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SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 10-Q

(Mark One)

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

For the quarterly period ended September 30, 2001

OR

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

For the transition period from to _____ 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)	(IRS 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 /x/ No / / (2) Yes /x/ No / /

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	47,087,796 shares
(Class)	(Outstanding at September 30, 2001)

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ISIS PHARMACEUTICALS, INC.

CONDENSED BALANCE SHEETS

(in thousands, except share data)

	September 30, 2001	December 31, 2000
	(Unaudited)	(Note)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 12,311	$ 39,615
Short-term investments	200,891	87,647
Contracts receivable	4,097	3,346
Prepaids and other current assets	3,002	2,596
Total current assets	220,301	133,204
Property, plant and equipment, net	24,268	22,625
Licenses, net	29,349	500
Patents, net	15,784	13,815
Investments in affiliates	3,469	12,491
Deposits and other assets	1,241	621
Total assets	$ 294,412	$ 183,256
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 2,949	$ 2,231
Accrued compensation	3,173	3,598
Accrued liabilities	2,833	1,429
Current portion of deferred revenues	20,057	2,771
Current portion of long-term obligations	7,437	4,607
Total current liabilities	36,449	14,636
Long-term obligations, less current portion	123,651	102,254
Long-term deferred revenue, less current portion	16,282	-
Stockholders' equity:		
Series A Convertible Exchangeable 5% Preferred stock, $.001 par value, 120,150 shares authorized, issued and outstanding at September 30, 2001 and December 31, 2000	12,015	12,015
Accretion of Series A Preferred stock dividends	1,542	1,050
Series B Convertible Exchangeable 5% Preferred stock, $.001 par value, 16,620 shares authorized, 12,015 shares issued and outstanding at September 30, 2001 and December 31, 2000	12,015	12,015
Accretion of Series B Preferred stock dividends	1,060	584

Common stock, $.001 par value, 100,000,000 shares authorized, 47,087,796 shares and 40,086,447 shares issued and outstanding at September 30, 2001 and December 31, 2000, respectively	47	40
Additional paid-in capital	461,267	352,854
Deferred compensation	(297)	(858)
Accumulated other comprehensive income	1,016	126
Accumulated deficit	(370,635)	(311,460)
Total stockholders' equity	118,030	66,366
Total liabilities and stockholders' equity	$ 294,412	$ 183,256

Note: The balance sheet at December 31, 2000 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,	
	2001	2000	2001	2000
Revenue:				
Research and development revenues under collaborative agreements	$ 16,892	$ 5,754	$ 24,795	$ 12,640
Research and development revenues from affiliates	2,360	1,759	6,508	5,688
Licensing and royalty revenue	52	10,767	226	10,991
Total revenue	19,304	18,280	31,529	29,319
Expenses:				
Research and development	19,895	16,001	58,954	41,986
General and administrative	2,333	2,073	7,926	6,311
Compensation related to stock options	1,783	560	3,054	560
Restructuring activities	-	27	-	1,635
Total operating expenses	24,011	18,661	69,934	50,492
Loss from operations	(4,707)	(381)	(38,405)	(21,173)
Equity in loss of affiliates	(5,142)	(3,659)	(13,300)	(11,748)
Interest income	1,554	1,976	4,637	4,464
Interest expense	(4,022)	(3,345)	(11,139)	(9,581)
Net loss	(12,317)	(5,409)	(58,207)	(38,038)
Accretion of dividends on preferred stock	(326)	(311)	(968)	(898)
Net loss applicable to common stock	$ (12,643)	$ (5,720)	$ (59,175)	$ (38,936)
Basic and diluted net loss per share	$ (0.29)	$ (0.15)	$ (1.43)	$ (1.08)
Shares used in computing basic and diluted Net loss per share	43,869	38,448	41,517	36,172

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

CONDENSED STATEMENTS OF CASH FLOWS

(In thousands)

(Unaudited)

	Nine months ended September 30,	
	2001	**2000**
Net cash provided by (used in) operating activities	$ 4,774	$ (17,268)
Investing activities:		
Short-term investments	(112,354)	(44,114)
Property, plant and equipment	(5,151)	(2,775)
Licenses and other assets	(18,637)	(1,340)
Investment in affiliates	(4,851)	(15,865)
Net cash used in investing activities	(140,993)	(64,094)
Financing activities:		
Net proceeds from issuance of equity securities	101,895	103,474
Proceeds from long-term borrowings	9,277	3,850
Principal payments on debt and capital lease obligations	(2,257)	(2,228)
Net cash provided from financing activities	108,915	105,096
Net (decrease) increase in cash and cash equivalents	(27,304)	23,734
Cash and cash equivalents at beginning of period	39,615	35,296
Cash and cash equivalents at end of period	$ 12,311	$ 59,030
Supplemental disclosures of cash flow information:		
Interest paid	$ 1,740	$ 878
Supplemental disclosures of non-cash investing and financing activities:		
Additions to debt for licensing costs	$ 13,500	$ -
Additions to receivables from sales of property, plant and equipment	$ -	$ 27
Repayment of debt with common stock	$ 5,000	$ -

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

NOTES TO FINANCIAL STATEMENTS

(Unaudited)

1. Basis of Presentation

The unaudited interim financial statements for the nine month periods ended September 30, 2001 and 2000 have been prepared on the same basis as the Company's audited financial statements for the year ended December 31, 2000. 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, 2000 included in the Company's Annual Report on Form 10-K/A 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 contract revenues from cost-reimbursement agreements are recorded as the related expenses are incurred, up to the contractual limits. Payments received that are related to future performance are deferred and recorded as revenue as they are earned over specified future performance periods. License and royalty payments for which no services are required to be performed in the future are recognized as revenues upon receipt of such payments. Revenues related to

nonrefundable, upfront fees are 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. Revenue from product sales is recognized at the time products are shipped.

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 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. For the quarter and nine month periods ended September 30, 2001, Isis recognized $2.4 million and $6.5 million, respectively, in revenue for research and development activities performed for these joint ventures. For the three and nine month periods ended

September 30, 2000, Isis reported $1.8 million and $5.7 million in revenue, respectively. These amounts are included as research and development revenues from affiliates for the respective periods.

The results of operations of Orasense for the quarter and nine month periods ended September 30, 2001 and 2000 are as follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2001	2000	2001	2000
Revenue	$ —	$ —	$ —	$ —
Research and development expense	3,661	2,884	9,294	9,035
Net loss	$ (3,661)	$ (2,884)	$ (9,294)	$ (9,035)

The results of operations of HepaSense for the quarter and nine month periods ended September 30, 2001 and 2000 are as follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2001	2000	2001	2000
Revenue	$ —	$ —	$ —	$ —
Research and development expense	2,760	1,693	6,976	5,632
Net loss	$ (2,760)	$ (1,693)	$ (6,976)	$ (5,632)

Hybridon, Inc.

In May 2001, Isis and Hybridon, Inc. entered into an agreement under which Isis acquired an exclusive license to all of Hybridon's antisense chemistry and delivery patents and technology subject to retained rights by Hybridon. Hybridon received a license to Isis' suite of RNase H patents. In exchange for the license to Hybridon's antisense patents, Isis paid $15.0 million in cash and agreed to pay Hybridon $19.5 million in Isis common stock over two years. In return for access to Isis' patents, Hybridon agreed to pay Isis $6.0 million in Hybridon common stock over three years. In September 2001, Isis issued 357,143 shares of common stock, valued at $5 million, in accordance with this agreement. Isis' balance sheet at September 30, 2001 reflects a licensing asset, net of amortization, of $27.9 million related to this agreement.

Celera Genomics Group

In July 2001, Celera and Isis' GeneTrove division entered into a collaboration to identify the biological role of more than 200 genes. Celera has the right to select for study a portfolio of genes, from which Celera can further select a limited number of genes for its exclusive use. The data for the remainder of the genes will be included in Isis' human gene function database. Isis retains the rights to develop and commercialize antisense drugs to genes in the collaboration. Celera has agreed to pay Isis fees for this 18-month collaboration.

Eli Lilly and Company

In August 2001, Isis licensed to Lilly, ISIS 3521, a non small-cell lung cancer drug in Phase III trials. In an ongoing Phase II trial in combination with chemotherapy, ISIS 3521 showed a median patient survival of 15.9 months as compared with approximately eight months median patient survival with standard

chemotherapy alone.

In addition to the license of ISIS 3521, the companies have formed a four-year collaboration to discover antisense drugs for metabolic and inflammatory diseases. As part of this collaboration the companies will use GeneTrove's antisense technology to rapidly determine the functional role of up to a 1,000 genes.

Lilly has committed more than $200 million in funding to Isis over a four-year period, which is comprised, of the following: (1) Lilly has made a $75 million equity investment in Isis through the purchase of stock at $18 per share. (2) Lilly has paid Isis $25 million in upfront fees for ISIS 3521. (3) Lilly has committed to loan Isis up to $100 million, interest-free and repayable in cash or stock at $40 per share at the end of the four-year term, to fund the research collaboration. (4) Lilly has committed to reimburse Isis an undisclosed amount for remaining development and registration costs for ISIS 3521.

Assuming success of ISIS 3521 and the success of multiple drugs from the drug discovery collaboration, the cumulative contingent funds over the life of the development process have the potential to exceed the committed funds.

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 (in thousands):

	Statements of Comprehensive Loss (Unaudited)			
	Three Months Ended September 30,		Nine Months Ended September 30,	
	2001	2000	2001	2000
Comprehensive loss:				
Change in unrealized gains (losses)	$ 447	$ (5)	$ 890	$ (2)
Net loss	(12,643)	(5,720)	(59,175)	(38,936)
Comprehensive loss	$ (12,196)	$ (5,725)	$ (58,285)	$ (38,938)

4. Financing

In September 2001, Isis issued 4,166,667 shares of common stock at $18.00 per share to Lilly.

5. Subsequent Events

On October 5, 2001, Isis filed a registration statement on Form S-3 with the Securities and Exchange Commission for the sole purpose of registering the resale of 357,143 shares of Isis' common

stock, which Isis issued to Hybridon in September 2001 in accordance with Isis' agreement with Hybridon entered into in May 2001.

On October 9, 2001, Isis filed a registration statement on Form S-3 with the Securities and Exchange Commission for a potential public offering of up to 5,000,000 shares of Isis common stock and up to 750,000 shares to cover over-allotments.

Ibis Therapeutics was awarded a new DARPA contract to develop a sensor to detect infectious agents used in biological attacks. This award extends and expands the company's four-year relationship with DARPA. Isis expects to receive approximately $1.8 million in revenue in 2001 for the program titled **T**riangulation **I**dentification **G**enetic **E**valuation of biological **R**isks (TIGER). Work will be completed with San Diego-based Science Applications International Corporation (SAIC).

Ibis Therapeutics achieved a second milestone in its drug discovery program with Pfizer. The $1.5 million Pfizer milestone is related to the identification of a group of small molecules, which bind to previously undiscovered RNA targets identified by proprietary Ibis technology. Earlier this year Ibis received a $2.5 million research milestone as part of this collaboration.

Isis earned a $1.5 million research milestone payment from Merck & Co. for progress in a collaboration to discover drug candidates to treat patients infected with the Hepatitis C virus (HCV). Earlier this year, Isis announced a one-year extension to the original three-year research collaboration with Merck, in which Merck pays Isis annual research support, development milestones and royalties for products that arise from this collaboration.

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 in development. Such statements are subject to certain risks and uncertainties, particularly those inherent in working under government contracts and in developing technology and devices used in the detection of infectious agents used in biological attacks and in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, in the process of conducting gene functionalization and target validation activities and in launching new products and services for or with collaborators, and the endeavor of building a business around such potential products. 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 the section entitled "Risk Factors" beginning on page 14 of this Report. As a result, you are cautioned not to rely on these forward-looking statements.

Since our inception in January 1989, almost all of our resources have been devoted to our research, drug discovery and drug development programs. We are currently not profitable and we expect to continue to have operating losses for the next several years. Our revenue comes primarily from collaborative research and development agreements with pharmaceutical companies, research grants and interest income. Our revenue from the collaborations increases the amount of research and development activity that we are able to fund and offsets a portion of our research and development costs.

Results of Operations

Research and development revenues under collaborative agreements for the quarter and nine months ended September 30, 2001 was $16.9 million and $24.8 million, respectively, compared to $5.8 million and $12.6 million for the same periods of 2000. This increase for the quarter and nine months ended September 30, 2001 compared to the same periods of 2000, was due primarily to our licensing of ISIS 3521, a non-small cell lung cancer drug in Phase III trials, to Lilly in August 2001. Revenue from our license agreement with Merck for ISIS 113715, our preclinical drug for adult onset, or Type 2, diabetes and revenue from our collaboration with Celera also added to the quarter to quarter increase in revenues. Our total revenue for the quarter and nine months ended September 30, 2001 was $19.3 million and $31.5 million, respectively, compared to $18.3 million and $29.3 million for the same periods of 2000. Total revenue for the quarter and nine months ended September 30, 2000 included a one-time payment of $10.7 million from Coley Pharmaceutical Group for the sale of certain of our patents.

Our research and development expenses were $19.9 million for the three months ended September 30, 2001, and $59.0 million for the nine months ended September 30, 2001, compared with $16.0 million and $42.0 million for the same periods of 2000. The increase in expenses in 2001 compared to 2000 was driven by the cost of preclinical and clinical activities to advance the development of our drugs. Currently we have twelve products in development, up from seven in the same period of last year. Additionally, eight of the twelve products are in human clinical trials designed to assess efficacy. These trials are more expensive than the earlier human trials designed primarily to assess safety.

Our general and administrative expenses increased slightly to $2.3 million for the third quarter and $7.9 million for the nine months ended September 30, 2001, from $2.1 million and $6.3 million, respectively, for the same periods of 2000. The increase was primarily due to additional expenses required to support our increasing research and development activities.

Our compensation related to stock options for the quarter and nine months ended September 30, 2001 was $1.8 million and $3.1 million, respectively, compared with $0.6 million for the same periods of 2000. The expense was primarily a result of an option exchange program we offered to non-officer

employees in January 2000. These exchanged options are required to be accounted for as variable stock options in accordance with Accounting Principles Board Opinion No. 25 and Financial Accounting Standards Board Interpretation No. 44. Variable stock options can result in significant increases and decreases in compensation expense, as a result of the variability of our stock price. In addition, we account for stock options granted to consultants in accordance with EITF 96-18, which also contributed to these expenses.

Our interest expense for the quarter and nine months ended September 30, 2001 was $4.0 million and $11.1 million, respectively, compared to $3.3 million and $9.6 million, respectively, for the same periods of 2000. The increase was due to the increase in debt on the convertible debt facilities available to us from Elan to fund research and development activities for Orasense and HepaSense. During the third quarter, we borrowed an additional $3.3 million from Elan resulting in a September 30, 2001 balance of $17.6 million, compared to $6.4 million for the same period of 2000. Also contributing to the increase in our interest expense, was the interest accruing on our $40 million debt financing that was completed in the fourth quarter of 1997 and the second quarter of 1998. In that financing, interest accrues for the first five years and no principal payments are due for 10 years. Additionally, imputed interest of $77,000 for the quarter ended September 30, 2001 on our initial $10 million draw down of the $100 million loan from Lilly contributed to the increase in interest expense.

Interest income decreased to $1.6 million for the third quarter and increased to $4.6 million for the nine months ended September 30, 2001, from $2.0 million and $4.5 million, respectively, for the same periods of 2000. The decrease in interest income for the quarter ended September 30, 2001 compared to the same period of 2000 was primarily related to lower rates of return on investments in 2001 compared to 2000. The increase in interest income for the nine months ended September 30, 2001 compared to the same period in 2000 was due to higher average investment balances during the 2001 period offset in part by lower rates of return in 2001 compared to 2000.

During the quarter and nine months ended September 30, 2001, we recorded a net loss applicable to common stock of $12.6 million and $59.2 million, or $0.29 and $1.43 per share, respectively, compared with $5.7 million and $38.9 million, or $0.15 and $1.08 per share, respectively, for the same periods in 2000. Our loss from operations was $4.7 million for the third quarter of 2001, compared to $0.4 million for the same period in 2000. The increases in our net loss applicable to common stock and loss from operations were primarily the result of increased operating expenses related to the twelve products we have in development, including the ongoing Phase III trial of ISIS 3521 in patients with non small cell lung cancer. This program, the planned Phase III trial of ISIS 2302 in patients with Crohn's disease, and the continued aggressive development of the remaining drugs in our pipeline, will result in increased expenses and lead to an increase in our net loss from operations for 2001 over our 2000 net loss from operations. We expect operating losses to fluctuate from quarter to quarter because of differences in the timing of revenue recognized and expenses incurred.

We believe that inflation and changing prices have not had a material effect on our operations to date.

Liquidity and Capital Resources

We have financed our operations to date 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 September 30, 2001, we have earned approximately $248 million in revenue from contract research and development and the sale and licensing of our intellectual property. Since we were founded, we have raised net proceeds of approximately $494 million from the sale of equity securities. We have borrowed approximately $95 million under long-term debt arrangements to finance a portion of our operations.

As of September 30, 2001, we had cash, cash equivalents and short-term investments totaling $213.2 million and working capital of $183.9 million. In comparison, we had cash, cash equivalents and

short-term investments of $127.3 million and working capital of $118.6 million as of December 31, 2000. The increases in our cash, cash equivalents and short-term investments, and working capital in 2001 from 2000 were due primarily to cash received from our strategic alliance with Lilly. We received from Lilly $75 million for the purchase of our common stock at $18 per share, $34 million related to the license of ISIS 3521 and $10 million from the first draw down on the interest-free $100 million loan to support the research collaboration. Cash received from Merck, Pfizer and Celera related to our collaborations with each of those companies also added to our cash, cash equivalents and short-term investments, and working capital in 2001. In addition, our cash, cash equivalents and short-term investments, and working capital increased in 2001 from 2000 by the sale of our common stock to an institutional investor in the second quarter of 2001. The increase was partially offset by payments to Hybridon in connection with our decision to strengthen our intellectual property by entering into a licensing agreement with Hybridon.

In 1997 and 1998, we borrowed a total of $40 million in private transactions. The loans bear interest at 14% per annum and must be repaid on November 1, 2007. The interest accrues during the first five years of the loans. After the first five years, interest must be paid quarterly. No principal payments are required until November 1, 2007. In conjunction with these transactions, we issued warrants to purchase 800,000 shares of common stock at an exercise price of $25 per share. The warrants issued in connection with both of these financings expire on November 1, 2004. Because interest is accrued during the first five years, the balance of these borrowings will accrue to a total of $78 million on November 1, 2002. The debt under these arrangements is carried on our balance sheet, net of the amortized amount allocated to the warrants and including accrued interest. The combined carrying amount of these notes at September 30, 2001 was $65.5 million.

As of September 30, 2001, our long-term obligations totaled $123.7 million, versus $102.3 million at December 31, 2000. The increase was primarily due to the accrual of interest on the ten-year notes described above and our convertible debt facilities. This increase was partially offset by principal repayments on existing obligations. 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. We believe that our existing cash, cash equivalents and short-term investments at September 30, 2001, combined with contract revenue and interest income should be sufficient to fund our operations for at least the next three years**.** On October 9, 2001, we filed a registration statement with the Securities and Exchange Commission for a potential public offering of up to 5,000,000 shares of our common stock, plus up to 750,000 shares to cover the underwriters' over-allotments. The potential net proceeds, which are contingent on a successful offering, to us are estimated to be $85.7 million or $98.6 million if the underwriters' exercise all of their over-allotment option.

Prospective Information

On October 5, 2001, we filed a registration statement on Form S-3 with the Securities and Exchange Commission for the sole purpose of registering the resale of 357,143 shares of our common stock, which we issued to Hybridon in September 2001 in accordance with our agreement with Hybridon entered into in May 2001.

On October 9, 2001, we filed a registration statement on Form S-3 with the Securities and Exchange Commission for a potential public offering of up to five million shares of our common stock and up to 750,000 shares to cover over-allotments.

Our Ibis Therapeutics division was awarded a new DARPA contract to develop a sensor to detect infectious agents used in biological attacks. This award extends and expands our four-year relationship with DARPA. We expect to receive approximately $1.8 million in revenue in 2001 for the program titled **T**riangulation **I**dentification **G**enetic **E**valuation of biological **R**isks (TIGER). Work will be completed with San Diego-based Science Applications International Corporation (SAIC).

Our Ibis Therapeutics division achieved a second milestone in its drug discovery program with Pfizer. The $1.5 million Pfizer milestone is related to the identification of a group of small molecules, which bind to previously undiscovered RNA targets identified by proprietary Ibis technology. Earlier this year Ibis received a $2.5 million research milestone as part of this collaboration.

We earned a $1.5 million research milestone payment from Merck & Co. for progress in a collaboration to discover drug candidates to treat patients infected with the Hepatitis C virus (HCV). Earlier this year, we announced a one-year extension to the original three-year research collaboration with Merck, in which Merck pays us annual research support, development milestones and royalties for products that arise from this collaboration.

On October 10, 2001 we announced that data from a Phase II clinical trial of our antisense drug, ISIS 2302, demonstrated improved symptoms in patients with active distal ulcerative colitis. Patients receiving an enema formulation of ISIS 2302 experienced a dose-dependent reduction in disease activity index score and clinical activity index score. In the trial, the median percent reduction in disease activity index score at the highest dose studied was highly statistically significant compared to placebo at the end of one month of dosing (p=0.004) and two months following cessation of dosing (p=0.04). The Phase II randomized, placebo-controlled dose-escalation study involved 40 people with active distal ulcerative colitis at 11 European trial sites.

RISK FACTORS

Investing in our common stock involves a high degree of risk. In addition to the information in this Report, you should carefully consider the risks described below before purchasing our common stock. 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 common stock 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, 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 doing so. 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 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 or 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. We cannot be sure that any of these collaborations will be continued 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, ISIS 3521, 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 Merck & Company, Inc. and Elan Corporation, plc. 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 avail themselves of 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.

If we fail to introduce our human gene function database in a timely fashion or if potential 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 September 30, 2001, our accumulated losses were approximately $371 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 and existing sources of revenue and credit will be adequate to satisfy our capital needs for the next several years. 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 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 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 are successful in commercializing 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. The manufacturers may not be able to comply or maintain compliance with Good Manufacturing Practices regulations. Non-compliance could significantly delay our receipt or marketing approval 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 such 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 adequately protect our competitive advantage. Furthermore, our issued patents or patents licensed to us could potentially 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 infringement of U.S. Patent 6,001,653. If we do not prevail in the defense of this patent, 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 U.S. are filed confidentially. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain unresolved.

If we do not progress in our programs as anticipated, our stock price 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 our stock price 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.

Our stock price may continue to be highly volatile. This could make it harder for our stockholders 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. During the twelve months preceding September 30, 2001, the market price of our common stock has ranged from $7.88 to $18.05 per share. The market price 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 president, or by any holder of 10% or more of our outstanding common stock. We also have implemented a stockholders' rights plan, which is 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.

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, Isis 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 our suit, Sequitur has filed certain counterclaims. The Company believes it has meritorious defenses to all of these counterclaims.

ITEM 2. CHANGES IN SECURITIES

On September 21, 2001 Isis issued 357,143 shares of its common stock to Hybridon in exchange for an exclusive license to all of Hybridon's antisense chemistry and delivery patents and technology. The sale and issuance of the common stock was deemed to be exempt from registration under the Securities Act of 1933, as amended, in reliance upon Section 4(2) of the Securities Act promulgated thereunder, as a transaction by an issuer not involving a public offering. Hybridon represented its intention to acquire the common stock for investment only and not with a view to or for sale in connection with any distribution thereof, and an appropriate legend was affixed to the stock certificate. Hybridon had access to information about Isis, through its relationship with us.

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

4.1 Amended and Restated Certificate of Incorporation filed June 19, 1991. (1)

4.2 Certificate of Amendment to Restated Certificate of Incorporation filed April 9, 2001. (7)

4.3 Bylaws.(7)

4.4

Certificate of Designation of the Series A Convertible Preferred Stock.(2)

4.5
Certificate of Designation of the Series B Convertible Preferred Stock.(6)

4.6
Certificate of Designation of the Series C Junior Participating Preferred Stock.(8)

4.7
Specimen Common Stock Certificate.(1)

4.8
Specimen Series A Preferred Stock Certificate.(9)

4.9
Specimen Series B Preferred Stock Certificate.(9)

4.10
Form of Right Certificate.(8)

4.11
Purchase Agreement between the Registrant and Reliance Insurance Company for 14% Senior Subordinated Discount Notes due November 1, 2007 and Warrants for Common Stock dated October 24, 1997 (with certain confidential information deleted).(3)

4.12
First Supplement to Purchase Agreement between the Registrant and Reliance Insurance Company for 14% Senior Subordinated Discount Notes due November 1, 2007 and Warrants for Common Stock dated May 1, 1998 (with certain confidential information deleted).(4)

4.15
Stock Purchase Agreement between the Registrant and Boehringer Ingelheim International GmbH, dated as of July 18, 1995 (with certain confidential information deleted).(10)

4.16
Subscription, Joint Development and Operating Agreement, dated April 20, 1999 among the Registrant, Elan Corporation, plc, Elan International Services, Ltd. and OraSense Ltd. (with certain confidential information deleted), together with the related Securities Purchase Agreement, Convertible Promissory Note, Warrant to Purchase Shares of Common Stock, Registration Rights Agreement and License Agreements. (5)

4.17
Agreement dated August 31, 1999 between Boehringer Ingelheim International GmbH and the Registrant, together with the related Amendment to the Stock Purchase Agreement. (11)

4.18
Subscription, Joint Development and Operating Agreement dated January 14, 2000 among the Registrant, Elan Corporation, plc, Elan International Services, Ltd. and Hepasense, Ltd. (with certain confidential information deleted), together with the related Securities Purchase Agreement, Convertible Promissory Note, Warrant to Purchase Shares of Common Stock, Registration Rights Agreement and License Agreements.(6)

4.19
Securities Purchase Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company. (12)

4.20
Registration Rights and Standstill Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company. (12)

4.21
Loan Agreement, dated August 17, 2001, between the Registrant and Eli Lilly and Company.(12)

10.1
Collaboration Agreement, dated August 17, 2001, between Isis Pharmaceuticals, Inc. and Eli Lilly and Company. (with certain confidential information deleted). (12)

10.2
Development and License Agreement, dated August 14, 2001 between Isis Pharmaceuticals, Inc. and Eli Lilly and Company. (with certain confidential information deleted). (12)

10.3
Isis 3521 Clinical Supply Agreement, dated August 29, 2001 between Isis Pharmaceuticals, Inc. and Eli Lilly and Company which is Exhibit B to the Development and License Agreement dated August 14, 2001 (i.e., Exhibit 10.2). (with certain confidential information deleted). (12)

10.4 Agreement between the Registrant and PE Corporation through the Celera Genomics Group, dated July 9, 2001 (with certain confidential information deleted).(7)

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(1) Filed as an exhibit to the Registrant's Registration Statement on Form S-1 (No. 333-39640) or amendments thereto and incorporated herein by reference.

(2) Filed as an exhibit to the Registrant's Registration Statement on Form S-3 (No. 333-71911) or amendments thereto and incorporated herein by reference.

(3) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1997, and incorporated herein by reference.

(4) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 1998 and incorporated herein by reference.

(5) Filed as an exhibit to the Registrant's report on Form 8-K dated April 20, 1999 and incorporated herein by reference.

(6) Filed as an exhibit to the Registrant's report on Form 8-K dated January 28, 2000, as amended on October 5, 2001, and incorporated herein by reference.

(7) Filed as an exhibit to the Registrant's report on Form 10-Q/A for the quarter ended June 30, 2001 and incorporated herein by reference.

(8) Filed as an exhibit to the Registrant's Report on Form 8-K dated December 8, 2000 and incorporated herein by reference.

(9) Filed as an exhibit to the Registrant's Report on Form 10-Q/A for the quarter ended June 30, 2000 and incorporated herein by reference.

(10) Filed as an exhibit to the Registrant's Report on Form 8-K dated July 18, 1995 and incorporated herein by reference.

(11) Filed as an exhibit to the Registrant's Report on Form 8-K dated August 31, 1999 and incorporated herein by reference.

(12) Filed as an exhibit to the Registrant's Report on Form 8-K dated August 29, 2001 and incorporated herein by reference.

b. Reports on Form 8-K

On August 29, 2001, the Registrant filed the following report on Form 8-K:

Report dated August 29, 2001 which described the strategic alliance the registrant entered into with Eli Lilly and Company. No financial statements were filed with this report on Form 8-K. Seven documents, including the Securities Purchase Agreement, Loan Agreement, Registration Rights and Standstill Agreement, Collaboration Agreement, Development and License Agreement, ISIS 3521 Clinical Supply Agreement and related press release (with certain confidential information deleted) were filed as exhibits to the report.

ISIS PHARMACEUTICALS, INC.
SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

ISIS PHARMACEUTICALS, INC.
(Registrant)

Date: October 17, 2001 By: /s/ STANLEY T. CROOKE

Stanley T. Crooke, M.D., Ph.D.
Chairman of the Board and Chief Executive Officer (Principal Executive Officer)

Date: October 17, 2001 By: /s/ B. LYNNE PARSHALL

B. Lynne Parshall
Executive Vice President, Chief Financial Officer and Director (Principal Accounting and Financial Officer)

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