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SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 10-Q

(Mark One)

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

For the quarterly period ended March 31, 2002

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 ☒ Noo (2) Yes ☒ Noo

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

Common stock $.001 par value	**54,165,224 shares**
(Class)	(Outstanding at May 6, 2002)

ISIS PHARMACEUTICALS, INC.

FORM 10-Q

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ISIS PHARMACEUTICALS, INC.

CONDENSED BALANCE SHEETS

(in thousands, except share data)

	March 31, 2002 (Unaudited)	December 31, 2001 (Note)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 92,448	$ 127,011
Short-term investments	199,561	185,007
Contracts receivable	9,996	10,360
Other current assets	8,957	6,438
Total current assets	310,962	328,816
Property, plant and equipment, net	33,194	28,245
Licenses, net	31,754	32,361
Patents, net	17,726	16,735
Deposits and other assets	3,320	6,605
Long-term investments	2,708	4,299
Total assets	$ 399,664	$ 417,061
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 5,803	$ 6,126
Accrued compensation	2,505	5,646
Accrued liabilities	3,257	3,942
Current portion of deferred revenues	23,249	22,696
Current portion of long-term obligations	9,544	9,837
Total current liabilities	44,358	48,247
Long-term obligations, less current portion	133,923	125,710

Long-term deferred revenue, less current portion	18,472	20,005
Stockholders' equity:		
Series A Convertible Exchangeable 5% Preferred stock, $.001 par value, 120,150 shares authorized, issued and outstanding at March 31, 2002 and December 31, 2001	12,015	12,015
Accretion of Series A Preferred stock dividends	1,881	1,711
Series B Convertible Exchangeable 5% Preferred stock, $.001 par value, 16,620 shares authorized, 12,015 shares issued and outstanding at March 31, 2002 and December 31, 2001	12,015	12,015
Accretion of Series B Preferred stock dividends	1,387	1,222
Common stock, $.001 par value, 100,000,000 shares authorized, 53,972,968 shares and 53,750,318 shares issued and outstanding at March 31, 2002 and December 31, 2001, respectively	54	54
Additional paid-in capital	582,569	582,258
Deferred compensation	(67)	(245)
Accumulated other comprehensive income (loss)	(2,045)	660
Accumulated deficit	(404,898)	(386,591)
Total stockholders' equity	202,911	223,099
Total liabilities and stockholders' equity	$ 399,664	$ 417,061

Note: The balance sheet at December 31, 2001 has been derived from the audited financial statements at that date.

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

CONDENSED STATEMENTS OF OPERATIONS

(in thousands, except for per share amounts)

(Unaudited)

	Three months ended March 31,	
	2002	**2001**
Revenue:		
Research and development revenue under collaborative agreements	$ 14,714	$ 2,789
Research and development revenue from affiliates	3,034	1,716
Licensing and royalty revenue	211	128
Total revenue	17,959	4,633
Expenses:		
Research and development	26,983	19,134
General and administrative	2,226	2,816
Compensation related to stock options	(1,532)	(83)
Total operating expenses	27,677	21,867
Loss from operations	(9,718)	(17,234)
Equity in loss of affiliates	(5,767)	(3,964)
Interest income	2,144	1,977
Interest expense	(4,631)	(3,626)
Net loss	(17,972)	(22,847)
Accretion of dividends on preferred stock	(335)	(319)
Net loss applicable to common stock	$ (18,307)	$ (23,166)
Basic and diluted net loss per share	$ (0.34)	$ (0.58)
Shares used in computing basic and diluted net loss per share	53,923	40,150

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

CONDENSED STATEMENTS OF CASH FLOWS

(In thousands)

(Unaudited)

	Three months ended March 31,	
	2002	**2001**
Net cash used in operating activities	$ (15,730)	$ (17,062)
Investing activities:		
Short-term investments, net	(17,259)	(12,217)
Property and equipment	(6,230)	(1,094)
Other assets	(1,485)	(1,269)
Investment in affiliates	(2,332)	(32)
Net cash used in investing activities	(27,306)	(14,612)
Financing activities:		
Net proceeds from issuance of equity securities	2,021	877
Proceeds from long-term borrowings	7,332	—
Principal payments on debt and capital lease obligations	(880)	(761)
Net cash provided from financing activities	8,473	116
Net decrease in cash and cash equivalents	(34,563)	(31,558)
Cash and cash equivalents at beginning of period	127,011	39,615
Cash and cash equivalents at end of period	$ 92,448	$ 8,057
Supplemental disclosures of cash flow information:		
Interest paid	$ 207	$ 303

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

NOTES TO CONDENSED FINANCIAL STATEMENTS

March 31, 2002

(Unaudited)

1. Basis of Presentation

The unaudited interim financial statements for the three month period ended March 31, 2002 and 2001 have been prepared on the same basis as the Company's audited financial statements for the year ended December 31, 2001. 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, 2001 included in the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission.

Revenue Recognition

Revenue is generally recognized when all contractual obligations have been satisfied and collection of the resulting receivable is reasonably assured.

Research and development revenue under collaborative agreements.

Research and development revenue under collaborative agreements is recognized as the related expenses are incurred, up to contractual limits. Payments received under these agreements that are related to future performance are deferred and recorded as revenue as they are earned over the specified future performance period. Revenue related to nonrefundable, upfront fees is recognized over the period of the contractual arrangements as performance obligations related to the services to be provided have been satisfied. Revenue related to milestones is recognized upon completion of the milestone's performance

requirement. Revenue from federal research grants are recorded during the period in which the related expenditures are incurred. Revenue from product sales, which have not been material, is recognized as the products are shipped.

As part of the Company's alliance with Eli Lilly and Company, Lilly provided a $100 million interest free loan to fund the research collaboration. As of March 2002 Isis had drawn down $25 million on the $100 million loan. Isis discounted the $25 million that had been drawn on the loan as of March 31, 2002, to its net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time Isis entered into the loan. Isis is accreting the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan, represents value given to Isis by Lilly to help fund the research collaboration, and is accounted for as deferred revenue and is recognized as revenue over the period of performance.

Research and development revenue from affiliates

Research and development revenue from affiliates is recognized as the related expenses are incurred, up to contractual limits. Revenue related to milestones is recognized upon completion of the milestone's performance requirement.

Licensing and royalty revenue

Licensing and royalty revenue for which no services are required to be performed in the future is recognized immediately, if collectibility is reasonably assured.

Use of Estimates

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

2. Strategic Alliances

Affiliates

Isis currently has two joint ventures with Elan Corporation, plc (Elan). In April 1999, Orasense Ltd. (Orasense) was formed to develop technology for the oral formulation of oligonucleotide drugs. In January 2000, the second joint venture, HepaSense Ltd. (HepaSense), was formed to treat patients chronically infected with the Hepatitis C virus. Both affiliates are Bermuda limited companies. Each entity's outstanding common stock is owned 80.1% by Isis and 19.9% by Elan.

Elan and its subsidiaries have retained significant minority investor rights that are considered "participating rights' as defined in EITF 96-16 in each entity. Therefore, Isis does not consolidate the financial statements of Orasense or HepaSense, but instead accounts for the investments in each under the equity method of accounting. During the three-month period ended March 31, 2002, Isis recognized $1.6 million and $1.4 million for Orasense and HepaSense, respectively, in revenue for research and development activities performed for these joint ventures. During the three-month period ended March 31, 2001, Isis reported $0.8 million and $0.9 million in revenue for Orasense and HepaSense, respectively. These amounts are included as research and development revenue from affiliates for the respective periods.

The results of operations of Orasense for the quarter ended March 31, 2002 and 2001 are as follows (in thousands):

	Three Months Ended March 31,	
	2002	2001
Revenue	$ —	$ —
Research and development expense	3,231	2,460
Net loss	$ (3,231)	$ (2,460)

The results of operations of HepaSense for the quarter ended March 31, 2002 and 2001 are as follows (in thousands):

	Three Months Ended March 31,	
	2002	2001
Revenue	$ —	$ —
Research and development expense	3,969	2,154
Net loss	$ (3,969)	$ (2,154)

Merck and Co., Inc.

In February 2002, GeneTrove, a division of Isis, initiated a functional genomics collaboration with Merck & Company, Inc. (Merck). Under the agreement, GeneTrove is performing gene functionalization and target validation services to help Merck validate and prioritize genes for its drug discovery program.

Pharmacia Corporation

In March 2002, GeneTrove initiated a functional genomics collaboration with Pharmacia Corporation (Pharmacia). Under the agreement, GeneTrove is performing gene functionalization and target validation services to help Merck validate and prioritize genes for its drug discovery program. As part of the collaboration, Isis also granted Pharmacia a license to specific patents covering Ribonuclease H, or Rnase H, mechanism of action for Pharmacia's in-house antisense based functional genomics program.

U.S. Army Medical Research Institute & Infectious Diseases

In March, 2002, Ibis Therapeutics, a division of Isis, transitioned its government-sponsored research program to discover novel antibacterial drugs for biological warfare defense to the U.S. Army Medical Research Institute of Infectious Diseases, or USAMRIID. Through this transition, Ibis has achieved a new three-year contract valued at up to $2.4 million from USAMRIID to advance its work in developing therapeutic countermeasures to biological warfare. This contract builds on Ibis's earlier research programs with DARPA. Transition from DARPA to other government agencies for later-stage program development is a direct result of agency selection and demonstration of a successful initiative.

3. 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:

Statements of Comprehensive Loss
(Unaudited)

	Three Months Ended March 31,	
	2002	2001
	(in thousands)	
Comprehensive loss:		
Change in unrealized gains (losses) on available for sale securities	$ (2,705)	$ 473
Net loss	(18,307)	(23,166)
Comprehensive loss	$ (21,012)	$ (22,693)

4. Subsequent Events

In April 2002, Isis extended its collaboration with Merck to discover drug candidates to treat patients with HCV. The objective of the one-year extension is to continue Isis' discovery efforts to identify additional novel compounds for Merck to potentially develop as new treatments for HCV. Merck has agreed to pay Isis research support for an additional year, as well as a research milestone, clinical development milestone payments for compounds that arise from the collaboration and royalties from product sales. Isis began the original three-year drug discovery collaboration with Merck in June 1998 and announced the first one-year extension in May 2001. Isis achieved a research milestone in October 2001.

In April 2002, Isis achieved of a development milestone in its HepaSense Ltd. joint venture with Elan triggering a $3.75 million equity purchase by Elan of Isis common stock at a price of $29.74. Elan also received a warrant to purchase 6,304 shares of Isis common stock at an exercise price of $59.48 per share.

In May 2002, Isis issued $125 million of $5^{1}/_{2}$% convertible subordinated notes due 2009 in a private placement. The Company received approximately $121 million net of offering costs.

In May 2002, Isis retired its 14% Senior Subordinated Notes. The total amount of this debt, including principal plus interest, was approximately $74 million.

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 in 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, 2001, 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 16 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 can design antisense drugs to treat a wide variety of diseases. Due to their gene selectivity, antisense drugs have the potential to be highly effective and less toxic than traditional drugs. We have made significant progress in understanding the capabilities of antisense drugs in treating disease. We have developed new chemistries and novel formulations to

enhance the potency and utility of antisense drugs, and we have successfully turned our expertise into a broad pipeline of 13 antisense products currently in all phases of clinical development. Our drugs in development treat a variety of health conditions, including cancer and inflammatory, viral, metabolic and dermatological diseases, and are being studied in intravenous, subcutaneous, topical cream, enema and oral formulations. We achieved marketing clearance for the world's first antisense drug Vitravene® (fomivirsen) in 1998.

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 thereto. 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 all contractual obligations have been satisfied and we are reasonably assured of collecting the resulting receivable. We often enter into collaborations where we receive nonrefundable up-front payments for prior or future expenditures. In compliance with current accounting rules, we recognize revenue related to up-front payments over the period of the contractual arrangements as we satisfy our performance obligations. Occasionally, we are required to estimate the period of a contractual arrangement or our performance obligation when the information is not clearly defined in the agreements we enter into. Should different estimates prevail, revenue recognized could be materially different. Agreements where we have made estimates of our continuing obligations include our collaborations with Lilly, Antisense Therapeutics Limited, Amgen, Merck and our government contract with DARPA entered into in fiscal 2001.

As part of our Lilly alliance, Lilly provided a $100 million interest free loan to fund the research collaboration. As of March 31, 2002 we had drawn down $25 million on the $100 million loan. We discounted the $25 million that had been drawn on the loan as of March 31, 2002 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 given to us by Lilly to help fund the research collaboration, and is accounted for as deferred revenue and is recognized as revenue over the period of performance.

Additionally, licensing and royalty agreements we enter into for which we have no future performance obligations and are reasonably assured of collecting the resulting receivable are recognized as revenue immediately. Licensing and royalty agreements where we have no future obligations include Eyetech Pharmaceuticals and Coley Pharmaceuticals Group entered into in 2001 and 2000, respectively.

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 it is determined that an impairment exists where we had previously determined that one did not exist, it may result in a material adjustment to our financial statements.

Valuation of Short-Term Investments

We 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. 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. To date, we have not had any material losses related to our cash or short-term investments.

Results of Operations

Revenue

Our total revenue was $18.0 million for the three months ended March 31, 2002, compared with $4.6 million for the same period in 2001. The $13.3 million increase in revenue was primarily due to an increase in research and development revenue under collaborative agreements which was a result of our success in attracting new collaboration partners and signing new technology licenses during 2001 and the first quarter of 2002, which have contributed to revenue in the first quarter of 2002. The most significant contributor to the increase in revenue was our strategic alliance with Lilly. As part of the Lilly alliance, we licensed our Phase III investigational drug, Affinitac™ (formerly known as LY900003, ISIS 3521).

Under the category of research and development revenue under collaborative agreements, for the quarter ended March 31, 2002, we reported $14.7 million, compared to $2.8 million for the same period in 2001. The increase of $11.9 million is a result of our entering into a variety of new collaboration agreements. Contributing to a majority of the increase was revenue associated with our strategic alliance with Lilly which we entered into in August 2001. The revenue from the Lilly alliance included revenue from the reimbursement of development costs and the license of Affinitac and revenue from the $25 million draw down of the $100 million interest free loan to fund the research

collaboration. Also contributing to the increase was revenue associated with our GeneTrove division's partnerships with Celera Genomics, Chiron Corporation and Amgen, each entered into in the second half of 2001. Additionally, in October 2001, our Ibis division initiated a new biological warfare defense research program with DARPA, which also contributed to the quarter-to-quarter increase in revenues.

Research and development revenue from affiliates consisted of revenue associated with our two joint ventures with Elan, Orasense and HepaSense. For the three months ended March 31, 2002, we recognized $1.6 million and $1.4 million from Orasense and HepaSense, respectively, as revenue. During the same period in 2001, we recognized $0.8 million and $0.9 million as revenue from Orasense and HepaSense, respectively. The increase of $1.3 million in revenue from affiliates was a result of increased development activities performed for each joint venture.

Our revenue from licensing activities and royalties was $0.2 million for the period ended March 31, 2002, compared with $0.1 million in 2001.

Operating Expenses

Total operating expenses for the quarter ended March 31, 2002 totaled $27.7 million compared to $21.9 million for the same period of 2001. The increase of $5.8 million was the result of an increase in research and development expenses in 2002 over 2001, partially offset by a decrease in general and administrative expenses, and a reversal of compensation expense related to stock options. Partially offsetting the increase in research and development expenses, and contributing to the decrease in general and administration expenses, was the impact of capitalizing costs related to the production of our drugs. Historically, we had expensed drug manufacturing costs as they were incurred. In 2002, in response to the advancement of our pipeline into later stages of clinical development and as a result of the increasing number of clinical supply agreements where we sell drug that we manufacture to partners, we began capitalizing all manufacturing cost for our drugs. We will expense manufacturing costs when we ship our drugs to partners and as we use our drugs in our own trials.

Our research and development expenses consist of costs for antisense drug discovery, including GeneTrove, antisense drug development, our Ibis Therapeutics' division and R&D Support costs. For the quarter ended March 31, 2002, we reported total research and development expenditures of $27.0 million, compared to $19.1 million reported in 2001. The $7.9 million increase in 2002 over 2001 was primarily due to an increase in our antisense drug discovery costs and the investment in our 13 products in development, including costs for the on-going Phase III trials for Affinitac and ISIS 2302 for Crohn's disease. The increase was partially offset by the effect of capitalizing costs associated with the production of our drugs.

Antisense drug discovery costs for the quarter ended March 31, 2002 totaled $8.8 million compared to $4.5 million for the same period of 2001. The increase was principally a result of increased gene functionalization and target validation activities, continued database development and costs associated with our Lilly research collaboration.

Antisense drug development expenditures totaled $11.5 million and $9.3 million for the three months ended March 31, 2002 and 2001, respectively. The increase of $2.2 million consists of $3.9 million of additional expenses resulting from the expansion and advancement of our pipeline. At March 31, 2002 we had 13 products in development including two products, Affinitac and ISIS 2302, in Phase III clinical trials and six products in Phase II clinical trials compared to six in Phase II and III combined for the same period in 2001. Offsetting the increase in development expenses was the impact of capitalizing $1.7 million in costs related to the production of our drugs as discussed above.

Expenditures related to Affinitac for the quarter ended March 31, 2002 were $2.5 million compared to $2.2 million reported for the same period of 2001. The increase of $0.3 million was related to increased patient enrollment in our Phase III trial, which completed enrollment in

January 2002. Additionally, we have begun to incur costs associated with preparing a New Drug Application, or NDA. Lilly also plans to conduct a Phase III clinical trial in patients with non-small cell lung cancer. If we and Lilly determine that the data from our Phase III trial are sufficiently positive to support a single study NDA, Lilly and we plan to file the NDA in 2003. If we and Lilly determine that two Phase II studies are required, Lilly and we plan to file the NDA in 2004 with data from both our Phase III trial and Lilly's Phase III trial.

Our second drug in Phase III clinical trials, ISIS 2302 for Crohn's disease, had development expenditures totaling $1.5 million for the three months ended March 31, 2002 compared to $1.1 million for the same period of 2001. The increase of $0.4 million is a result of our initiation of a Phase III trial in November 2001, which resulted in additional expenses for the first quarter 2002 over the same period of 2001.

Ibis expenditures for the three months ended March 31, 2002 totaled $2.0 million, compared to $1.8 million in 2001. The increase of $0.2 million was primarily a result of Ibis' continued drug discovery collaboration with Pfizer. Additionally, Ibis incurred expenses related to its performance obligations under its multi-year government contract with DARPA, awarded in the fourth quarter 2001.

R&D Support costs for the three months ended March 31, 2002, totaled $4.7 million, compared to $3.5 million for 2001. The increase of $1.2 million is a direct result of increases in our research and development efforts. While we work to control R&D Support costs, these costs will increase as direct research and development costs increase. We expect R&D Support costs will increase in 2002 as we hire scientific personnel to support our Lilly collaboration, our government contracts, our GeneTrove collaborations and our expanding pipeline.

General and administration expenses for the first quarter totaled $2.2 million in 2002 compared to $2.8 million for the same period of 2001. The decrease in expense was primarily a result of capitalizing costs related to the production of our drugs as previously discussed.

Compensation expense related to stock options for the quarter ended March 31, 2002 included a reversal of $1.5 million in previously recorded compensation expense related to for stock options accounted for as variable stock options. The Company reported a reversal of $0.1 million for the same period in 2001. Variable stock options can result in significant increases and decreases in compensation expense as a result of the variability in our stock price.

Equity in Loss of Affiliates

Equity in loss of affiliates for the quarter ended March 31, 2002 was $5.8 million compared to $4.0 million for the quarter ended March 31, 2001. We use the equity method of accounting for our investments in Orasense and HepaSense. As a result, we recognized 80.1% of the total loss reported by Orasense and HepaSense under equity in loss of affiliates. The increase in 2002 of $1.8 million is a result of increased development activities performed by Orasense and HepaSense.

Investment Income

Investment income remained relatively unchanged from the first quarter in 2001 to the respective quarter in 2002. For the quarter ended March 31, 2002 and 2001, investment income was $2.1 million and $2.0 million, respectively. Although our average cash balance was significantly higher in the first quarter of 2002 compared to the first quarter of 2001, our investment income was directly affected by the decline in interest rates.

Interest Expense

Interest expense increased to $4.6 million in 2002, compared with $3.6 million in 2001. The increase of $1.0 million in 2002 over 2001 is primarily related to debt arrangements where interest and

principal payments are deferred resulting in increased debt carrying balances in 2002 over 2001. Interest and principal payments are deferred on our $40.1 million debt financing initiated in 1997 and 1998, and our borrowings of $0.9 million and $1.4 million under the Elan lines of credit for our Orasense and HepaSense joint ventures, respectively, during the first quarter of 2002. As a result, interest expense increased in 2002 over that reported in 2001. Also contributing to the increase during 2002 were the effects of the outstanding cummulative borrowing of $25 million from our $100 million loan made available to us by Lilly. In 2002, $4.4 million of the $4.6 million in interest expense, which was primarily accrued under various long-term debt agreements, did not require cash payments.

Net Loss Applicable to Common Stock

For the quarter ended March 31, 2002 and 2001, we reported a net loss of $18.0 million and $22.8 million, respectively. Our net loss applicable to common stock was $18.3 million for the quarter ended March 31, 2002, and $23.2 million in 2001, which included $0.3 million of accreted dividends on preferred stock as of March 31, 2002 and 2001. The decrease of $4.9 million was primarily a result of significant increases in our revenue in 2002 from 2001. The increase was partially offset by an increase in our research and development expenses.

Liquidity and Capital Resources

We have financed our operations with revenue from contract research and development, revenue from the sale or licensing of our intellectual property, the sale of our equity securities, and the issuance of long-term debt. From our inception through March 31, 2002, we have earned approximately $288.3 million in revenue from contract research and development and the sale and licensing of our intellectual property. From our inception through March 31, 2002, we have raised net proceeds of approximately $580.5 million from the sale of equity securities. We have borrowed approximately $120.6 million under long-term debt arrangements to finance a portion of our operations.

As of March 31, 2002, we had cash, cash equivalents and short-term investments totaling $292.0 million and working capital of $266.6 million. In comparison, we had cash, cash equivalents and short-term investments of $312.0 million and working capital of $280.6 million as of December 31, 2001. The decreases in our cash, cash equivalents and short-term investments, and working capital are due primarily to cash used to fund our operations and the purchase of property and equipment.

In May 2002, we completed the issuance of $125 million $5^1/_2$% convertible subordinated notes due in 2009 in a private placement which resulted in net proceeds to us of approximately $121 million. Approximately $74 million of the proceeds was used to retire debt acquired in 1997 and 1998, which had a 14% interest rate.

As of March 31, 2002, our long-term obligations totaled $133.9 million, versus $125.7 million at December 31, 2001. The increase was primarily due to the accrual of interest on the ten-year notes and our convertible debt facilities. This increase was partially offset by principal repayments on existing obligations. In May 2002, we increased our long-term obligations by completing a convertible debt offering, which raised approximately $121 million net of offering costs. As previously mentioned, $74 million was used to repay debt which was outstanding as of March 31, 2002. We expect that capital lease obligations will increase over time to fund capital equipment acquisitions required for our growing business. We will continue to use lease financing as long as the terms remain commercially attractive. Based on our current operating plan, we believe that our available cash, cash equivalents and short-term investments at March 31, 2002 combined with investment income, committed contractual cash payments and proceeds from our May 2002 convertible debt offering, will be sufficient to meet our anticipated requirements for at least the next 36 months.

Prospective Information

In April 2002, we extended our collaboration with Merck to discover drug candidates to treat patients with the HCV. The objective of the one-year extension is to continue our discovery efforts to identify additional novel compounds for Merck to potentially develop as new treatments for HCV. Merck has agreed to pay us research support for an additional year, as well as a research milestone, clinical development milestone payments for compounds that arise from the collaboration and royalties from product sales. We began the original three-year drug discovery collaboration with Merck in June 1998 and announced the first one-year extension in May 2001. We achieved a research milestone in October 2001.

In April 2002, we achieved a development milestone in our HepaSense Ltd. joint venture with Elan triggering a $3.75 million equity purchase by Elan of our common stock at a price of $29.74. Elan also received a warrant to purchase 6,304 shares of our common stock at an exercise price of $59.48 per share.

In May 2002, we issued $125 million of $5^1/_2$% convertible subordinated notes due 2009 in a private placement. We received approximately $121 million net of offering costs.

In May 2002, we retired our 14% Senior Subordinated Notes. The total amount of this debt, including principal plus interest, was approximately $74 million.

RISK FACTORS

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

RISKS RELATED TO OUR BUSINESS

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 will be successfully commercialized by us or our partners.

If the results of clinical testing indicate that any of our drugs under development are not suitable for commercial use, or if additional testing is required to demonstrate 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. Most of our resources are being applied 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.

If our products are not accepted by the market, we are not likely to generate significant revenues or become profitable.

Our success will depend upon the medical community, patients and third-party payors accepting our products as medically useful, cost-effective and safe. We cannot guarantee that any of our products in development, if approved for commercialization, will be used by doctors 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. We and our partners may not be successful in commercializing additional products.

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

- the receipt and scope of regulatory approvals;
- the establishment and demonstration in the medical and patient community of the efficacy and safety of our drug candidates and their potential advantages over competing products;
- the cost of our drug candidates compared to other available therapies;
- the patient convenience of the dosing regimen for our drug candidates; and
- reimbursement policies of government and third-party payors.

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

If any of our collaborative partners fail to fund our collaborative programs or develop or sell any of our products under development, or if we are unable to obtain additional partners, progress on our drug development programs could be delayed or stop.

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; and
- successfully commercialize existing and future product candidates.

If any of our partners fails to develop or sell any drug in which we have retained a financial interest, our business may be negatively affected. 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. Our most advanced drug candidate, Affinitac, is being developed collaboratively with Lilly, with the development funded by Lilly. Additional drug candidates in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics Limited, Elan Corporation, plc, Merck & Co., Inc. and OncoGenex Technologies Inc. Failure by any of these pharmaceutical company partners to continue to fund and/or develop these drug candidates would have a material adverse effect on our business.

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.

If our GeneTrove business is unable to market its products and services as planned, we could lose our investment in this technology.

Our business could suffer if pharmaceutical companies do not use our GeneTrove target validation or gene functionalization services. We have invested in the development of a gene target validation and

gene functionalization service business for validation and functionalization of gene targets for drug discovery. If pharmaceutical companies fail to use these services due to competition or other factors, our GeneTrove business could fail to make the planned contribution to our financial performance.

In addition, if customers do not subscribe to the database at the level we have planned, our GeneTrove business could fail to make the planned contribution to our financial performance.

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

Because drug discovery and development and the development of database products and research services require substantial lead time and money prior to commercialization, our expenses have exceeded our revenues since we were founded in January 1989. As of March 31, 2002, our accumulated losses were approximately $405 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. Our current product revenues are derived 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 at March 31, 2002 combined with investment income, committed contractual cash payments and proceeds from our May 2002 convertible debt offering, will be sufficient to meet our anticipated requirements for at least the next 36 months. If we fail to meet our goals regarding commercialization of our drug products, gene function database product and research services and licensing of 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 gene function database and research service products; 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 additional funds are raised 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 be required to cut back on one or more of our research, drug discovery or development programs or obtain funds

through arrangements with collaborative partners or others. These arrangements may require us to give up rights to certain of our technologies, product candidates or products.

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

If we successfully commercialize any of our drug candidates, we may be required to establish large-scale commercial manufacturing capabilities. In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. Pharmaceutical products of the chemical class represented by our drug candidates, called oligonucleotides, have never been manufactured on a large scale, and to our knowledge there is no commercial scale oligonucleotide manufacturer in business today. We have a limited number of suppliers for certain capital equipment and raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our product costs. We may not be able to manufacture at a cost or in quantities necessary to make commercially successful products.

Also, manufacturers, including us, must adhere to the FDA's current Good Manufacturing Practices regulations, which are enforced by the FDA 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.

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

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

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

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

If we are unable to protect our patents or our proprietary rights, others may be able to 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, patents may not be granted 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.

On July 9, 2001, we initiated litigation against Sequitur, Inc. alleging patent infringement. On December 12, 2001, we initiated a second action against Sequitur, Inc. alleging patent infringement. On May 2, 2002 we initiated a third action against Sequitur, Inc. alleging patent infringement. If we do not prevail in the defense of these patents, it could impact our ability to realize future licensing revenues.

If a third party claims that our products or technology infringe their patents or other intellectual property rights, we might be forced 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.

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. Our collaboration with Lilly requires us to add a significant number of skilled scientific personnel. Our inability to add these employees may impact the success of our Lilly collaboration.

The price of our securities may continue to be highly volatile, which could make it harder for investors to liquidate their investment and could increase their 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 the convertible notes. During the 12 months preceding March 31, 2002, the market price of our common stock has ranged from $7.88 to $27.15 per share. The market price of our securities can be affected by many factors, 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, special meetings of our stockholders may be called only by the board of directors, the chairman of the board or the chief executive officer. 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, Hybridon, Inc., Reliance Insurance Company and the holders of our $5^{1}/_{2}$% convertible subordinated notes. In the aggregate, these registration rights cover approximately 4,464,286 shares of our common stock which are currently outstanding, an additional $4.5 million of our common stock we are obligated to issue to Hybridon, 7,518,796 shares of our common stock issuable upon conversion of our $5^{1}/_{2}$% convertible subordinated notes and additional shares of our common stock which may become outstanding upon the conversion of outstanding convertible securities. If these registration rights are exercised by the holders, it will bring additional shares of our common stock into the market, which may have an adverse effect on the price of our securities.

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

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

connection with their purchase of the convertible notes or, if they have already sold the convertible notes, to recover any losses resulting from their purchase of the convertible notes.

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.

PART II—OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

On July 9, 2001, we filed suit against Sequitur, Inc. in the United States District Court for the Southern District of California. The suit alleges infringement of United States Patent No. 6,001,653 entitled "Human Type 2 RNase H", which was issued to Isis on December 14, 1999. In response to this suit, Sequitur has filed certain counterclaims. We believe that we have meritorious defenses to all of these counterclaims. On December 12, 2001, we filed a second suit against Sequitur, Inc. in the U.S. District Court for the Southern District of California. The suit alleges infringement of U.S. Patent No. 6,326,199 entitled "Gapped 2' Modified Oligonucleotide", which was issued to us on December 4, 2001. Sequitur has answered but not filed any counterclaims. On May 2, 2002, we filed a third suit against Sequitur, Inc. in the United States District Court for the Southern District of California. The suit alleges infringement of (i) United States patent No. 5,959,097 entitled "Antisense Modulation of MEK2 Expression," which was issued to Isis on September 28, 1999, (ii) United States patent No. 5,958,733 entitled "Antisense Modulation of Akt-1 Expression," which was issued to Isis on September 28, 1999, (iii) United States patent No. 6,043,090 entitled "Antisense Inhibition of Human Akt-2 Expression," which was issued to Isis on September 28, 2000, and (iv) United States patent No. 6,096,543 entitled "Antisense Inhibition of Human MEK1 Expression," which was issued to Isis on August 1, 2000. Sequitur has not answered this suit.

ITEM 2. CHANGES IN SECURITIES

Not applicable

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable.

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

Not applicable.

ITEM 5. OTHER INFORMATION

Not applicable.

ITEM 6. EXHIBITS AND REPORTS ON FORM 8-K

a. Exhibits

Exhibit Number	Description of Document
10.1	Letter Agreement dated April 24, 2002 between Reliance Insurance Company and the Registrant

b. Reports on Form 8-K

On January 4, 2002, the Registrant filed a report on Form 8-K which described several agreements the Registrant entered into with Amgen, Inc., Integrated DNA Technologies, Inc., and Antisense Therapeutics Limited. In total, seven documents were filed with related press releases. The following is a list of the agreements: a Collaboration Agreement dated December 11, 2001 with Amgen, Inc.; Oligonucleotide Manufacturing and Supply Agreement dated December 4, 2001 and Amended and Restated IDT-Isis Agreement dated December 4, 2001 with Integrated DNA Technologies, Inc.; and a Master Agreement, Collaboration and License Agreement, Clinical Supply Agreement, and Stock Purchase Agreement, each dated October 31, 2001 with Antisense Therapeutics Limited.

On January 7, 2002, the Registrant filed a report on Form 8-K for a license agreement between the Registrant and Eyetech Pharmaceuticals, Inc., dated December 31, 2001 and related press release dated January 7, 2002.

Isis Pharmaceuticals, Inc.
(Registrant)

SIGNATURES

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

Signature	Title	Date
/s/ STANLEY T. CROOKE, M.D., PH.D. Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	May 15, 2002

/s/ B. LYNNE PARSHALL B. Lynne Parshall, Esq.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	May 15, 2002

QuickLinks

Exhibit 10.1

April 24, 2002

Reliance Insurance Company
Attn: Chief Investment Officer
55 East 52nd Street
New York, NY 10055

The purpose of this letter agreement is to set forth the terms upon which Isis Pharmaceuticals, Inc. will repay those certain 14% Senior Subordinated Discount Notes due November 1, 2007 (the "Notes") issued to Reliance Insurance Company.

Under the Notes, Isis may only redeem the Notes after November 1, 2002. By signing this letter agreement, Reliance waives this redemption restriction (including all notice provisions related thereto), such that Isis may redeem the Notes at any time following the execution of this letter agreement.

Notwithstanding the Redemption Price agreed to in the Notes, Isis and Reliance agree that the aggregate Redemption Price for the Notes will be equal to (i) $72,685,271 (representing the aggregate accreted value of the Notes through May 1, 2002, plus (ii) $1,544,562 (representing one half of the aggregate interest that would have accrued on the Notes between May 1, 2002 and November 1, 2002 at an assumed interest rate of 8.5%).

In addition, Isis and Reliance agree that, notwithstanding this letter agreement, the warrants to purchase Isis' common stock issued to Reliance in connection with this Note will remain in full force and effect in accordance with the terms of such warrants.

Isis and Reliance further agree that this letter agreement is contingent upon (i) the closing on or before May 1, 2002 of Isis' convertible subordinated note offering announced by Isis on April 23, 2002, and (ii) the repayment of the Notes on or before May 1, 2002.

By signing below, Reliance agrees to the terms of this letter agreement.

Sincerely,

/s/ B. LYNNE PARSHALL

B. Lynne Parshall,
Executive Vice President,
Chief Financial Officer and Director

/s/ JOHN H. PANKRATZ

Reliance Insurance Company
By: John H. Pankratz
Title: SR. Vice President