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SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 10-Q

(Mark One)

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

For the quarterly period ended March 31, 2001

OR

/ / **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 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	40,165,390 shares
(Class)	(Outstanding at March 31, 2001)

ISIS PHARMACEUTICALS, INC.

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ISIS PHARMACEUTICALS, INC.

CONDENSED BALANCE SHEETS

(in thousands, except share data)

	March 31, 2001 (Unaudited)	December 31, 2000 (Note)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 8,057	$ 39,615
Short-term investments	100,337	87,647
Contract receivable	4,800	3,346
Prepaids and other current assets	2,993	2,596
Total current assets	116,187	133,204
Property, plant and equipment, net	22,596	22,625
Patent costs, net	13,943	13,815
Investments in affiliates	7,987	12,491
Deposits and other assets	2,651	1,121
Total assets	$ 163,364	$ 183,256
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 3,328	$ 2,231
Accrued compensation	1,852	3,598
Accrued liabilities	1,954	1,429
Deferred contract revenues	2,907	2,771
Current portion of long term obligations	4,400	4,607
Total current liabilities	14,441	14,636

Long-term obligations, less current portion	104,455	102,254
Stockholders' equity:		
Series A Convertible Exchangeable 5% Preferred stock, $.001 par value, 120,150 shares authorized, issued and outstanding at March 31, 2001 and December 31, 2000	12,015	12,015
Accretion of Series A Preferred Stock dividends	1,211	1,050
Series B Convertible Exchangeable 5% Preferred stock, $.001 par value, 16,620 shares authorized, 12,015 shares issued and outstanding at March 31, 2001 and December 31, 2000	12,015	12,015
Accretion of Series B Preferred Stock dividends	742	584
Common stock, $.001 par value, 50,000,000 shares authorized, 40,165,390 shares and 40,086,000 shares issued and outstanding at March 31, 2001 and December 31, 2000, respectively	40	40
Additional paid-in capital	352,880	352,854
Deferred compensation	(408)	(858)
Accumulated other comprehensive income	599	126
Accumulated deficit	(334,626)	(311,460)
Total stockholders' equity	44,468	66,366
Total liabilities and stockholders' equity	$ 163,364	$ 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 March 31,	
	2001	**2000**
Revenue:		
Research and development revenues under collaborative agreements	$ 2,789	$ 2,748
Research and development revenues from affiliates	1,716	1,168
Licensing and royalty revenue	128	138
Total revenue	4,633	4,054
Expenses:		
Research and development	19,134	13,239
General and administrative	2,816	1,824
Compensation related to stock options	(83)	—
Restructuring activities	—	1,608
Total operating expenses	21,867	16,671
Loss from operations	(17,234)	(12,617)
Equity in loss of affiliates	(3,964)	(3,495)
Interest income	1,977	892
Interest expense	(3,626)	(3,107)
Net loss	(22,847)	(18,327)
Accretion of dividends on preferred stock	(319)	(281)
Net loss applicable to common stock	$ (23,166)	$ (18,608)

Basic and diluted net loss per share	$ (0.58)	$ (0.56)
Shares used in computing basic and diluted net loss per share	40,150	33,063

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

CONDENSED STATEMENTS OF CASH FLOWS

(In thousands)

(Unaudited)

	Three months ended March 31,	
	2001	**2000**
Net cash used in operating activities	$ (17,062)	$ (11,053)
Investing activities:		
Short-term investments	(12,217)	(11,387)
Property and equipment	(1,094)	(601)
Other assets	(1,269)	(453)
Investment in affiliates	(32)	(13,996)
Net cash used in investing activities	(14,612)	(26,437)
Financing activities:		
Net proceeds from issuance of equity securities	877	65,275
Proceeds from long-term borrowings	—	2,452
Principal payments on debt and capital lease obligations	(761)	(800)
Net cash provided from financing activities	116	66,927
Net (decrease) increase in cash and cash equivalents	(31,558)	29,437
Cash and cash equivalents at beginning of period	39,615	35,296
Cash and cash equivalents at end of period	$ 8,057	$ 64,733
Supplemental disclosures of cash flow information:		
Interest paid	$ 303	$ 308

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

NOTES TO FINANCIAL STATEMENTS

(Unaudited)

1. Basis of Presentation

The unaudited interim financial statements for the three month periods ended March 31, 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.

2. Strategic Alliances

Orasense™

In April 1999, Isis Pharmaceuticals, Inc., a Delaware corporation (Isis or the Company) and Elan Corporation, plc (Elan) formed a joint venture to develop technology for the formulation of oral oligonucleotide drugs. The joint venture, Orasense Ltd. (Orasense), a Bermuda limited company, is initially owned 80.1% by the Company and 19.9% by Elan.

While Isis owns 80.1% of the outstanding common stock of Orasense, Elan and its subsidiaries have retained significant minority investor rights that are considered "participating rights" as defined in EITF 96-16. Therefore, Isis does not consolidate the financial statements of Orasense, but instead accounts for its investment in Orasense under the equity method of accounting. During the three month period ended March 31, 2001, Isis recognized $836,000 in contract revenues for research and development activities performed for Orasense. This amount is included as research and development revenues from affiliates for the related period.

The results of operations of Orasense for the three month periods ended March 31, are as follows (in thousands):

	Three Months Ended March 31,	
	2001	2000
Revenue	$ —	$ —
Research and development expense	2,460	3,114
Net loss	$ (2,460)	$ (3,114)

HepaSense™

In January 2000, Isis and Elan formed a new joint venture to develop an antisense drug, ISIS 14803, to treat patients chronically infected with the Hepatitis C virus (HCV). The new joint venture, called HepaSense, is developing and plans to commercialize this novel drug for HCV while investigating delivery of the drug with Elan's proprietary MEDIPAD® Drug Delivery System, a disposable subcutaneous infusion device. HepaSense is initially owned 80.1% by the Company and 19.9% by Elan. Isis and Elan have each licensed technology to HepaSense.

While Isis owns 80.1% of the outstanding common stock of HepaSense, Elan and its subsidiaries have retained significant minority investor rights that are considered "participating rights" as defined in EITF 96-16. Therefore, Isis does not consolidate the financial statements of HepaSense, but instead accounts for its investment in HepaSense under the equity method of accounting. During the three month period ended March 31, 2001, Isis recognized $880,000 in contract revenues for research and development activities performed for HepaSense. This amount is included as research and development revenues from affiliates for the related period.

The results of operations of HepaSense for the three month periods ended March 31, 2001 are as follows (in thousands):

	Three Months Ended March 31,	
	2001	2000
Revenue	$ —	$ —
Research and development expense	2,154	1,250
Net loss	$ (2,154)	$ (1,250)

Abbott Laboratories, Inc.

In February 2001, GeneTrove™, a division of Isis, extended its antisense target validation research program with Abbott Laboratories, Inc. (Abbott) for an additional two years. The partnership, which started in January 1999, is to validate gene targets in both in-vivo and in-vitro models, identify the functions of genes, and prioritize gene targets for Abbott's internal drug discovery programs.

Merck & Company, Inc.

In March 2001, Isis and Merck & Company, Inc. (Merck) announced an extension of a research collaboration, which originally was entered into in June 1998. The collaboration's purpose is to discover small molecule drug candidates to treat patients infected with the Hepatitis C virus. During this one-year extension of the original three-year program Merck will pay Isis research support as part of the collaboration. Merck will also pay Isis clinical development milestone payments from developments that arise from the collaboration and royalties from product sales.

Molecular Biosystems, Inc.

In March 2001, Isis and Molecular Biosystems, Inc. (MBI) amended a non-exclusive Patent License Agreement originally entered into in September 1992. The amendment provided Isis with a fully paid up license to certain patents and patent applications in exchange for a one-time payment of $1 million. Isis capitalized the payment as licensed technology and is amortizing the amount over the estimated useful life of the technology.

3. Comprehensive Loss

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

Statements of Comprehensive Loss
(Unaudited)

	Three Months Ended March 31,	
	2001	2000
Comprehensive loss:		
Change in unrealized gains and (losses)	$ 473	$ 71
Net loss	(23,166)	(18,608)
Comprehensive loss	$ (22,693)	$ (18,537)

4. Subsequent Events

On May 8, 2001, Ibis Therapeutics, a division of Isis, achieved a $2.5 million milestone related to the research agreement entered into with Agouron Pharmaceuticals, Inc., a Pfizer Company (Pfizer) in June 2000. The milestone achieved by Isis was related to the discovery of small molecule drugs that bind to RNA.

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

This Form 10-Q contains forward-looking statements regarding our business and the therapeutic and commercial potential of our technologies and products in development. Such statements are subject to certain risks and uncertainties, particularly those risks or 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, 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 our Annual Report on Form 10-K/A for the year ended December 31, 2000 which is on file with the U.S. Securities and Exchange Commission and those identified in the section of Item 2 entitled "Risk Factors" of this report. As a result, the reader is cautioned not to rely on these forward-looking statements.

Since our inception in January 1989, almost all of our resources have been devoted to research, drug discovery and drug development programs. We are not yet profitable and expect to continue to have operating losses for the next several years. Our revenue comes from collaborative research and development agreements with pharmaceutical companies, the sale and licensing of our intellectual property, research grants and interest income. The revenue from the collaboration agreements increases the amount of research and development activity that we are able to fund and offsets a portion of our research and development costs. In 1998, we received approval from the U.S. Food and Drug Administration, or FDA, to begin marketing our first product, Vitravene, a drug used to treat CMV retinitis.

Results of Operations

Our total revenue was $4.6 million for the three months ended March 31, 2001, compared with $4.1 million for the same period in 2000. The increase in revenue was primarily due to the development services provided to HepaSense™, which resulted from the collaboration we initiated during the first quarter of 2000, offset by collaborations that did not continue into 2001.

Our research and development expenses were $19.1 million for the three months ended March 31, 2001, compared to $13.2 million for the same period last year. For both periods, research and development expenses were driven by the cost of pre-clinical and clinical activities to advance the development of our drugs. The increase of $5.9 million in research and development expenditures in the current quarter from that of the same period in 2000 was primarily a result of the eleven products we have in development, an increase from seven in the same period last year. Additionally, six of the eleven products are currently in Phase II or Phase III trials, which are the later, more expensive, stages of development. To support this progress, we incurred additional costs in the current quarter compared to the same quarter in 2000.

Our general and administrative expenses increased to $2.8 million for the quarter ended March 31, 2001, from $1.8 million for the same period in 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 ended March 31, 2001 resulted in a decrease to compensation expense of approximately $83,000. This was primarily a result of an exchange we made regarding certain existing options to non-officer employees completed in January 2000. These exchanged options are required to be accounted for as variable stock options in accordance with Financial Accounting Standards Board Interpretation Number 44. Variable stock options can result in significant increases and decreases in compensation expense subject to the variability of our stock price. In addition, we account for stock options granted to consultants in accordance with EITF 96-18, which partially offset the decrease to compensation previously discussed.

Interest expense was $3.6 million for the first quarter 2001 compared with $3.1 million for the same quarter last year. The increase in interest expense was primarily due to borrowings under our $18.4 million and $12.0 million convertible debt facilities available to us from Elan to fund research and development activities for Orasense and HepaSense, respectively. At March 31, 2001, we had $11.9 million outstanding under the convertible facilities compared to $4.8 milllion at March 31, 2000. Also contributing to the increase in our interest expense, is 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 this financing, payment of interest accrues for the first five years and no principal payments are due for 10 years.

We had interest income totaling $2.0 million for the three months ended March 31, 2001, compared with $0.9 million for the same period in 2000. This increase in interest income was due primarily to our higher average cash and investment balances during the quarter ended March 31, 2001 compared to the same period in 2000.

During the quarter ended March 31, 2001 we recorded a net loss applicable to common stock of $23.2 million, or $0.58 per share, compared with $18.6 million, or $0.56 per share, for the same period in 2000. Our loss from operations was $17.2 million for the first quarter of 2001, compared to $12.6 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 eleven 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 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, 2001, we have earned approximately $222 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 $369 million from the sale of equity securities. We have borrowed approximately $82.3 million under long-term debt arrangements to finance a portion of our operations.

As of March 31, 2001, we had cash, cash equivalents and short-term investments totaling $108.4 million and working capital of $101.7 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 decreases in our cash, cash equivalents and short-term investments, and working capital are due primarily to cash used to fund our operations.

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 a 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 March 31, 2001 was $60.4 million.

As of March 31, 2001, our long-term obligations totaled $104.5 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 March 31, 2001, combined with contract revenue and interest income should be sufficient to fund our operations for the next 30 to 36 months.

RISK FACTORS

Please consider the following risk factors carefully in addition to the other information contained in this report.

Our business will suffer if we fail to obtain regulatory approval for our products.

We must conduct time-consuming, extensive and costly clinical trials, in compliance with U.S. Food and Drug Administration regulations, and by comparable authorities in other countries, to show the safety and efficacy of each of our drug candidates, as well as the optimum dosage for each, before the FDA can approve a drug candidate for sale. We may not be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our products under development. Delays in receiving these approvals, failure by us or our partners to receive these approvals at all or failure to comply with existing or future regulatory requirements could have a material adverse effect on our business, financial condition and results of operations.

Significant additional trials may be required, and we may not be able to demonstrate that our drug candidates are safe or effective. We have only introduced one commercial product, Vitravene. We cannot guarantee that any of our other product candidates will obtain required government approvals or that we can successfully commercialize any products.

Our business will suffer if our products are not used by doctors to treat patients.

We cannot guarantee that any of our products in development, if approved for marketing, will be used by doctors to treat patients. We currently have one product, Vitravene, a treatment for CMV retinitis in AIDS patients, which addresses a small commercial market with significant competition. However, we 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 clinical efficacy and safety of our product candidates and their potential advantages over competitive products; and reimbursement policies of government and third-party payors. In addition, physicians, patients, patient advocates, payors or the medical community in general may not accept and use any products that we may develop.

Our business will suffer if any of our collaborative partners fail to develop, fund or sell any of our products under development or if we are unable to obtain additional partners.

If any collaborative partner fails to develop or sell any product in which we have rights, our business may be negatively affected. While we believe that our collaborative partners will have sufficient motivation to continue their funding, development and commercialization activities, we cannot be sure that any of these collaborations will be continued or result in commercialized products.

The failure of a corporate partner to continue funding any particular program could delay or stop the development or commercialization of any products resulting from such program.

Collaborative partners may be 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.

We also may wish to rely on additional collaborative arrangements to develop and commercialize our products in the future. However, we may not be able to negotiate acceptable collaborative arrangements in the future, and, even if successfully negotiated, the collaborative arrangements themselves may not be successful.

Our business could suffer if the results of clinical testing indicate that any of our products under development are not suitable for commercial use.

Drug discovery and development involves inherent risks, including the risk that molecular targets prove unsuccessful and the risk that compounds that demonstrate attractive activity in preclinical studies do not demonstrate similar activity in human beings or have undesirable side effects. Most of our resources are dedicated to applying molecular biology and medicinal chemistry to the discovery and development of drug candidates based upon antisense technology, a novel drug discovery tool for designing drugs that work at the genetic level to block the production of disease-causing proteins.

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

Because of the nature of the business of drug discovery and development, our expenses have exceeded our revenues since we were founded in January 1989. As of March 31, 2001, our accumulated losses were approximately $335 million. Most of the losses have resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our growth and operations. These costs have exceeded our revenues, most of which have come from collaborative arrangements, interest income and research grants. Our product revenues to date have been 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 we expect losses to increase as our preclinical testing and clinical trial efforts continue to expand. We cannot guarantee that we will successfully develop, receive regulatory approval for, commercialize, manufacture, market or sell any additional products, or achieve or sustain future profitability.

Our business will suffer if we fail to obtain timely funding.

Based on our current operating plan, we believe that our available cash and existing sources of revenue and credit, together with the interest earned on those funds, will be adequate to satisfy our capital needs for the next 30 to 36 months. We expect that we will need substantial additional funding in the future. Our future capital requirements will depend on many factors, such as the following: 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; the costs involved in filing, prosecuting and enforcing patent claims; competing technological and market developments, including the introduction of new therapies that address our markets; costs of commercialization of products; and changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements.

Additional funds will need to be raised through public or private financing. Additional financing may not be available, or, if available, may not be available on acceptable terms. If additional funds are raised by issuing equity securities, the shares of existing stockholders will be subject to further dilution and share prices 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 if available. These arrangements may require us to give up rights to certain of our technologies, product candidates or products.

Our business will suffer if we cannot manufacture our products or have a third party manufacture our products at low costs so as to enable us to charge competitive prices to buyers.

To establish additional commercial manufacturing capability on a large scale, we must improve our manufacturing processes and reduce our product costs. The manufacture of sufficient quantities of new drugs is typically a time-consuming and complex process. Pharmaceutical products based on chemically modified oligonucleotides have never been manufactured on a large commercial scale. There are 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. We may not be able to manufacture at a cost or in quantities necessary to make commercially successful products.

Our business will suffer if we fail to compete effectively with our competitors.

Our competitors are engaged in all areas of drug discovery in the United States and other countries, are numerous, and include, among others, major pharmaceutical and chemical companies, specialized biopharmaceutical firms, universities and other research institutions. Our competitors may succeed in developing other new therapeutic drug candidates that are more effective than any drug candidates that we are developing. These competitive developments could make our technology and products obsolete or non-competitive before we have had enough time to develop and commercialize our products, or to recover our research, development or commercialization expenses.

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 manufacturing efficiency and marketing capabilities, areas in which we have limited or no experience.

Our business will suffer if we are unable to protect our patents or our proprietary rights.

Our success depends to a significant degree upon our ability to develop proprietary products. 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 offer meaningful protection. 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 harm our business.

It is possible that we may have to defend our intellectual property rights in the future. In the event of an intellectual property dispute, we may be forced to litigate or otherwise defend our intellectual property assets. Disputes could involve litigation or proceedings declared by the United States Patent and Trademark Office or the International Trade Commission. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business.

If a third party claimed an intellectual property right to technology we use, 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.

The loss of key personnel, or the inability to attract and retain highly skilled personnel, could adversely affect our business.

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 stock price may continue to be highly volatile.

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 past twelve months, the market price of our common stock has ranged from $8.00 to $15.56 per share. The market price can be affected by many factors, including, for example, fluctuations in our operating results, announcements of 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. These provisions, as well as Delaware law and other of our agreements including our stockholders' Rights Plan, 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 Isis without action by the 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

The Company is not party to any material legal proceedings.

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

On April 6, 2001, the Company's Annual Meeting of Stockholders was held in Carlsbad, California for the following purposes:

(1) To elect two (2) directors to serve as Class I directors of the Company. The number of votes for and abstaining was 33,645,600 and 156,015, respectively.

(2) To amend the Company's Restated Certificate of Incorporation to increase the authorized number of shares of common stock from 50,000,000 to 100,000,000. The number of votes for, against and abstaining was 31,803,576, 1,897,688 and 100,351, respectively.

(3) To ratify the appointment of Ernst & Young LLP as the Company's independent auditors for the fiscal year ending 2001. The number of votes for, against and abstaining was 33,674,748, 70,967 and 55,900, respectively.

ITEM 5. OTHER INFORMATION

Not applicable.

ITEM 6. EXHIBITS AND REPORTS ON FORM 8-K

a. *Exhibits*

None

b. *Reports on Form 8-K*

Not applicable.

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: May 14, 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: May 14, 2001 By: /s/ B. LYNNE PARSHALL

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