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, 2000

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 incorporation 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	39,013,173 SHARES
(Class)	(Outstanding at November 6, 2000)

ISIS PHARMACEUTICALS, INC.
FORM 10-Q

INDEX

ISIS PHARMACEUTICALS, INC.
CONDENSED BALANCE SHEETS
(IN THOUSANDS)

ASSETS

	SEPTEMBER 30, 2000 (Unaudited)	DECEMBER 31, 1999 (Note)
Current assets:		
Cash and cash equivalents	$ 59,030	$ 35,296
Short-term investments	61,655	17,543
Contract revenue receivable	6,942	5,429
Prepaid expenses and other current assets	1,145	929
Total current assets	128,772	59,197
Property, plant and equipment, net	23,322	23,945
Patent costs, net	12,135	11,250
Deposits and other assets	1,238	1,724
Investment in joint ventures	11,108	6,991
Total assets	$ 176,575	$ 103,107
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 732	$ 3,148
Accrued payroll and related expenses	2,782	1,215
Accrued liabilities	3,119	2,563
Deferred contract revenues	4,109	4,166
Current portion of long term debt and capital lease obligations	3,538	3,892
Total current liabilities	14,280	14,984
Long-term debt and capital lease obligations, less current portion	96,330	87,254
Stockholders' equity:		
Series A Convertible Exchangeable 5% Preferred stock, $.001 par value; 15,000,000 shares authorized, 120,150 shares issued and outstanding at September 30, 2000 and December 31, 1999, respectively	12,623	12,315
Accretion of Series A Preferred stock dividends	280	120
Series B Convertible Exchangeable 5% Preferred stock, $.001 par value; 16,620 shares authorized, 12,015 shares issued and outstanding at September 30, 2000 and no shares issued and outstanding at December 31, 1999	12,315	-
Accretion of Series B Preferred stock dividends	130	-
Common stock, $.001 par value; 50,000,000 shares authorized, 38,474,485 shares and 31,613,000 shares issued and outstanding at September 30, 2000 and December 31, 1999, respectively	38	32
Additional paid-in capital	337,600	245,192
Deferred compensation	(1,293)	-
Unrealized gain (loss) on investments	(31)	(29)
Accumulated deficit	(295,697)	(256,761)
Total stockholders' equity	65,965	869
Total liabilities and stockholders' equity	$ 176,575	$ 103,107

NOTE: THE BALANCE SHEET AT DECEMBER 31, 1999 HAS BEEN DERIVED FROM THE AUDITED FINANCIAL STATEMENTS AT THAT DATE.

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
CONDENSED STATEMENTS OF OPERATIONS
(IN THOUSANDS, EXCEPT PER SHARE DATA)
(UNAUDITED)

	Three months ended, September 30,		Nine months ended, September 30,	
	2000	1999	2000	1999
Revenue:				
Research and development revenues under collaborative agreements	$ 16,521	$ 9,641	$ 23,631	$ 22,032
Research and development revenues from joint ventures	1,759	997	5,688	2,390
Total Revenue	18,280	10,638	29,319	24,422
Expenses:				
Research and development (not including compensation related to variable stock options of $502 for the three and nine months ended September 30, 2000)	16,001	16,273	41,986	47,032
General and administrative (not including compensation related to variable stock options of $58 for the three and nine months ended September 30, 2000)	2,073	2,406	6,311	7,983
Compensation related to variable stock options	560	-	560	-
Restructuring activities	27	-	1,635	-
Total Operating Expenses	18,661	18,679	50,492	55,015
Loss from operations	(381)	(8,041)	(21,173)	(30,593)
Equity in loss of joint ventures	(3,659)	(2,018)	(11,748)	(4,295)
Interest income	1,976	553	4,464	1,760
Interest expense	(3,345)	(2,924)	(9,581)	(8,429)
Net loss	(5,409)	(12,430)	(38,038)	(41,557)
Accretion of dividends on preferred stock	(311)	(150)	(898)	(267)
Net loss applicable to common stock	$ (5,720)	$ (12,580)	$ (38,936)	$ (41,824)
Basic and diluted net loss per share	$ (0.15)	$ (0.44)	$ (1.08)	$ (1.49)
Shares used in computing basic and diluted net loss per share	38,448	28,838	36,172	28,027

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
CONDENSED STATEMENTS OF CASH FLOWS
(IN THOUSANDS)
(UNAUDITED)

	NINE MONTHS ENDED SEPTEMBER 30,	
	2000	1999
Cash used in operations	$ (17,268)	$ (37,422)
Investing activities:		
Short-term investments	(44,114)	25,704
Property and equipment	(2,775)	(3,355)
Other assets	(1,340)	(2,235)
Investment in joint venture	(15,865)	(9,174)
Net cash (used for) provided from investing activities	(64,094)	10,940
Financing activities:		
Net proceeds from issuance of equity securities	103,474	36,734
Proceeds from long-term borrowings	3,850	2,468
Principal payments on debt and capital lease obligations	(2,228)	(2,005)
Net cash provided from financing activities	105,096	37,197
Net increase in cash and cash equivalents	23,734	10,715
Cash and cash equivalents at beginning of period	35,296	27,618
Cash and cash equivalents at end of period	$ 59,030	$ 38,333
SUPPLEMENTAL DISCLOSURES OF CASH FLOW INFORMATION:		
Interest paid	$ 878	$ 2,017
SUPPLEMENTAL DISCLOSURES OF NON-CASH INVESTING AND FINANCING ACTIVITIES:		
Additions to long-term debt obligations for acquisitions of property, plant and equipment	$ -	$ 2,071
Additions to receivables from sales of property, plant and equipment	27	-
Conversion of preferred stock dividends into preferred stock	608	-

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, 2000 and 1999 have been prepared on the same basis as the Company's audited financial statements for the year ended December 31, 1999. The financial statements include all adjustments (consisting only of normal recurring adjustments) that 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, 1999, included in the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission.

2. STRATEGIC ALLIANCES

ORASENSE-TM-

On April 20, 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 nine month period ended September 30, 2000, Isis recognized $3,834,724 in contract revenues for research and development activities performed for OraSense Ltd. This amount was included as research and development revenues from joint ventures for the related periods.

The results of operations of OraSense Ltd. for the nine month period ended September 30, 2000 was as follows (in thousands):

	NINE MONTHS ENDED SEPTEMBER 30, 2000
Revenue	$ --
Research and Development expense	9,035
Net Loss	$ (9,035)

HEPASENSE

On January 14, 2000, Isis and Elan formed a new joint venture to develop an antisense drug, ISIS 14803, to treat patients infected with the Hepatitis C virus (HCV). The new joint venture, called HepaSense, plans to develop and commercialize this novel drug for HCV while investigating delivery of the drug with Elan's proprietary MEDIPAD-TM- Drug Delivery System, a disposable subcutaneous infusion device. HepaSense is initially owned 80.1% by the Company and 19.9% by Elan. ISIS 14803 is in Phase II clinical trials. 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 nine month period ended September 30, 2000, Isis recognized $1,853,144 in contract revenues for research and development activities performed for HepaSense Ltd. This amount was included as research and development revenues from joint ventures for the related periods.

The results of operations of HepaSense Ltd. for the nine month period ended September 30, 2000 was as follows (in thousands):

	NINE MONTHS ENDED SEPTEMBER 30, 2000
Revenue	$ --
Research and Development expense	5,632
Net Loss	$ (5,632)

AGOURON PHARMACEUTICALS, INC., a PFIZER COMPANY

In June 2000, Ibis Therapeutics-TM- ("Ibis"), a division of Isis Pharmaceuticals, Inc. and Agouron Pharmaceuticals, Inc., a Pfizer Company ("Pfizer"), entered into a collaboration for the discovery and development of small molecule drugs against certain RNA targets in an undisclosed therapeutic area. Using Ibis' proprietary technology and Pfizer's expertise in small molecule drug discovery, the collaboration will focus on discovering drugs that bind to RNA. Pfizer will fund collaborative research, pay an upfront technology access fee and make milestone payments totaling up to $37 million for the first product. In addition, Pfizer will develop and commercialize drugs discovered by the collaboration and will pay Isis royalties on the sales of drugs.

THE R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE

In August 2000, GeneTrove-TM-, a division of Isis, initiated an antisense target validation collaboration with The R.W. Johnson Pharmaceutical Research Institute ("PRI"), a member of the Johnson & Johnson family of companies, to assess and prioritize genes as drug discovery targets. GeneTrove will use its proprietary antisense technology to assist PRI to study the function and therapeutic relevance of novel gene targets. PRI will make milestone payments for the successful validation of such novel gene targets.

COLEY PHARMACEUTICAL GROUP

In September 2000, Isis sold its patents concerning the use of phosphorothioate oligonucleotides for activating the immune system to Coley Pharmaceutical Group ("Coley"). The patents were originally licensed to Coley in 1998 for a limited scope of use, at which time Coley paid Isis $5 million in cash and issued preferred stock to Isis. In exchange for all non-antisense rights to this group of immunomodulation patents and in lieu of any and all future payments that could potentially be owed under the original agreement, Coley paid Isis an additional $10.7 million. A portion of the fee, $3.7 million, was paid to repurchase the Coley preferred stock that was granted to Isis as part of the total consideration given for the original patent license. During the three and nine month period ended September 30, 2000, Isis recognized $10.7 million in licensing revenue from the transaction. This amount was included in research and development revenues under collaborative agreements for the related periods.

3. FINANCING

Over the nine months ended September 30, 2000, Isis sold 2,939,460 shares of its common stock to institutional investors at negotiated prices ranging from $10.45 per share to $27.25 per share. In addition, over the nine months ended September 30, 2000 the Company sold 1,997,879 shares of its common stock to Ridgeway Investment Limited at prices ranging from $7.57 per share to $14.45 per share under the terms of the Common Stock Purchase Agreement filed as an exhibit to the Company's registration statement on Form S-3, No. 333-90811. The per share average purchase prices reflect the average trading prices of the common stock over a period of time less a discount percentage ranging from 4.5% to 5.875%.

4. SUBSEQUENT EVENTS

In September 2000, Isis entered into an agreement to license its novel antisense chemistry, Peptide Nucleic Acid ("PNA"), to Pantheco A/S ("Pantheco"), a Danish biotechnology company, on a nonexclusive basis to treat diabetes and cardiovascular diseases. Pantheco completed financing to raise funds to support its current business and to fund this expansion of therapeutic focus on October 18, 2000. Subsequent to the completion of Pantheco's financing, Isis received, as a fee for this license, 9 million DKK, or $1.1 million, which was paid in Pantheco shares. In addition, Pantheco will pay Isis royalties and milestones on products developed using the PNA. This is the second license of PNA technology from Isis to Pantheco. As part of the first licensing transaction completed in November 1998, Isis received an equity position in Pantheco for which no carrying value was given as realization of the value of the equity interest in Pantheco was uncertain. As a result of the current transaction, Isis' ownership of Pantheco is approximately 22%.

On October 6, 2000, pursuant to the Company's registration statement on Form S-3, No. 333-90811, Isis sold 483,092 shares of its common stock to an institutional investor at a negotiated price of $10.35 per share.

On October 10, 2000, Isis completed the licensing of novel chemistry patents to Roche Molecular Systems, Inc. ("RMS"), a business unit of Roche Diagnostics, for use in the production of RMS's diagnostic products. The royalty-bearing license grants RMS non-exclusive worldwide access to proprietary Isis chemistry, in exchange for initial and ongoing payments.

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 Isis' business and products and their projected prospects and qualities, as well as our relationships with our corporate partners. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are 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. As a result, the reader should not place undue reliance on these forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed below under "Risk Factors".

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

RESULTS OF OPERATIONS

Isis' revenue from collaborative research and development agreements with corporate and government partners was $16.5 million for the three months ended September 30, 2000, and $23.6 million for the nine months ended September 30, 2000, compared with $9.6 million and $22.0 million, respectively, for the same periods in 1999. The revenue increase was due primarily to $10.7 million in licensing revenue from the sale to Coley of Isis' patents concerning the use of phosphorothioate oligonucleotides for activating the immune system. In addition, Isis earned revenue from ongoing collaborations, including the Pfizer collaboration that began in the second quarter, as well as from government grants and contracts, . These increases were partially offset by a decrease in revenues in 2000, due to the conclusion of development funding in December 1999 by Novartis and Boehringer Ingelheim . Isis recognized contract revenues for research and development activities performed for its joint ventures, OraSense and HepaSense, of $1.8 million and $5.7 million, respectively, for the three and nine months ended September 30, 2000, compared with $1.0 million and $2.4 million, respectively, for the same periods in 1999. The increase in the current year was due to the start of the HepaSense joint venture in January 2000. Isis also had interest income of $2.0 million for the quarter ended September 30, 2000, and $4.5 million for the nine months ended September 30, 2000, compared with $0.6 million and $1.8 million, respectively, for the same periods in 1999. This increase in interest income was primarily due to higher average cash and investment balances and, in part, to higher interest rates.

Research and development expenses were $16.0 million and $42.0 million, respectively, for the three and nine months ended September 30, 2000, compared with $16.3 million and $47.0 million, respectively, for the same periods in 1999. For both periods, research and development expenses were driven by the cost of activities to support the progress of drugs in clinical trials. The decrease in expenses was primarily the result of our restructuring activities and reduction in staff previously announced in January 2000 offset by increased spending related to the

initiation of Phase III clinical trials for ISIS 3521 in non-small cell lung cancer.

General and administrative expenses decreased to $2.1 million for the three months ended September 30, 2000 and $6.3 million for the nine months ended September 30, 2000, from $2.4 million and $8.0 million, respectively, for the same periods in 1999. This decrease in general and administrative expenses was primarily related to the Company's restructuring activities mentioned above.

Compensation related to variable stock options was $0.6 million for the three and nine months ended September 30, 2000. Stock options granted to consultants are required to be accounted for as variable stock options in accordance with EITF 96-18. Isis granted options to consultants with exercise prices of fair market value at the time of issuance. In addition, in January 2000 Isis offered non-officer employees an opportunity to exchange certain of their existing options. These 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 Isis' stock price.

The estimated cost of restructuring activities was recorded in the first quarter of 2000, and totaled $1.6 million. For the nine months ended September 30, 2000, we have incurred actual costs of approximately $1.6 million, a nominal portion of which was incurred in the third quarter. We do not anticipate the actual costs to substantially exceed the amount incurred to date. This expense primarily consisted of costs associated with our reduction in work force.

Interest expense increased to $3.3 million and $9.6 million, respectively, for the three and nine months ended September 30, 2000, compared to $2.9 million and $8.4 million, respectively, for the same periods in 1999. The increase was due primarily to interest accrued 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. The increase in interest expense was also due to borrowings by Isis during the second quarter of 1999 and the first and second quarters of 2000 under a debt facility from Elan related to the OraSense joint venture to fund Isis' share of OraSense expenses. Of the $3.3 million of interest expense recognized in the third quarter of 2000, $2.4 million was accrued under long-term debt agreements and will not require current cash payments. Similarly, of the $8.4 million of interest expense incurred during the nine months ended September 30, 2000, $7.0 million was accrued under long-term debt arrangements and will not require current cash payments.

During the three and nine month periods ended September 30, 2000, Isis recorded a net loss applicable to common stock of $5.7 million and $38.9 million, respectively, or $0.15 and $1.08 per share, respectively, compared with $12.6 million and $41.8 million, respectively, or $0.44 and $1.49 per share, respectively, for the same periods in 1999. The third quarter 2000 loss included $1.8 million in joint venture revenue together with $3.7 million for Isis' equity in the losses from OraSense and HepaSense, the joint ventures, compared to $1.0 million and $2.0 million, respectively, for the same period in 1999. The increases were primarily due to the formation of the HepaSense joint venture in January 2000. Isis' loss from operations was $0.4 million for the third quarter of 2000, compared to $8.0 million for the same period in 1999. The decrease in loss from operations in the third quarter was primarily attributable to the $10.7 million in licensing revenue from the sale to Coley of Isis' patents concerning the use of phosphorothioate

oligonucleotides for activating the immune system and, in part, to our restructuring activities. Operating losses may fluctuate from quarter to quarter because of differences in the timing of revenue and expense recognition.

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

LIQUIDITY AND CAPITAL RESOURCES

Isis has financed its operations with revenue from contract research and development, product sales, patent licensing, through the sale of equity securities and the issuance of long-term debt. From our inception through September 30, 2000, we have earned approximately $209 million in revenue from contract research and development, patent licensing and product sales. Isis has also raised net proceeds of approximately $353 million from the sale of equity securities since we were founded. To date, Isis has borrowed approximately $79 million under long-term debt arrangements to finance a portion of its operations.

As of September 30, 2000, Isis had cash, cash equivalents and short-term investments totaling $120.7 million and working capital of $114.5 million. In comparison, we had cash, cash equivalents and short-term investments of $52.8 million and working capital of $44.2 million as of December 31, 1999. The increases in cash and working capital during the first nine months of 2000 were primarily due to the sales of common stock to institutional investors and the sale of common stock to Elan International Services, Ltd. ("EIS") in conjunction with the formation of HepaSense, funding from Ibis' collaboration with Pfizer, and proceeds from the sale of Isis' patents to Coley.

Isis' collaborative agreement with Boehringer Ingelheim provided us with a line of credit that was used to support the collaboration's cell adhesion programs. As of September 30, 2000, the outstanding balance of this obligation was $22.6 million. In 1999, Isis reacquired the rights to ISIS 2302 from Boehringer Ingelheim. Therefore, there will be no further draws against this line.

In 1997 and 1998, Isis 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, Isis 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 of the loans, 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 the 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, 2000 was $55.7 million.

As of September 30, 2000, Isis' long-term obligations totaled $96.3 million, compared to $87.3 million at December 31, 1999. The increase was due to the accrual of interest on the ten-year notes described above and the addition of $3.9 million in loans related to partnership agreements, including the OraSense joint venture. This increase was partially offset by principal repayments on existing obligations. The Company expects that capital lease obligations will increase over time to fund capital equipment acquisitions required for Isis' growing business. Isis 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, combined

with interest income and contract revenue will be sufficient to meet our anticipated requirements for at least the next 36 months.

PROSPECTIVE INFORMATION

On October 4, 2000, We announced that we will reinitiate development of its antisense ICAM-1 inhibitor, ISIS 2302 in Crohn's disease. A recently completed analysis of the randomized trial indicates that those patients who received higher exposure to ISIS 2302 were more likely to experience complete clinical remission, the primary endpoint of the study. Patients in complete clinical remission were completely off steroids and symptom-free. The analysis showed that patients' exposure to ISIS 2302 varied based on gender and weight. Isis is planning additional clinical studies in Crohn's patients using higher doses of ISIS 2302 to reproduce the drug exposure levels that correlated with higher response rates in the analysis.

On October 18, 2000, we announced that the first patient had been dosed in a Phase III trial of ISIS 3521 in non-small cell lung cancer. The study will evaluate the ability of ISIS 3521 to safely prolong the lives of patients' with non-small cell lung cancer when given in combination with a standard chemotherapy regimen, used to treat non-small cell lung cancer. In early November 2000 we announced that the U.S. Food and Drug Administration ("FDA") granted fast track review status to ISIS 3521. The FDA's fast track review process is intended to expedite the review of treatments that have the potential to address unmet medical needs for serious life-threatening diseases.

On October 25, 2000, we announced that we had initiated Phase I clinical studies of ISIS 104838, a novel antisense drug to treat inflammatory and autoimmune diseases such as rheumatoid arthritis and Crohn's disease. ISIS 104838, an inhibitor of TNF-alpha, employs Isis' proprietary second-generation antisense chemistry which is more potent and more stable than first generation chemistries. The clinical program for ISIS 104838 will investigate the safety and efficacy of the drug administered intravenously and subcutaneously. Oral formulations of ISIS 104838 are being developed in parallel by Isis' joint venture with Elan, OraSense. OraSense plans to test solid dosage forms (tablets or capsules) of ISIS 104838 in human clinical trials in 2001.

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, 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 cannot guarantee that we will 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, VitraveneTM. 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. We delivered our first commercial shipment of Vitravene to our partner CIBA Vision in 1998, earning product revenue of $560,000. No commercial shipments of Vitravene were made in 1999 or to date in 2000, and no product revenue was earned.

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, we cannot guarantee that physicians, patients, patient advocates, payors or the medical community in general will 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.

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 September 30, 2000, our accumulated losses were approximately $296 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 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 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 at least the next three years. 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 market acceptance of Vitravene;
- 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; 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. 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, we cannot assure you that patents will be granted on any of our pending patent applications in the United States or in other countries. We also cannot assure you that the scope of any of our issued patents will be sufficiently broad to offer meaningful protection. In addition, 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 nine months, the market price of our common stock has ranged from $5.88 to $33.81 per share. The market price can be affected by many factors, including, for example, fluctuations in our operating results, announcements of 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 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 the outstanding common stock. These provisions 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.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

Isis is exposed to changes in interest rates primarily from its long-term debt arrangements and, secondarily, its investments in certain short-term investments. Isis invests its excess cash in highly liquid short-term investments that are typically held for the duration of the term of the respective instrument. Isis does 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

Not applicable.

ITEM 5. OTHER INFORMATION

On September 26, 2000, Isis announced that B. Lynne Parshall had been elected to the Company's Board of Directors, increasing the Board to seven. Ms. Parshall is Executive Vice President and Chief Financial Officer of Isis Pharmaceuticals. She is responsible for overseeing the operations of regulatory affairs, development chemistry and manufacturing, business development, finance, and the Company's legal and patent affairs.

Pursuant to the Company's bylaws, stockholders who wish to bring matters or propose nominees for director at the Company's 2001 annual meeting of stockholders must provide specified information to the Company by January 31, 2001 (unless such matters are included in the Company's proxy statement pursuant to Rule 14a-8 under Securities Exchange Act of 1934, as amended).

ITEM 6. EXHIBITS AND REPORTS ON FORM 8-K

a. Exhibits

Not applicable

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: November 14, 2000

By: /s/ STANLEY T. CROOKE

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

Date: November 14, 2000

By: /s/ B. LYNNE PARSHALL

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

5

THIS SCHEDULE CONTAINS SUMMARY FINANCIAL INFORMATION EXTRACTED FROM THE COMPANY'S CONDENSED BALANCE SHEET AS OF SEPTEMBER 30, 2000 (UNAUDITED) AND CONDENSED STATEMENTS OF OPERATIONS FOR THE NINE MONTHS ENDED SEPTEMBER 30, 2000 (UNAUDITED) AND IS QUALIFIED IN ITS ENTIRETY BY REFERENCE TO SUCH FINANCIAL STATEMENTS.

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DEC-31-2000
JAN-01-2000
SEP-30-2000
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