2003 included non-cash loss on investments of $2.4 million related to the other-than-temporary impairment of our investments in ATL and Hybridon. The increase in the net loss applicable to common stock was primarily a result of the increase in loss from operations and the absence of a net gain on debt extinguishment recorded in the same period of 2002.

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 September 30, 2003, we have earned approximately $390.8 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 $589.1 million from the sale of equity securities. We have borrowed approximately $319.0 million under long-term debt arrangements to finance a portion of our operations.

As of September 30, 2003, we had cash, cash equivalents and short-term investments totaling $234.8 million and working capital of $195.6 million. In comparison, we had cash, cash equivalents and short-term investments of $289.4 million and working capital of $244.2 million as of December 31, 2002. The decreases in our cash, cash equivalents and short-term investments and working capital 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.

As of September 30, 2003, our debt obligations totaled $237.4 million, compared to $242.6 million at December 31, 2002. Our debt obligations include long-term and current deferred contract revenue and contractual obligations that represent our payment obligations. The decrease was primarily due to the renegotiation of our manufacturing relationship with Lilly, including Lilly's waiver on repayment of the $21.2 million manufacturing loan it provided to us to

build the Affinitak manufacturing facility, of which we had $15.4 million outstanding at December 31, 2002. In addition, we repaid principal and interest related to a note payable to Abbott Laboratories and we repaid certain of our capital leases. The decreases were offset by the 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 amount at 20% and accreting to their face value over their terms by recording interest expense, and by the accrued interest on our convertible debt facility with Elan. We expect that capital lease obligations will increase over

time to fund capital equipment acquisitions required for our growing business. We will continue to use lease financing as long as the terms remain commercially attractive. Based on our current operating plan with reasonable assumptions for new sources of revenue and cash, we believe that our available cash, cash equivalents and short-term investments as of September 30, 2003, when combined with investment income and committed contractual cash payments from our partners, will be sufficient to meet our anticipated requirements for at least the next 36 months. The following table summarizes our contractual obligations as of September 30, 2003. The table provides a breakdown of when obligations become due. A more detailed description of the major components of our debt is provided in the paragraphs following the table:

	Payments Due by Period (in thousands)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
Convertible Partner Debt	$ 97,951	$ 22,576	$ 75,375	$ —	$ —
5 1/2% Convertible Subordinated Notes	$ 125,000	$ —	$ —	$ —	$ 125,000
Standard Operating Debt	$ 7,726	$ 726	$ 1,453	$ 5,547	$ —
Capital Lease Obligations	$ 6,759	$ 3,397	$ 3,362	$ —	$ —
Operating Leases	$ 13,086	$ 2,676	$ 4,530	$ 3,310	$ 2,570

Our contractual obligations are composed primarily of publicly traded convertible debt and partner debt that we can repay on favorable terms with equity at our option. Convertible partner debt includes: 1) the interest-free loan Lilly made available to us to fund the joint research collaboration; 2) the convertible promissory note provided by Elan to us in conjunction with the Orasense joint venture; and 3) the convertible debt provided by Boehringer Ingelheim International BmbH, or BI, associated with the collaborative agreement between the two companies.

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 September 30, 2003, we had drawn down $67.5 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 September 30, 2003, the balance in long-term obligations was $46.2 million and the balance in deferred revenue was $21.3 million.

In April 1999, in conjunction with the Orasense joint venture, Elan made available to us an $18.4 million line of credit evidenced by a convertible promissory note. The terms of the convertible promissory note provide for interest at 12% per annum, compounded semi-annually, maturing April 19, 2005. No principal or interest payments are required until the end of the loan. The loan may be prepaid by us at any time, at our option, in whole or in part, in cash or in common stock at a price equal to the average market value of the common stock for the 60 trading days ending two business days prior to the date of prepayment. At any time prior to maturity, Elan may convert all or any portion of the loan outstanding into shares of our common stock. Elan's conversion price for each amount we drew on the line of credit was set at the time we drew such amount. As of September 30, 2003, Elan's weighted average conversion price for the outstanding debt was $16.63 per share. The balance under this borrowing facility, including accrued interest, as of September 30, 2003 was $7.9 million. We cannot borrow any additional principal under this promissory note.

In 1996 and 1997, we borrowed a total of $22.6 million under a $40.0 million line of credit made available under the terms of our collaborative agreement with BI. The borrowed funds were used to fund research and development costs associated with the collaboration. Borrowings under the line of credit bear interest at the seven year U.S. interbanking rate plus 2.0%, determined at the time each advance was made, and range from 8.36% to 8.46%. Interest payments are due twice each year with principal repayment due seven years after the advance date. The principal may be repaid in cash or stock, at our option. If we elect to repay the loan in shares of our common stock, repayment will be made at a share price equal to 90% of the average market value over the 20 trading days preceding the maturity date. The balance under this line of credit as of September 30, 2003 was $22.6 million. In October 2003, we repaid the first installment of $8.3 million in cash.

The 5 1/2% convertible subordinated notes are due May 2009 and interest on these notes is payable on a semi-annual basis. The notes are convertible by its holders into shares of our common stock at a conversion price of $16.625 per share. As of September 30, 2003, the principal balance on this debt was $125.0 million.

Prospective Information

In November 2003, we received a grant of up to $8.0 million over three years from the Singapore Economic Development Board which will fund, in part, the broadening of two of Isis' RNA-based drug discovery and development programs: micro-RNA drug discovery and antisense drug discovery targeting the coronavirus associated with Severe Acute Respiratory Syndrome, or SARS.

RISK FACTORS

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

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

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

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

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

Drug discovery and development has inherent risks, including the risk that molecular targets prove not to be important in a particular disease, the risk that compounds that demonstrate attractive activity in preclinical studies do not demonstrate similar activity in human beings, and the risk that a compound is not safe or effective for use in humans. Antisense technology in particular is relatively new and unproven. We are applying most of our resources to create safe and effective drugs for human use. Any of the risks described above could prevent us from meeting this goal. In the past, we have invested in clinical studies of drug candidates, including some that remain in our pipeline, that have not resulted in proof of efficacy against targeted indications. In March 2003, we reported the results of our Phase III clinical trial of Affinitak in patients with late stage non-small cell lung cancer. In this trial, Affinitak, when added to carboplatin and paclitaxol, failed to demonstrate improved survival sufficient enough to support an NDA filing. A similar result could occur with the Affinitak trial Lilly is currently conducting as well as the trials for our other drugs.

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

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

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

- the receipt and scope of regulatory approvals;
- the establishment and demonstration in the medical and patient community of the efficacy and safety of our drug candidates and their potential advantages over competing products;
- the cost of our drug candidates compared to other available therapies;
- the patient convenience of the dosing regiment 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 of our Hepatitis C research collaboration with Merck at the end of May 2003, the termination in 2002 of our HepaSense and Orasense collaborations with Elan and the termination of our collaboration with Merck to develop ISIS 113715.

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

Additional drug candidates in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics Limited, OncoGenex Technologies Inc. and Lilly with respect to ISIS 23722, the antisense inhibitor to survivin. If any of these pharmaceutical company partners were to stop funding and/or developing these drug candidates, our business 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. Such competition may negatively impact the partners' focus on and commitment to our drug candidate and, as a result, could delay or otherwise negatively affect the commercialization of such drug candidate.

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

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

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

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

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

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

Because drug discovery and development and research services require substantial lead-time and money prior to commercialization, our expenses have exceeded our revenue since we were founded in January 1989. As of September 30, 2003, our accumulated losses were approximately $530.0 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from interest income and research grants and the sale or licensing of patents. We currently derive our current product revenue solely from sales of Vitravene. This product has limited sales potential. We expect to incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or services, or achieve or sustain future profitability.

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

Most of our product candidates are still undergoing clinical trials or are in the early stages of research and development. All of our products under development will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and a commitment of significant additional resources prior to their commercialization. Based on our current operating plan, we believe that our available cash, cash equivalents and short-term investments as of September 30, 2003, combined with investment income and committed contractual cash payments will be sufficient to meet our anticipated requirements for at least the next 36 months. If we do not meet our goals to commercialize our drug products and research services or to license our proprietary technologies, we may need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- the profile and launch timing of our drugs;
- continued scientific progress in our research, drug discovery and development programs;
- the size of these programs and progress with preclinical and clinical trials;
- the time and costs involved in obtaining regulatory approvals;
- competing technological and market developments, including the introduction by others of new therapies that address our markets;
- success in the marketing of our target validation service and licensing program; and
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements.

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

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

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

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

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

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

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

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

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

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

It is possible that in the future we may have to defend our intellectual property rights. In the event of an intellectual property dispute, we may be forced to litigate to defend our rights or assert them against others. Disputes could involve litigation or proceedings declared by the U.S. Patent and Trademark Office or the International Trade Commission. Intellectual property litigation can be

extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business.

If a third party claims that our products or technology infringe their patents or other intellectual property rights, we may have to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to such intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of patents or applications held by others that relate to our business. This is especially true since patent applications in the United States are filed confidentially. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain unresolved.

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

For planning purposes, we estimate the timing of a variety of clinical, regulatory and other milestones, such as when a certain product candidate will enter the clinic, when a clinical trial will be completed or when an application for marketing approval will be filed. Our estimates are based on present facts and a variety of assumptions. Many of the underlying assumptions are outside of our control. If milestones are not achieved when we expect them to be, investors could be disappointed and the price of our securities would likely decrease.

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

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

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

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our convertible notes. During the 12 months preceding September 30, 2003, the market price of our common stock has ranged from $2.50 to $11.00 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial results, technological innovations or new drug products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

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

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66 $^{2}/_{3}$% of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15% or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. We also have implemented a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. These provisions, as well as Delaware law and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests. In addition, our board of directors has the authority to fix the rights and preferences of and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

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

We have granted registration rights in connection with the issuance of our securities to Elan International Services, Ltd., Eli Lilly and Company, and Reliance Insurance Company. In the aggregate, these registration rights cover approximately 4,166,667 shares of our common stock, which are currently outstanding and additional shares of our common stock, which may become outstanding upon the conversion of outstanding convertible securities. If these holders exercise their registration rights, it will bring additional shares of our common stock into the market, which may have an adverse effect on the price of our securities.

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

For the period ended September 30, 2003, an evaluation was performed under the supervision and with the participation of our management, including the Chief Executive Officer (CEO) and the Chief Financial Officer (CFO), of the effectiveness of the design and operation of our disclosure controls and procedures. Based on that evaluation, our management, including the CEO and CFO, concluded that our disclosure controls and procedures were effective as of September 30, 2003. There have been no

significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to September 30, 2003.

PART II—OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

Not applicable

ITEM 2. CHANGES IN SECURITIES AND USE OF PROCEEDS

Not applicable

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

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

Not applicable

ITEM 5. OTHER INFORMATION

Not applicable

ITEM 6. EXHIBITS AND REPORTS ON FORM 8-K

a. Exhibits

Exhibit Number		Description of Document
10.1	—	Grant letter dated September 29, 2003 from the Centers for Disease Control and Prevention (with certain confidential information deleted).
10.2	—	Amendment No. 1 to Isis Pharmaceuticals Inc. 2000 Employee Stock Purchase Plan.
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 August 5, 2003, 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, 2003.

On November 4, 2003, the Registrant filed a report on Form 8-K for the announcement of its third quarter results and the related press release dated November 4, 2003.

Isis Pharmaceuticals, Inc.
(Registrant)

SIGNATURES

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

Signatures	Title	Date
/s/ STANLEY T. CROOKE, M.D., PH.D. Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	November 12, 2003
/s/ B. LYNNE PARSHALL B. Lynne Parshall, Esq.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	November 12, 2003

ISIS PHARMACEUTICALS, INC. FORM 10-Q INDEX
ITEM 2. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS
ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK
ITEM 4. CONTROLS AND PROCEDURES
PART II—OTHER INFORMATION
ITEM 1. LEGAL PROCEEDINGS
ITEM 2. CHANGES IN SECURITIES AND USE OF PROCEEDS
ITEM 3. DEFAULT UPON SENIOR SECURITIES
ITEM 4. SUBMISSION OF MATTERS TO A VOTE OF SECURITY HOLDERS
ITEM 5. OTHER INFORMATION
ITEM 6. EXHIBITS AND REPORTS ON FORM 8-K

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Exhibit 10.1

*** CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)4, AND 240.24b-2

NOTICE OF GRANT AWARD

RESEARCH
Department of Health and Human Services
Centers for Disease Control and Prevention

Issue Date: 09/29/2003

CENTER FOR INFECTIOUS DISEASES, CDC

Grant Number: 1 R01 CI000099-01
Principal Investigator: ECKER, DAVID J PHD
Project Title: Automated Simultaneous Detection of Bioterrorism Agents

PRESIDENT IBIS THERAPEUTICS
IBIS THERAPEUTICS
1891 RUTHERFORD
CARLSBAD, CA 92008
CARLSBAD, CA 92008
UNITED STATES

Budget Period: 09/15/2003 - 09/14/2004
Project Period: 09/15/2003 - 09/14/2006

Dear Business Official:

The Centers for Disease Control and Prevention hereby awards a grant in the amount of $2,629,242 (see "Award Calculation" in Section I) to IBIS THERAPEUTICS, INC. in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to terms and conditions referenced below.

Acceptance of this award including the Terms and Conditions is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Award recipients are responsible for reporting inventions derived or reduced to practice in the performance of work under this grant. Rights to inventions vest with the grantee organization provided certain requirements are met and there is acknowledgement of CDC support. In addition, recipients must ensure that patent and license activities are consistent with their responsibility to make unique research resources developed under this award available to the scientific community, in accordance with CDC policy. For additional information, please visit http://www.iedison.gov.

If you have any questions about this award, please contact the individual(s) referenced in the information below.

Sincerely yours,

Mildred Garner
Grants Management Officer
Centers for Disease Control and Prevention

See additional information below

SECTION I - AWARD DATA - 1 R01 CI000099-01

AWARD CALCULATION (U.S. Dollars):	
Salaries and Wages	[***]
Fringe Benefits	[***]
Personnel Costs	[***]
Consultant Services	[***]
Equipment	[***]
Supplies	[***]
Travel Costs	[***]
Other Costs	[***]

Federal Direct Costs		[***]
Federal F&A Costs		[***]
APPROVED BUDGET	$	2,629,242
TOTAL FEDERAL AWARD AMOUNT	$	2,629,242

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project, is as follows.

02	$	2,313,198
03	$	1,036,103

FISCAL INFORMATION:
CFDA Number: 93.856
EIN: 1330336973A1
Document Number: RCI000099A

IC	CAN	FY2003	FY2004	FY2005
CI	92100B9	2,629,242	2,313,198	1,036,103

ADMINISTRATIVE DATA:
PCC: / OC: 41.4A /Processed: GARNERM 030929 1244

SECTION II - PAYMENT/HOTLINE INFORMATION - 1 R01 CI000099-01

For payment information see Payment Information section in Additional Terms and Conditions.

To report fraud, waste or abuse see Inspector General section in Additional Terms and Conditions.

SECTION III - TERMS AND CONDITIONS - 1 R01 CI000099-01

This award is based on the application submitted to, and as approved by, the CDC on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Grant Award.

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b. The restrictions on the expenditure of federal funds in appropriations acts, to the extent those restrictions are pertinent to the award.

c. 45 CFR Part 74 or 45 CFR Part 92 as applicable.

d. The PHS Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.

e. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

Treatment of Program Income:
Additional Costs

Approval List C0-84-G03

1. INCORPORATION:

Program Announcement Number PA-03-080, Bio-defense and Emerging Infectious Diseases Research Opportunities and applicable amendments and the application dated January 30, 2003 are made a part of this award by reference.

2. INDIRECT COSTS:

Indirect Costs are awarded at a rate of 51%, as requested.

3. HUMAN SUBJECTS RESTRICTION: No Restrictions-Per Summary Statement, SRG concerns noted.

Notice: Under governing regulations, Federal funds administered by the Department of Health and Human Services shall not be expended for research involving human subjects, and individuals shall not be enrolled in such research, without prior approval by the Office for Human Research Protections (OHRP) of an assurance to comply with the requirements of 45 CFR 46 to protect human research subjects.

4. REPORTING REQUIREMENTS: All reports (original and two copies) should be submitted to the CDC Grants Management Officer ("GMO"), ATTN: Grants Management Specialist, Centers for Disease Control & Prevention, Procurement and Grants Office, AABB, 2920 Brandywine Road, Atlanta, Georgia 30341.

a. An interim progress narrative report/non-competing continuation application is required to be submitted to the Grants Management Officer, no later than June 1, 2004. The report must contain the following: (1) Progress on current budget period objectives and activities to include explanation on unmet objectives; (2) Interim Financial Status Report (SF 269). The FSR would reflect projected unobligated balance as of September 14, 2004; (3) New

budget period proposed program objectives and activities; and (4) Detailed line-item budget and justification for next budget period, September 15, 2004 through September 14, 2005.

b. Annual Progress Reports are required to be submitted to the Grants Management Officer ninety (90) days after the end of the budget period. The due date is October 14, 2004.

c. An Annual Financial Status Report (FSR) (SF 269) (Long Form) for the budget period is required to be submitted to the Grants Management Officer ninety 90 days after the end of the budget period. The due date is December 14, 2004. (NOTE: The FSR is prepared on a budget year and NOT on a cumulative basis. FSR may be downloaded from the following website: http://www.whitehouse.gov/omb/grants/index.html

e. Audit Requirement: You must comply with the audit requirements of OMB Circular A-133, revised June 24, 1997 which rescinded OMB Circular A-128 "Audits of State and Local Governments." Please send a courtesy copy of completed audits and any management letters on a voluntary basis to the following:

Centers for Disease Control and Prevention (CDC)
Attention: Head, Acquisition Assistance Oversight and Evaluation
2920 Brandywine Road, NE
Atlanta, Georgia 30341

You are required to ensure that subrecipients receiving CDC funds also meet the requirements of OMB A-133 (total Federal grant or cooperative agreement funds received exceed $300,000). Additionally, you must also ensure that appropriate corrective action is taken within six months after receipt of the subrecipient audit report in instances of non- compliance with Federal laws and regulations. You are to consider whether subrecipient audits necessitate adjustment of your own records.

If a subrecipient is not required to have an OMB A-133 audit, you are still required by OMB A-133 to perform adequate monitoring of subrecipient activities. You should require each subrecipient to permit independent auditors to have access to the subrecipient's records and financial statements. YOU SHOULD INCLUDE THESE REQUIREMENTS IN SUBRECIPIENT CONTRACTS.

All reports must be submitted within the specified time frame and location. Delinquent reporting may impact future funding.

5. EXPANDED AUTHORITIES: The recipient of this award is granted "expanded authorities" in the administration of the award. The grantee may elect to extend the project period for up to 12 months without additional funds. At least 10 days prior to the original project end date, the grantee must notify the awarding agency GMO in writing (e-mail or letter) of the extension. The notification must be signed by the authorizing business official and must include the new project end date. Extensions beyond the initial notification must be REQUESTED by the grantee organization and be APPROVED by the awarding GMO.

6. CORRESPONDENCE: All correspondence regarding this award must be identified with the award number as shown at the top right of this page.

7. PRIOR APPROVAL: In accordance with the Code of Federal Regulations, Part 74, "ALL" requests which require prior approval must bear the signature of an authorized official of the business office of the grantee organization as well as the principal investigator or program or project director." Any requests received which reflect only one signature will be returned to the grantee unprocessed. Additionally, any requests involving funding issues must include a new proposed budget and a narrative justification of the requested changes.

8. PUBLICATIONS: Publications, journal articles, etc. produced under a CDC grant support project must bear an acknowledgment and disclaimer, as appropriate, such as: This publication (journal article, etc.) was supported by Grant/Cooperative Agreement Number _____ from (name of awarding agency). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of (name of awarding agency).

9. EQUIPMENT AND PRODUCTS: To the greatest extent practicable, all equipment and products purchased with CDC funds should be American-made.

10. ACKNOWLEDGMENT OF FEDERAL SUPPORT: When issuing statements, press releases, requests for proposals, bid solicitations and other documents describing projects or programs funded in whole or in part with Federal money, all awardees receiving Federal funds, including and not limited to State and local governments and recipients of Federal research grants, shall clearly state (1) the percentage of the total costs of the program or project which will be financed with Federal money, (2) the dollar amount of Federal funds for the project or program, and (3) percentage and dollar amount of the total costs of the project or program that will be financed by nongovernmental sources.

11. INSPECTOR GENERAL: For your information, the United States Department of Health and Human Services Inspector General maintains a toll-free telephone number, 800-447-8477 (800-HHS-TIPS), for receiving information concerning fraud, waste or abuse under grants and cooperative agreements. Such reports are kept confidential, and callers may decline to give their names if they choose to remain anonymous.

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12. PAYMENT INFORMATION

Automatic Drawdown:

Payment under this award will be made available through the Department of Health and Human Services (HHS) Payment Management System (PMS). PMS is administered by the Division of Payment Management, Program Support Center, HHS. PMS will forward the DHHS Manual for Recipients Financed Under the Payment Management System (PMS), PMS-270 and PMS-272 forms.

A. PMS correspondence, mailed through the U.S. Postal Service, should be addressed as follows: Division of Payment Management, FMS/PSC/HHS, P.O. Box 6021 Rockville, MD 20852.

B. If a carrier other than the U.S. Postal Service is used, such as United Parcel Service, Federal Express, or other commercial service, the correspondence should be addressed as follows: Division of Payment Management, FMS/PSC/HHS, Rockwall Building #1, Suite 700, 11400 Rockville Pike, Rockville, MD 20852.

To expedite your first payment from this award, attach a copy of the Notice of Grant/Cooperative Agreement to your payment request form.

13. CDC CONTACT NAMES:

Business and Grants Policy Contact
Sharron Orum, Grants Management Specialist
Acquisition and Assistance Branch B, CDC
2920 Brandywine Road, Room 3000
Atlanta, Georgia 30341-4146
Telephone: (770) 488-2716
Internet Address: spo2@cdc.gov

Programmatic Contact
Barbara Stewart, Public Health Analyst
National Center for Infectious Diseases (NCID)
1600 Clifton Road, C-19
Atlanta, GA 30333
Telephone: (404) 639-0044
Internet Address: BSG2@cdc.gov

Sharon Orum, Grants Specialist

SPREADSHEET
GRANT NUMBER: 1 R01 CI000099-01

P.I.: ECKER, DAVID J
INSTITUTION: IBIS THERAPEUTICS, INC.

	YEAR 01	YEAR 02	YEAR 03
Salaries and Wages	[***]	[***]	[***]
Fringe Benefits	[***]		
Personnel Costs	[***]	[***]	[***]
Consultant Services	[***]	[***]	[***]
Equipment	[***]	[***]	
Supplies	[***]	[***]	[***]
Travel Costs	[***]	[***]	[***]
Other Costs	[***]	[***]	
TOTAL FEDERAL DC	2,222,511	1,540,363	687,512
TOTAL FEDERAL F&	406,731	772,835	348,591
TOTAL COST	2,629,242	2,313,198	1,036,103

QuickLinks

NOTICE OF GRANT AWARD

QuickLinks -- Click here to rapidly navigate through this document

Exhibit 10.2

AMENDMENT NO. 1 TO
ISIS PHARMACEUTICALS, INC.
2000 EMPLOYEE STOCK PURCHASE PLAN

This Amendment No. 1 to the Isis Pharmaceuticals, Inc. 2000 Employee Stock Purchase Plan (the "Amendment"), is effective as of September 23, 2003.

A. WHEREAS, the Board of Directors of Isis wish to amend the Isis Pharmaceuticals, Inc. 2000 Employee Stock Purchase Plan (the "ESPP"), as more fully described below.

NOW THEREFORE, the Board of Directors hereby approves the amendment of the ESPP as follows:

All capitalized terms not otherwise defined herein, will have the meanings ascribed to them in the ESPP.

ARTICLE 1. AMENDMENT

1.1 *Amendment and Restatement of Section 3(a).* Section 3(a) of the ESPP is hereby amended, restated and replaced in its entirety by the following language:

"(a) Subject to the provisions of Section 12 relating to adjustments upon changes in stock, the stock that may be sold pursuant to rights granted under the Plan shall not exceed in the aggregate two hundred thousand (200,000) shares of Common Stock (the "Reserved Shares"). Through the first nine (9) anniversaries of the Effective Date of the Plan, on January 1 of each year the number of Reserved Shares will be increased automatically by the lesser of (i) one percent (1%) of the total number of shares of Common Stock outstanding on such date or (ii) two hundred thousand (200,000) shares. If any right granted under the Plan shall for any reason terminate without having been exercised, the Common Stock not purchased under such right shall again become available for the Plan."

1.2 Except as specifically provided in this Amendment, all other terms and conditions of the ESPP will remain in full force and effect.

QuickLinks

AMENDMENT NO. 1 TO ISIS PHARMACEUTICALS, INC. 2000 EMPLOYEE STOCK PURCHASE PLAN

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: November 12, 2003

/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: November 12, 2003

/s/ B. LYNNE PARSHALL

B. Lynne Parshall, Esq.
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 September 30, 2003, 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: November 12, 2003

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

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