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 June 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	38,448,777 SHARES
(Class)	(Outstanding at July 31, 2000)

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ISIS PHARMACEUTICALS, INC.
CONDENSED BALANCE SHEETS
(In Thousands)

ASSETS

	June 30, 2000 (Unaudited)	December 31, 1999 (Note)
Current assets:		
Cash and cash equivalents	62,043	35,296
Short-term investments	58,291	17,543
Contract revenue receivable	4,644	5,429
Prepaid expenses and other current assets	1,210	929
Total current assets	126,188	59,197
Property, plant and equipment, net	22,596	23,945
Patent costs, net	11,886	11,250
Deposits and other assets	1,587	1,724
Investment in joint ventures	14,767	6,991
Total assets	177,024	103,107
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	1,134	3,148
Accrued payroll and related expenses	2,344	1,215
Accrued liabilities	3,210	2,563
Deferred contract revenues	2,351	4,166
Current portion of long term debt and capital lease obligations	3,723	3,892
Total current liabilities	12,762	14,984
Long-term debt and capital lease obligations, less current portion	94,504	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 June 30, 2000 and December 31, 1999, respectivley	12,623	12,315
Accretion of Series A Preferred stock dividends	122	120
Series B Convertible Exchangeable 5% Preferred stock, $.001 par value; 16,620 shares authorized, 12,015 shares and no shares issued and outstanding at June 30, 2000 and December 31, 1999, respectively	12,015	--
Accretion of Series B Preferred stock dividends	277	--
Common stock, $.001 par value; 50,000,000 shares authorized, 38,375,438 shares and 31,613,000 shares issued and outstanding at June 30, 2000 and December 31, 1999, respectively	38	32
Additional paid-in capital	334,687	245,192
Unrealized gain (loss) on investments	(26)	(29)
Accumulated deficit	(289,978)	(256,761)
Total stockholders' equity	69,758	869
Total liabilities and stockholders' equity	177,024	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)

	Three months ended, June 30,		Six months ended, June 30,	
	2000	1999	2000	1999
Revenue:				
Research and development revenues under collaborative agreements	$4,224	$5,815	$7,110	$12,391
Research and development revenues from joint ventures	2,761	1,393	3,929	1,393
Total Revenue	6,985	7,208	11,039	13,784
Expenses:				
Research and development	12,746	16,443	25,985	30,759
General and administrative	2,414	2,762	4,238	5,577
Restructuring activities	-	-	1,608	-
Total Operating Expenses	15,160	19,205	31,831	36,336
(Loss) from operations	(8,175)	(11,997)	(20,792)	(22,552)
Equity in loss of joint ventures	(4,594)	(2,277)	(8,089)	(2,277)
Interest income	1,596	551	2,488	1,207
Interest expense	(3,129)	(2,800)	(6,236)	(5,505)
Net loss	(14,302)	(16,523)	(32,629)	(29,127)
Accretion of dividends on preferred stock	(306)	(117)	(587)	(117)
Net loss applicable to common stock	(14,608)	(16,640)	(33,216)	(29,244)
Basic and diluted net loss per share	($0.40)	($0.59)	($0.95)	($1.06)
Shares used in computing basic and diluted net loss per share	36,979	28,047	35,021	27,615

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
CONDENSED STATEMENTS OF CASH FLOWS
(In Thousands)
(Unaudited)

	Six Months Ended June 30, 2000	1999
Cash used in operations	(19,385)	(28,351)
Investing activities:		
Short-term investments	(40,745)	22,632
Property and equipment	(924)	(894)
Other assets	(876)	(1,423)
Investment in joint venture	(15,865)	(12,015)
Net cash used for investing activities	(58,410)	8,300
Financing activities:		
Net proceeds from issuance of equity securities	102,103	28,144
Proceeds from long-term borrowings	3,850	-
Principal payments on debt and capital lease obligations	(1,411)	(1,338)
Net cash provided from financing activities	104,542	26,806
Net increase (decrease) in cash and cash equivalents	26,747	6,755
Cash and cash equivalents at beginning of period	35,296	27,618
Cash and cash equivalents at end of period	62,043	34,373
SUPPLEMENTAL DISCLOSURES OF CASH FLOW INFORMATION:		
Interest paid	530	1,654
SUPPLEMENTAL DISCLOSURES OF NON-CASH INVESTING AND FINANCING ACTIVITIES:		
Additions to long-term debt obligations for acquisitions of property, plant and equipment	-	2,071
Conversion of preferred stock dividends into preferred stock	308	-

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

NOTES TO FINANCIAL STATEMENTS

1. BASIS OF PRESENTATION

The unaudited interim financial statements for the six month periods ended June 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) 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, 1999 included in the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission.

2. STRATEGIC ALLIANCES

ORASENSE

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. Isis and Elan each contributed rights to certain oral drug delivery technology to the joint venture. In addition, Isis contributed rights to ISIS 104838, an antisense oligonucleotide to inhibit TNF-(alpha), which will be the first candidate for oral formulation by Orasense. Isis and Elan will provide development and manufacturing services to Orasense and will be entitled to a portion of milestone payments and royalties received by Orasense for development of orally formulated oligonucleotide drugs. If Isis enters into an agreement with Orasense for oral formulation of any Isis oligonucleotide drug, Isis will pay Orasense royalties and a portion of certain third party milestone payments with respect to the drug.

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 six month period ended June 30, 2000, Isis recognized $2,490,566 in contract revenues for research and development activities performed for Orasense Ltd. This amount is included as research and development revenues from joint ventures for the related periods.

The results of operations of Orasense Ltd. for the six month period ended June 30, 2000 is as follows (in thousands):

	SIX MONTHS ENDED JUNE 30, 2000
Revenue	$ --
Research and Development expense	$ 6,151
Net Loss	$ 6,151

HEPASENSE

On January 14, 2000, Isis and Elan Corporation 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 is called HepaSense and plans to develop and commercialize this novel therapeutic for HCV while investigating delivery of the therapeutic with Elan's proprietary MEDIPAD-Registered Tradmark- Drug Delivery System, a disposable subcutaneous infusion device. ISIS 14803 began Phase I clinical trials in early 2000. Isis and Elan have each licensed technology to HepaSense.

In conjunction with the formation of HepaSense, Elan International Services, Ltd. ("EIS") purchased 12,015 shares of Isis' Series B Preferred stock for $12,015,000. In April 2000, EIS purchased an additional 298,000 shares of Isis' common stock for $7,500,000. EIS will purchase an additional $7.5 million of common stock at a premium to Isis' market price upon completion of a mutually agreed milestone.

After June 30, 2002, the preferred stock (including accrued dividends) will

be convertible at EIS' option, into shares of Isis' common stock at 125% of the 60-trading day average closing price of Isis' common stock ending two business days prior to June 30,

2002 (as adjusted for stock splits, stock dividends and the like). In the event of a liquidation of Isis or certain transactions involving a change of control of Isis, the agreement provides for automatic conversion of the preferred stock on terms similar to those set forth above.

Isis is not obligated to issue shares representing more than 19.99% of its then outstanding Common Stock upon conversion of the Preferred Stock if it would result in a violation of the rules of any securities market or exchange upon which the Common Stock is traded.

At any time until June 30, 2002, the holders of preferred stock may exchange their preferred stock with Isis for preferred shares of HepaSense, Ltd. held by Isis that represent 60.2% of the total outstanding preferred stock of HepaSense. The exchange right will terminate if the Isis Series B Convertible Preferred stock is converted into Isis' common stock, unless such conversion occurs as a result of a liquidation or certain transactions involving a change of control of Isis.

Isis contributed $12,015,000 to HepaSense as the purchase price for 6,001 shares of common stock of HepaSense and 3,612 shares of HepaSense preferred stock. Until July 14, 2002, EIS will, at Isis' request, purchase convertible debt of Isis in an amount equal to Isis' share of budgeted funding for HepaSense. The convertible debt will have a term of six years, bear interest at the rate of 12% and be convertible into Isis' common stock at a premium. Isis may prepay the convertible debt in cash or Isis' common stock. Isis will use the proceeds of the sale of the convertible debt to provide additional development funding 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 six month period ended June 30, 2000, Isis recognized $1,439,126 in contract revenues for research and development activities performed for HepaSense Ltd. This amount is included as research and development revenues from joint ventures for the related periods.

The results of operations of HepaSense Ltd. for the six month period ended June 30, 2000 is as follows (in thousands):

	SIX MONTHS ENDED JUNE 30, 2000
Revenue	$ --
Research and Development expense	$ 3,939
Net Loss	$ 3,939

AGOURON

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

3. FINANCING

On March 8, 2000, Isis sold 1,000,000 shares of its common stock to an institutional investor at a negotiated price of $27.25 per share. In addition, over the six months ended June 30, 2000 the company sold 4,937,289 shares of its common stock to Ridgeway Investment Limited at prices ranging from an average of $7.57 per share to $21.66 per share under the terms of the Common Stock Purchase Agreement filed as an exhibit to the prospectus dated December 6, 1999. The per share average purchase prices reflect the average trading prices of the common stock on the Nasdaq National Market during the respective drawdown periods.

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 under "Risk Factors".

Since its inception in January 1989, almost all of Isis' resources have been devoted to its research, drug discovery and drug development programs. Isis is not yet profitable and expects 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 its research and development costs.

RESULTS OF OPERATIONS

Isis' revenue from collaborative research and development agreements with corporate and government partners was $4.2 million for the second quarter and $7.1 million for the six months ended June 30, 2000, compared with $5.8 million and $12.4 million respectively, for the same periods in 1999. The revenue decrease was due primarily to the conclusion of development funding at December 1999 by Novartis for the cancer drugs ISIS 5132 and ISIS 3521 and Boehringer Ingelheim for ISIS 2302. This decrease was partially offset by an increase in revenues from ongoing collaborations including government grants and contracts and the Agouron collaboration that began in the second quarter. Isis recognized contract revenues for research and development activities performed for its joint ventures, OraSense and HepaSense, of $2.7 million and $3.9 million for the three and six months ended June 30, 2000, respectively, compared with $1.4 million for the same periods in 1999. The increase in the current period is due to the start of the HepaSense joint venture in January 2000. The Company also had interest income of $1.6 million for the quarter and $2.5 million for the six months ended June 30, 2000, compared with $0.6 million and $1.2 million for the same periods in 1999. This increase in interest income was due primarily to higher average cash and investment balances and, in part to higher interest rates.

Research and development expenses were $12.7 million for the three months ended June 30, 2000, and $26.0 million for the six months ended June 30, 2000, compared with $16.4 million and $30.8 million respectively, for the same periods in 1999. For both periods, research and development expenses were driven by the cost of preclinical and clinical activities to support the progress of drugs in clinical trials. The decrease in research and development expenses is directly related to the implementation of the company's restructuring plan, which was announced in January 2000.

General and administrative expenses decreased to $2.4 million for the second quarter and $4.2 million for the six months ended June 30, 2000, from $2.8 million and $5.6 million for the same periods in 1999. This decrease in general and administrative expenses is primarily related to the company's restructuring activities.

The total cost of restructuring was recorded in the first quarter and totaled $1.6 million. To date, we have incurred actual costs of approximately $1.5 million and do not anticipate the actual costs to exceed $1.6 million. This expense is comprised primarily of labor costs for our reduction in work force.

Interest expense increased to $3.1 million for the second quarter and $6.2 million for the six months ended June 30, 2000, compared to $2.8 million and $5.5 million for the same periods in 1999. The increase is due primarily to accruing interest 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 is also due to borrowings by Isis during the second quarter of 1999 and the first quarter of 2000 under a debt facility from Elan related to the OraSense joint venture to fund Isis' share of OraSense expenses. Of the $3.1 million of interest expense recognized in the second quarter of 2000, $2.3 million was accrued under long-term debt agreements and will not require current cash payment. Similarly, of the $6.2 million of interest expense incurred during the six months ended June 30, 2000, $4.6 million was accrued under long-term debt arrangements and will not require current cash payments.

During the quarter and six month periods ended June 30, 2000, Isis recorded a net loss applicable to common stock of $14.6 million and $33.2 million, or $0.40 and $0.95 per share respectively, compared with $16.6 million and $29.2 million, or $0.59 and $1.06 per share respectively, for the same periods in 1999. The second quarter 2000 loss included $2.8 million in joint venture revenue together with $4.6 million for Isis' equity in the loss of Orasense and

HepaSense, the joint ventures, compared to $1.4 million and $2.3 million respectively, for the same period in 1999. Isis' loss from operations was $8.2 million for the second quarter of 2000, compared

to $12.0 million for the same period in 1999. The decrease in loss from operations in the second quarter is primarily attributable to our restructuring activities. Operating losses may fluctuate from quarter to quarter because of differences in the timing of revenue and expense recognition.

Isis believes that inflation and changing prices have not had a material effect on its operations to date.

LIQUIDITY AND CAPITAL RESOURCES

The company has financed its operations with revenue from contract research and development, through the sale of equity securities and the issuance of long-term debt. From Isis' inception through June 30, 2000, Isis has earned approximately $191 million in revenue from contract research and development. Isis has also raised net proceeds of approximately $352 million from the sale of equity securities since it was founded. The company has borrowed approximately $76 million under long-term debt arrangements to finance a portion of its operations.

As of June 30, 2000, Isis had cash, cash equivalents and short-term investments totaling $120.3 million and working capital of $113.4 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 half of the year are due primarily to the sales of common stock to institutional investors along with the sale of common stock to Elan International Services, Ltd. ("EIS") in conjunction with the formation of HepaSense and funding from Ibis' collaboration with Agouron.

Isis' collaborative agreement with Boehringer Ingelheim provided a line of credit which was used to support the collaboration cell adhesion programs. As of June 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, 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 June 30, 2000 was $53.4 million.

As of June 30, 2000, Isis' long-term obligations totaled $94.5 million, versus $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 $2.5 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. The company will continue to use lease financing as long as the terms remain commercially attractive. The company believes 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 August 3, 2000, Isis' GeneTrove-TM- division 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.

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, Vitravene-TM-. We cannot guarantee that any of our other product candidates will obtain required government approvals or that we can successfully commercialize any products. We expect to have ongoing discussions with the FDA and foreign regulatory agencies with respect to all of our drugs in clinical development.

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-TM-, 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-TM- to our partner CIBA Vision in 1998, earning product revenue of $560,000. No commercial shipments of Vitravene-TM- 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 FURTHER 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 in designing drugs that work at the genetic level to block the production of disease-causing proteins.

In late 1999, we completed a Phase III trial of ISIS 2302 in Crohn's disease. The data from that study did not demonstrate efficacy and did not support an NDA filing. This negative outcome was unexpected. In late 1998, the company conducted an

interim analysis of the first 150 patients enrolled in the study. Based on the positive data from the interim analysis, the company believed that the 300 patient study was likely to support an NDA filing. This same result could occur with other products under development.

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 Isis was founded in January 1989. As of June 30, 2000, our accumulated losses were approximately $290 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-TM-. This product has limited sales potential relative to most pharmaceutical products. 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 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-TM-;
- 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.

If we find that we do not have enough money, additional funds will need to be raised, including through public or private financing. Additional financing may not be available, or, if available, may not be 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.

In 1998, we entered into an antisense oligonucleotide manufacturing

collaboration with Avecia Life Science Molecules of Manchester, England pursuant to which Avecia LSM will supply a portion of our requirements of drugs for clinical trials. As of the date of this report, we have not yet received any supply of drugs under this arrangement, and we cannot guarantee that Avecia LSM will prove to be an acceptable alternative supplier.

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 have been developing. These competitive developments could make our technology and products obsolete or non-competitive before we have had enough time 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 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.

To date, we have not experienced any patent or other intellectual property litigation. However, we cannot guarantee that we will not 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 such 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 to 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 stiff 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. The market price can be affected by many factors, including, for example, fluctuation 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 the 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, 15% or more of our voting stockholders, 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 the stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of the stockholders to approve transactions that they think may be in their best interests. In addition, the 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

The Company is exposed to changes in interest rates primarily from its long-term debt arrangements and, secondarily, its investments in certain short-term investments. The Company invests its excess cash in highly liquid short-term investments that are typically held for the duration of the term of the respective instrument. The Company 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, the Company believes that, while the securities the Company holds are subject to changes in the financial standing of the issuer of such securities, the Company is 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 June 8, 2000, The Company's Annual Meeting of Stockholders was held in Carlsbad, California for the following purposes:

(1) To elect three (3) Class III Directors of the Company. The total number of votes cast for and against are as follows:

	FOR	WITHHELD
Nominees with terms to expire at the 2003 Annual Meeting:		
Alan C. Mendelson	34,038,339	185,612
William R. Miller	33,310,472	913,479
Christopher F.O. Gabrieli	34,027,525	196,426

(2) To approve the Company's 2000 Employee Stock Purchase Plan. The number of votes for, against and abstaining was 18,244,257, 1,216,187 and 116,292, respectively.

(3) To ratify the appointment of Ernst & Young LLP as the Company's independent auditors for the fiscal year ending

December 31, 2000. The total number of votes cast for, against and abstaining was 34,045,286, 135,500 and 43,165, respectively.

ITEM 5. OTHER INFORMATION

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

10.33 Agreement between Registrant and Agouron Pharmaceuticals dated June 9, 2000 (with certain confidential information deleted).

27.1 Financial Data Schedules

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: August 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: August 14, 2000

By: /S/ B. LYNNE PARSHALL
B. Lynne Parshall
Executive Vice President and
Chief Financial Officer
(Principal Financial Officer)

TEXT OMITTED AND FILED SEPARATELY
"CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. SECTIONS 200.80(B)(4)
200.83 AND 240.24B-2"

[*] RESEARCH COLLABORATION AND LICENSE AGREEMENT

BY AND BETWEEN

AGOURON PHARMACEUTICALS, INC.

AND

IBIS THERAPEUTICS,

A DIVISION OF ISIS PHARMACEUTICALS, INC.

JUNE 9, 2000

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EXHIBITS

Exhibit A - Research Plan

Exhibit B - [*]

[*] RESEARCH COLLABORATION AND LICENSE AGREEMENT

This [*] Research Collaboration and License Agreement ("Agreement"), dated June 9, 2000, is between Agouron Pharmaceuticals, Inc., a corporation organized and existing under the laws of California and a wholly owned subsidiary of the Warner-Lambert Company, having a principal place of business at 10350 North Torrey Pines Road, La Jolla, CA 92037-1022 ("Agouron"), and Isis Pharmaceuticals, Inc., a corporation organized and existing under the laws of Delaware, on behalf of its Ibis Therapeutics division, having a principal place of business at 2292 Faraday Avenue, Carlsbad, CA 92008 (because Isis will be conducting the work hereunder through its Ibis Therapeutics division, Isis will hereafter be referred to as "Ibis"; however all references to "Ibis" are intended to refer both to Isis and Ibis, unless otherwise indicated). Agouron and Ibis may each be referred to as a "Party" or together be referred to as the "Parties."

WHEREAS, Ibis has proprietary technology and experience in identifying therapeutically attractive drug targets in structural RNA and in designing and optimizing drug leads to bind to such targets;

WHEREAS, Agouron has proprietary technology and experience in discovering, developing and commercializing drug products for human therapeutic use; and

WHEREAS, Agouron and Ibis desire to enter into a research collaboration to discover new treatments for [*] infection using selected RNA targets [*] upon the terms and conditions set forth herein.

NOW, THEREFORE, in consideration of the mutual covenants contained in this Agreement, the Parties agree as follows:

ARTICLE 1
DEFINITIONS

For purpose of this Agreement, the following capitalized terms, whether used in the singular or plural, will have the following meanings:

1.1 "ACTIVE DEVELOPMENT/COMMERCIALIZATION PROGRAM" means an ongoing program for developing and commercializing a Collaboration Compound or a Collaboration Product, including preclinical and clinical development activities aimed at obtaining Registration for marketing, and marketing and selling activities, for the Collaboration Product.

1.2 "ADDITIONAL IDENTIFIED COMPOUNDS" has the meaning specified in Section 3.1.3.

1.3 "AFFILIATE" of a Party means any person, organization, corporation, or other business entity that is controlling, controlled by or under common control with such Party. The term "control" (including, with correlative meaning, the terms "controlled by" and "under common control with") as used with respect to any person, organization, corporation or other business entity, means the possession, directly or indirectly, of the power to direct, or cause the direction of, the management and policies of such person, organization, corporation or entity, whether through the ownership of voting securities or by contract or court order or otherwise. For purposes of this definition, an entity will be deemed to

control another entity if it owns or controls, directly or indirectly, at least fifty percent (50%) of the outstanding stock or other voting rights entitled to elect directors or their equivalent.

1.4 "AGOURON FIELD" means uses resulting from the mediation or inhibition of [*] through interaction with an RNA Target, including therapeutic, prophylactic, diagnostic and classification uses.

1.5 "AGOURON SCREENING COMPOUNDS" means compounds from proprietary libraries or collections of chemical compounds [*].

1.6 "ANNUAL EXTENSION PERIOD" has the meaning specified in Section 2.9.2.

1.7 "CALENDAR YEAR" means a period of 12 months commencing on January 1 and ending on December 31.

1.8 "COLLABORATION COMPOUND(S)" means Program Compound(s) and/or Derived Compound(s).

1.9 "COLLABORATION PATENT RIGHTS" means Patent Rights, Controlled by either Party or both Parties, filed anywhere in the world after the Effective Date, having any claims covering any of the following: (a) Collaboration Compounds; (b) Collaboration Products; or (c) any Collaboration Technology that is conceived or reduced to practice by either Party or both Parties during the Research Program Term.

1.10 "COLLABORATION PRODUCT" means any preparation in final form (e.g., final-dosage form for sale by prescription, over-the-counter or another method) containing at least one Collaboration Compound, for use in the Agouron Field, including for use in treating or preventing infections caused by [*] or for diagnosing or classifying [*] infection. If a Collaboration Product containing a specific Collaboration Compound is useful in the Agouron Field and a preparation in final form containing such Collaboration Compound is also useful in treating, preventing, diagnosing or classifying any human diseases or conditions other than [*], such preparation in final form containing such Collaboration Compound for such other use outside the Agouron Field will also be deemed a Collaboration Product.

1.11 "COLLABORATION TECHNOLOGY" means Technology, other than Collaboration Compounds and Collaboration Products, Controlled by either Party or both Parties that is necessary or useful to make, have made, use, import or sell Collaboration Compounds or Collaboration Products, including processes of making Collaboration Compounds or Collaboration Products, or methods for using Collaboration Compounds or Collaboration Products. Collaboration Technology will exclude [*].

1.12 "COMBINATION PRODUCT" means any Collaboration Product in any final form that contains, in addition to a Collaboration Compound, one or more other active ingredients having [*] activity.

1.13 "CONTROLLED" OR "CONTROLLING" means possession, now or in the future, of the ability to grant a license or sublicense of rights as provided for herein without violating the terms or any agreement or arrangement with, or the rights of, any Third Party.

1.14 "DERIVED COMPOUND" means any chemical compound having [*].

1.15 "DESIGNATED [*]" means A [*] potential RNA Target(s) suitable for the Research Program.

1.16 "EARLY TERMINATION" has the meaning specified in Section 2.9.1.

1.17 "EC APPROVAL" means the approval of a Collaboration Product for marketing in the European Union by the European Commission ("EC"), or any future equivalent approval process.

1.18 "EFFECTIVE DATE" means July 1, 2000.

1.19 "ELECTED RNA TARGET" has the meaning specified in Section 2.10.

1.20 "ELECTED RNA TARGET LIST" has the meaning specified in Section 2.10(b).

1.21 "EMEA FILING" means filing an application with the European Medicines Evaluation Agency ("EMEA"), or any successor agency having substantially the same regulatory functions, to obtain EC Approval.

1.22 "ENFORCEABLE CLAIM" means a claim included in an issued and unexpired patent that has not been: (i) abandoned or disclaimed; (ii) declared invalid or unenforceable by a decision of a court or other governmental agency of competent jurisdiction, which decision is unappealable or unappealed within the time allowed for appeal; or (iii) admitted by the Party owning or Controlling such patent to be invalid.

1.23 "FDA" means the United States Food and Drug Administration, or any successor agency having substantially the same regulatory functions.

1.24 "FTE RATE" means the compensatory rate to be paid per full-time equivalent ("FTE") scientist.

1.25 "FIRST COMMERCIAL SALE" means the initial transfer in title of a quantity of Collaboration Product to a Third Party purchaser by Agouron, its Affiliates or Sublicensees for consideration, or the initial use of a Collaboration Product by a Third Party in a country, following governmental approval in such country for such transfer or use, whichever occurs first. First Commercial Sale will not include transfer of reasonable quantities of any free samples Collaboration Product and/or the reasonable quantities transferred for development purposes, such as for use in experimental studies or clinical trials.

1.26 "IBIS EXISTING TECHNOLOGY" means all Technology, Controlled by Ibis as of the Effective Date, that is necessary or useful for the conduct of the Research Program, [*]; (b) genetic databases; and (c) biological materials and chemical compounds. Ibis Existing Technology will exclude [*].

1.27 "IBIS EXISTING TECHNOLOGY PATENT RIGHTS" means any Patent Rights Controlled by Ibis, filed anywhere in the world, containing any claims covering any Ibis Existing Technology. Ibis Existing Technology Patent Rights will exclude [*].

1.28 "INITIAL OPTION LICENSE FEE" means the license fee for the [*].

1.29 "INITIAL RESEARCH TERM" has the meaning set forth in Section 2.9.

1.30 "JAPANESE APPROVAL" means the approval of a Collaboration Product for marketing in Japan by the Japanese Ministry of Health and Welfare, or any future equivalent approval process.

1.31 "JAPANESE REGISTRATION FILING" means filing an application with the Japanese Ministry of Health and Welfare, or any successor agency having substantially the same regulatory functions, to obtain Japanese Approval.

1.32 "JOINT RESEARCH COMMITTEE" or "JRC" means the committee described in Section 2.5.

1.33 [*].

1.34 [*] means: (a) the patents and patent applications identified in Exhibit B hereto, and all patents and patent applications based on, corresponding to, or claiming the priority date(s) of any of the foregoing, and any reissues, term extensions (or other governmental actions which provide exclusive rights to the patent holder in the patented subject matter beyond the original patent expiration date), substitutions, confirmations, registrations, validations, re-examinations, additions, continuations, continued prosecutions, continuations-in-part, or divisions of or to any of the foregoing; and (b) any other Patent Rights Controlled by Ibis directed to Technology necessary or relating to the practice of [*].

1.35 [*] means Technology: (a) Controlled by Ibis during the Research Program Term that is necessary or relates to the performance of multi-target affinity specificity screening ("MASS"); or [*].

1.36 "MEDICINAL CHEMISTRY STAGE" means [*]

1.37 "MEDICINAL CHEMISTRY STAGE LIST" has the meaning specified in Section 2.10(c).

1.38 "NDA APPROVAL" means the approval of a Collaboration Product for marketing in the United States by the FDA, or any future equivalent approval process.

1.39 "NDA FILING" means the filing of a new drug application or other application ("NDA") with the FDA, to obtain NDA Approval.

1.40 "NET SALES REVENUE" means the total invoiced amount of all worldwide sales of Collaboration Product(s) by Agouron, its Affiliates or Sublicensees, to a Third Party, less (a) customary trade, quantity, or cash discounts and commissions allowed and taken by brokers or agents, (b) amounts repaid or credited by reason of rejection or returns, as well as rebates, chargebacks, retroactive price reductions and allowances, (c) sales, use and/or other taxes, import and/or export customs duties, and other similar governmental charges paid, but not including income taxes, and (d) to the extent separately stated on purchase orders, invoices, or other documents of sale, insurance costs and outbound transportation charges prepaid or allowed related to shipment of Collaboration Product(s). Net Sales Revenue excludes: (a) the transfer of reasonable and customary quantities of free samples of Collaboration Product(s), (b) the transfer of Collaboration Product(s) as clinical trial materials, other than for subsequent resale; and (c) use by Agouron, its

Affiliates or Sublicensees of Collaboration Product for any purpose connected with the securing of regulatory approval or validating of a manufacturing process or the obtaining of other necessary marketing approvals for Collaboration Product (unless such Collaboration Product is subsequently sold).

1.41 [*]

1.42 [*].

1.43 "PATENT RIGHTS" means: (a) patent applications (including applications for certificates of invention); (b) any patents issuing from such patent applications (including certificates of invention); (c) all patents and patent applications based on, corresponding to, or claiming the priority date(s) of any of the foregoing; and (d) any reissues, term extensions (or other governmental actions which provide exclusive rights to the patent holder in the patented subject matter beyond the original patent expiration date), substitutions, confirmations, registrations, validations, re-examinations, additions, continuations, continued prosecutions, continuations-in-part, or divisions of or to any of the foregoing.

1.44 "PHASE I CLINICAL STUDY" means the initial testing of a Collaboration Product in humans, whether the primary endpoint is safety, pharmacokinetics or any combination thereof.

1.45 "PHASE II STUDY COMPLETION" means completion of the first human clinical study in patients [*]. Initiation of a Pivotal Quality Clinical Study will be deemed to be a Phase II Study Completion, whether or not a Phase II Study is ongoing.

1.46 "PIVOTAL QUALITY CLINICAL STUDY" means a human clinical trial of a Collaboration Compound or Collaboration Product designed to demonstrate statistically significant treatment effect so as to achieve Registration. Initiation of a Phase III clinical study will be deemed to be initiation of a Pivotal Quality Clinical Study.

1.47 "POST RESEARCH PROGRAM TERM"

(a) Reserved RNA Target: The Post Research Program Term for a Reserved RNA Target means the [*] following the end of the Research Program Term.

(b) Elected RNA Target:

(i) The Post Research Program Term for an Elected RNA Target on the Elected Target List means the [*] period after the end of the Research Program Term; if such Elected RNA Target enters Medicinal Chemistry Stage on or before the [*] anniversary of the end of the Research Program Term, then its Post-Research Term will continue until a date which is [*] after the date upon which such Elected RNA Target entered Medicinal Chemistry Stage; provided further that if an Elected RNA Target continues in a Medicinal Chemistry Stage pursuant to Subsection 2.10(d)(ii), then the Post Research Program Term will continue until such Elected RNA Target completes the Medicinal Chemistry Stage.

(ii) Notwithstanding the foregoing, the Post Research Program Term for any Elected RNA Target will automatically end when such Elected RNA

Target ceases to be an Elected RNA Target pursuant to the provisions of Section 2.10.

1.48 "PROGRAM COMPOUND" means any Selected Compound having Threshold Activity against an Elected RNA Target, [*].

1.49 "PROPRIETARY INFORMATION" means any and all proprietary or confidential scientific, clinical, regulatory, marketing, financial and commercial information or data, whether communicated in writing, orally or by any other means, provided by one Party to the other Party in connection with this Agreement. Proprietary Information will not include information, as documented by written records, that:

(a) is known by the receiving Party at the time of its receipt, and not through a prior disclosure by the disclosing Party;

(b) is in the public domain without the fault of the receiving Party or its Affiliates or agents;

(c) is subsequently disclosed to a receiving Party by a Third Party who may lawfully do so and is not under an obligation of confidentiality to the disclosing Party; or

(d) is developed by the receiving Party independently of Proprietary Information received from the other Party.

1.50 "REGISTRATION" means the official approval by the government or health authority in a country (or supra-national organization, such as the European Commission) that is required for a product to be offered for sale in such country, including approval of a marketing application such as an NDA, and such other authorizations as may be required for the production, importation, pricing, reimbursement and sale of such product, and for subsequent regulatory filings, including filings for line extensions and/or additional indications of such product.

1.51 "RESEARCH PLAN" means the plan of goals and activities for the Research Program agreed to by the Parties and attached as Exhibit A, as may be amended from time-to-time in accordance with the terms of this Agreement.

1.52 "RESEARCH PROGRAM" means the research activities of the Parties to discover and develop RNA Targets and identify and discover Collaboration Compounds, which activities are outlined in Article II and in the Research Plan attached as Exhibit A. While the primary purpose of the Research Program is to discover RNA Targets for use in conducting drug discovery in the Agouron Field and to discover Collaboration Compounds against such RNA Targets for use in treating [*], the Parties acknowledge that Collaboration Compounds may also have use [*], and that activities aimed at developing Collaboration Compounds for such [*] use are within the scope of the Research Program.

1.53 "RESEARCH PROGRAM TECHNOLOGY" means any Technology (a) Controlled by Ibis and/or Agouron, (b) specifically concerning [*], RNA Targets or other research tools or procedures for discovering, identifying, selecting, and validating RNA Targets or for screening or assaying compounds, (c) developed or acquired by or on behalf of Ibis and/or Agouron after the Effective Date during the Research Program Term, and (d)

necessary or useful for the conduct of the Research Program. The Research Program Technology will exclude any chemical compounds, including Agouron Screening Compounds and Collaboration Compounds. Research Program Technology will also exclude Ibis Existing Technology, Collaboration Technology, and Mass Spectrometry Screening Technology.

1.54 "RESEARCH PROGRAM TECHNOLOGY PATENT RIGHTS" means any Patent Rights Controlled by Ibis and/or Agouron filed anywhere in the world after the Effective Date, containing any claims covering any Research Program Technology conceived or reduced to practice in the Research Program by either Party or both Parties during the Research Program Term. Research Program Technology Patent Rights will exclude Collaboration Patent Rights, Mass Spectrometry Screening Patent Rights, and Ibis Existing Patent Rights.

1.55 "RESEARCH PROGRAM TERM" means the term of the Research Program, as set forth in Section 2.9.

1.56 "RESERVED RNA TARGET" has the meaning specified in Section 2.10(a).

1.57 "RNA TARGET" means a specific site within a [*], the binding to which mediates or inhibits [*].

1.58 "SELECTED COMPOUND" means any Agouron Screening Compound, or any proprietary compound of either Party supplied for screening in the Research Program against an RNA Target, and determined to have Threshold Activity against an RNA Target, and for which compound Agouron has provided the structural information to Ibis pursuant to Section 3.1.3.

1.59 "SUBLICENSEE" means any Third Party to which Agouron grants a sublicense in connection with the development, manufacture, or commercialization of a Collaboration Compound or a Collaboration Product, as the case may be. A Third Party who is given only the right to sell a Collaboration Product (such as a wholesaler or a distributor) will not be considered a Sublicensee.

1.60 "TECHNOLOGY" means inventions (whether or not patentable), know-how, trade secrets, research tools, materials, and technical information, including but not limited to information in the form of research data, databases, experimental procedures, designs, formulas, process information, and expert opinions.

1.61 "TERRITORY" means the world.

1.62 "THIRD PARTY" means any party other than Ibis or Agouron and their respective Affiliates.

1.63 "THRESHOLD ACTIVITY" means an [*], which may be adjusted by the JRC as appropriate to meet the goals of the Research Program, considering the threshold [*] value deemed necessary for a compound to have potential utility in the Research Program and the percentage of compounds screened found to meet such threshold value.

1.64 "UNITED STATES" or "U.S." means the United States of America and its territories, possessions, and protectorates (including Puerto Rico) and the District of Columbia.

ARTICLE II
RESEARCH PROGRAM

2.1 GENERAL PURPOSE.

During the Research Program Term, Ibis and Agouron will cooperate exclusively to use the Mass Spectrometry Screening Technology, Ibis Existing Technology and Research Program Technology to discover and develop RNA Targets and to conduct activities to discover Collaboration Compounds in the Agouron Field, upon the terms and conditions set forth in this Agreement. The specific activities to be undertaken in the course of the Research Program are set forth in this Article II and in the Research Plan (Exhibit A), which may be amended from time to time as mutually agreed in writing by the Parties.

2.2 GENERAL RESEARCH PROGRAM ACTIVITIES.

During the Research Program Term, the Parties will use Mass Spectrometry Screening Technology, Ibis Existing Technology and Research Program Technology as necessary or useful to achieve the overall purpose and goals of the Research Program and to conduct their respective activities according to the Research Plan. Such activities are contemplated by the Parties to include, but not be limited to, the following: [*].

2.3 CONDUCT OF RESEARCH PROGRAM.

Ibis and Agouron each will conduct its activities in the Research Program in compliance in all material respects with all requirements of applicable laws, rules and regulations and all applicable standard laboratory practices, and attempt to achieve their objectives efficiently and expeditiously. Ibis and Agouron each will proceed diligently with the work set out in the Research Plan, using their respective good faith efforts.

2.4 RESEARCH WORK SITES.

Each Party will provide appropriate work sites for carrying out its respective activities pursuant to the Research Plan.

2.5 JOINT RESEARCH COMMITTEE.

The Parties hereby establish a JRC to direct and monitor the Research Program as follows:

2.5.1 COMPOSITION OF THE COMMITTEE.

The Research Program will be conducted under the direction of the Joint Research Committee, which will be comprised of three representatives of Agouron and three representatives of Ibis. Each Party will provide the other with a written list of its representatives within thirty (30) days of the Effective Date. Agouron and Ibis may change one or more of its representatives upon written notice to the other Party of such change. Each Party's representatives should have appropriate technical credentials and experience and ongoing familiarity with the activities in the Research Program.

2.5.2 MEETINGS AND DECISIONS.

(a) The Joint Research Committee will meet quarterly during the Research Program Term at locations determined by the Joint Research Committee, with the first such meeting to be held within 45 days of the Effective Date. Each Party will bear its own expenses related to attendance of such meetings by its representatives. The Joint Research Committee may meet by means of teleconference, videoconference or other similar communications equipment. Additional employees of Ibis or Agouron (or its Affiliates) may, by mutual consent of the Parties, be invited to attend Joint Research Committee meetings.

(b) The chairmanship of the JRC will alternate on a quarterly basis between the representatives of the Parties, with an Agouron representative chairing the first quarter. The chairperson will chair the meetings and will be responsible for preparing agenda and circulating agenda to the other JRC members prior to the meetings.

(c) The Joint Research Committee will confer and make decisions regarding oversight of the Research Program and the activities of the Parties in carrying out the Research Plan and will also advise the Parties on issues arising during the Research Program Term regarding any technical, budgetary or economic matters relating to the Research Program. After the expiration of the Research Program Term, the Parties will appoint a successor committee which will function for so long as is necessary to perform the responsibilities assigned to the JRC under the terms of this Agreement.

(d) Each Party will have one vote on the JRC regardless of the number of representatives of each Party on the JRC. All of the decisions of the JRC regarding the Research Plan must be unanimous in order for a JRC matter to be resolved. In the event of a deadlocked vote on an issue, Ibis and Agouron will each appoint a designee to discuss such issue in good faith and use their best efforts to find a resolution to the deadlock. If, after good faith efforts, no resolution is found within thirty (30) days, or such longer period of time as agreed upon by the JRC, then such issue will be resolved pursuant to Section 11.6.

2.5.3 RESPONSIBILITIES.

The responsibilities of the JRC will be, among others, to: (i) approve and implement the Research Plan and any modifications or amendments thereof, consistent with the terms of this Agreement; (ii) advise the Parties regarding the overall strategy, status and direction of the Research Program; (iii) review and monitor all results of the work performed under the Research Plan, and provide oversight and direction regarding such work in accordance with the Research Plan; (iv) prepare and circulate progress reports to the Parties; (v) decide whether to designate [*]; (vi) review and monitor the RNA Target advancement process, and maintain a list of RNA Targets, including Elected RNA Targets; and (vii)

perform any additional functions as specified in this Agreement. The Parties acknowledge that decisions pertaining to matters beyond the scope of the Research Program are not the responsibility of the JRC, and that Agouron will have the sole discretion to make decisions such as: (i) which RNA Targets will become Elected RNA Targets, and when and if those Elected RNA Targets will be entered into [*]; (ii) which Collaboration Compounds, if any, will be entered by Agouron into an Active Development/Commercialization Program; and (iii) which Collaboration Products will be commercialized by Agouron or its Affiliates.

2.5.4 JRC RECORDS.

The JRC will maintain accurate records to document the discussions and decisions at each meeting. Meeting minutes or summaries will be prepared by its chairperson in accordance with procedures established by the JRC at its first meeting and will be distributed to all members of the JRC after approval of drafts by the designated representatives of the Parties.

2.6 PROJECT TEAM.

2.6.1 RESPONSIBILITIES.

The Project Team will conduct research activities as necessary to achieve the objectives of the Research Program in accordance with the Research Plan, as such Research Plan may be modified by the JRC. The Project Team will provide written reports of its activities to the JRC.

2.6.2 COMPOSITION.

The Project Team will include representatives from both Ibis and Agouron as necessary for the proper conduct of the Research Program in accordance with the Research Plan, with such representatives to be designated at the sole discretion of each Party, provided that the designated representatives are qualified to carry out their respective activities in the Research Program and are generally familiar with the Research Program activities being conducted at their site.

2.6.3 MEETINGS.

The Project Team will meet monthly, in person or by telephone or videoconference, unless the JRC directs a different meeting schedule. Project Team meetings will alternate between the sites of the Parties. Expenses of a Party's representatives attending Project Team meetings will be borne by such Party.

2.7 RECORDS AND REPORTS.

2.7.1 RECORDS.

Ibis and Agouron will each maintain its records in sufficient detail and in good scientific manner appropriate for patent and regulatory purposes, which records will be complete and accurate and will fully and properly reflect all work done and results achieved by it in the performance of the Research Program.

2.7.2 COPIES AND INSPECTION OF RECORDS.

Agouron will have the right, during normal business hours and upon reasonable notice, to inspect and copy all such records of Ibis referred to in Section 2.7.1. Agouron will maintain such records and the information disclosed therein in confidence in accordance with Sections 10.1 and 10.2. Agouron will have the right to arrange for its employees, agents and outside consultants, and the employees, agents and outside consultants of its Affiliates, to visit Ibis at its offices and laboratories during normal business hours and upon reasonable notice, and to discuss the Research Program and its results in detail with the technical personnel of Ibis.

2.8 RESEARCH PROGRAM STAFFING LEVELS.

Ibis and Agouron will conduct the research activities necessary to maintain progress on the objectives of the Research Program as set forth in the Research Plan. To achieve these goals, Ibis will designate and assign qualified FTEs based upon the Research Plan staffing schedule set by and subject to approval by the JRC. Ibis will dedicate the efforts of at least [*] FTEs during the first year, and [*] FTEs during each of the second and third years, of the Research Program Term. During each year of the Research Program, Agouron will dedicate the efforts of the number of FTEs that it determines in its sole discretion is appropriate to perform its responsibilities under the Research Program as set forth in the Research Plan. The JRC will have the discretion to increase or decrease the minimum level of FTE support at Ibis to that level deemed reasonably necessary to implement the Research Plan.

2.9 RESEARCH PROGRAM TERM.

The Research Program Term will include the Initial Research Term and any Annual Extension Periods thereof pursuant to Section 2.9 below. The Initial Research Term will commence upon the Effective Date and continue for a period of [*] years, unless the Research Program Term is terminated prior thereto in accordance with the Early Termination provisions set forth below.

2.9.1 EARLY TERMINATION.

If Agouron determines that sufficient scientific progress has not been made during the Initial Research Term, Agouron may terminate the Research Program Term upon written notice given at least [*] months prior to the completion of the [*] year of the Research Program Term ("Early Termination"). Such Early Termination will be effective immediately prior to the [*] anniversary of the Effective Date. In such event: (i) Agouron will be liable for funding of the

Research Program under Section 5.2.1 until such [*] anniversary date, but any other payment obligations not due and owing as of the Early Termination date will terminate; and (ii) Agouron will have no further rights with respect to [*] Ibis Existing Technology.

2.9.2 ANNUAL EXTENSION PERIOD.

If Agouron agrees to continue to fund FTE support and Core Research Support for Ibis a level agreed upon by the JRC, then Agouron may extend the Research Program Term beyond the Initial Research Term on a year-to-year basis ("Annual Extension Period"). The Research Program will continue to operate under the terms and conditions of the Agreement, provided, however, [*].

2.10 POST RESEARCH PROGRAM TERM ACTIVITIES.

The Parties acknowledge that, in order to maximize the chances that a commercializable Collaboration Compound arises out of the collaboration, Agouron will need to continue certain activities following the end of the Research Program Term and during the Post-Research Program Term. To facilitate such activities, the Parties have agreed to the following procedures:

(a) [*].

(b) [*]

(c) [*]

(d) [*]

(e) [*]

(f) [*]

i. [*];

ii. [*];

iii. [*];

iv. [*]

v. [*].

[*].

g) If a Collaboration Compound is determined to actively bind to an RNA Target in addition to the Elected RNA Target to which it was previously determined to bind, and such RNA Target is not, at that time, an Elected RNA Target, Agouron

may cause such RNA Target to become an Elected RNA Target by written notice to Ibis, as long as Ibis has not independently previously initiated a drug discovery program, aimed at such RNA Target, of the same scope and magnitude as Ibis's efforts during the course of the Research Program. Upon receipt of Agouron's written notice that it desires to cause such RNA Target to become an Elected RNA Target, Isis will respond within 10 days in writing with either a confirmation that such RNA Target can become an Elected RNA Target (with no independent requirement to enter such Elected RNA Target into Medicinal Chemistry Stage) or with a certification that Ibis has independently, prior to the date of receipt of such notice, initiated a drug discovery program aimed at such RNA Target as described above, in which case such RNA Target will not become an "Elected RNA Target." If Ibis fails to timely respond to Agouron's written notice, then such RNA Target can become an Elected RNA Target.

2.11 EXCLUSIVE EFFORTS.

2.11.1 DURING THE RESEARCH PROGRAM TERM.

During the Research Program Term, Ibis will work exclusively in collaboration with Agouron to discover and develop products useful in the Agouron Field.

2.11.2 AFTER THE RESEARCH PROGRAM TERM.

After the end of the Research Program Term, Ibis will not collaborate with any other party to discover and develop products that bind to any Reserved RNA Target or an Elected RNA Target during the Post-Research Program Term for any Reserved RNA Target or Elected RNA Target.

2.11.3 IBIS RETAINED RIGHTS.

Notwithstanding the foregoing, Ibis retains the right to:

(a) [*]

(b) [*]

(c) [*]

ARTICLE III
CERTAIN RESEARCH PROGRAM; DEVELOPMENT AND COMMERCIALIZATION ACTIVITIES

3.1 SUPPLY OF AGOURON SCREENING COMPOUNDS; SELECTED COMPOUNDS; CONFIDENTIALITY.

3.1.1 SUPPLY OF AGOURON SCREENING COMPOUNDS.

[*]

3.1.2 SCREENING OF AGOURON SCREENING COMPOUNDS.

[*]

3.1.3 IDENTIFICATION OF AGOURON SCREENING COMPOUNDS.

[*]

3.1.4 CONFIDENTIALITY OF IDENTITY.

Ibis agrees and warrants that it will not attempt to characterize or determine the chemical identity or structure of any Agouron Screening Compound, including Additional Identified Compounds, or Selected Compound, except as expressly authorized by this Agreement. Ibis further agrees that it will not distribute, or provide any Ibis employee with access to any Agouron Screening Compound, including Additional Identified Compounds, or Selected Compounds, except on a "need-to-know" basis in connection with the performance of the Research Program. Further, Ibis will not provide Agouron Screening Compounds, including Additional Identified Compounds, or Selected Compounds to employees of any other division of Isis Pharmaceuticals, any Isis Affiliate, or any Third Party. At the end of the Research Program Term, Ibis will return to Agouron all samples of Agouron Screening Compounds, if requested to do so by Agouron.

3.1.5 NO OWNERSHIP BY IBIS.

Ibis acknowledges that it will have no ownership or other rights in any Agouron Screening Compound, including Additional Identified Compounds, or any Selected Compound, except as expressly provided in this Agreement, and is expressly prohibited from incorporating information pertaining to any Agouron Screening Compound, including Additional Identified Compounds, in any database of Ibis or any Affiliate or Third Party. Ibis further acknowledges that Agouron will retain at all times the right to research, develop, and commercialize any Agouron Screening Compounds for applications outside the Agouron Field, including the [*] by means other than through interaction with RNA Targets, or for any human or animal therapeutic, diagnostic, prophylactic or classification application, except as expressly provided herein.

3.2 REPORTING ON SCREENING ACTIVITIES.

On a regular basis (not less than once per month), Ibis will provide Agouron with an updated report on its RNA Target screening activities on all compounds screened in the Research Program. Such report will identify each compound by chemical structure, if available to Ibis, its proprietary designation, and summarize the screening activities for each such compound, including a description of the results of any screening activities against any RNA Targets. Prior to each JRC meeting, the Project Team will provide the

JRC with a list of Selected Compounds for which it has conducted such screening activities, and a written summary of the results thereof.

3.3 PROCESS OF ELECTION OF RNA TARGETS FOR MEDICINAL CHEMISTRY STAGE.

3.3.1 PERMITTED PRE-ELECTION MEDICINAL CHEMISTRY STAGE ACTIVITIES.

[*]

3.3.2 ELECTED RNA TARGETS.

[*]

3.4 SELECTION OF COLLABORATION COMPOUNDS FOR ACTIVE DEVELOPMENT/COMMERCIALZATION PROGRAMS.

Following the end of the Research Program Term, Agouron will provide Ibis annually with a written list of all Collaboration Compounds or Collaboration Products that are the subject of any Active Development/Commercialization Programs, as well as the Elected RNA Targets for such Collaboration Compounds or Collaboration Products, a written summary of the nature of each Active Development/Commercialization Program, the progress made in the prior year, and an estimate of planned progress. Whether or not there is an Active Development/Commercialization Program for a specific Collaboration Compound or Collaboration Product will be reasonably determined by Agouron, based on the level of resources applied to the program compared the level of resources applied to other programs with a similar likelihood of success and similar stage of development.

3.5 COMMERCIALLY REASONABLE EFFORTS.

For each Active Development/Commercialization Program, Agouron will use reasonable efforts, consistent with the usual practice followed by Agouron in pursuing the commercialization and marketing of pharmaceutical products, to develop and commercialize Collaboration Product(s) on a commercially reasonable basis in such countries in the Territory where it is commercially viable to do so.

ARTICLE IV
LICENSE GRANTS

4.1 RESEARCH AND DEVELOPMENT.

[*]

Agouron hereby grants to Ibis a non-exclusive license, without the right to sublicense, under the Research Program Technology Patent Rights Controlled by Agouron to use the Research Program Technology, during the Research Program Term, to conduct activities to the extent necessary or useful for Ibis to perform its obligations in the Research Program throughout the Territory.

4.2 DEVELOPMENT AND COMMERCIALIZATION.

Ibis hereby grants to Agouron and its Affiliates an exclusive license (even as to Ibis), with the right to sublicense, under Collaboration Patent Rights and to use Collaboration Technology Controlled by Ibis, to develop, make, have made, use, offer for sale, sell, and import Collaboration Compounds and Collaboration Products.

ARTICLE V
PAYMENTS, ROYALTIES AND REPORTS

5.1 LICENSE FEE.

In consideration for Ibis's commitment to perform its obligations under the Research Program and for [*] and Ibis Existing Technology under the licenses granted hereunder, Agouron will pay to Ibis a non-refundable license fee totaling [*] within [*] of the Effective Date.

5.2 RESEARCH PROGRAM FUNDING.

In consideration for Ibis's performance of its obligations under the Research Program:

5.2.1 FTE FUNDING.

(a) [*]

(b) [*]

5.2.2 CORE PROJECT SUPPORT FEES.

[*]

5.2.3 RESEARCH PROGRAM PROGRESS MILESTONES.

Ibis will also be entitled to the following Research Program validation progress milestone payments upon achievement of the indicated milestones:

(a) [*]

(b) [*]

5.3 MILESTONE PAYMENTS.

Subject to the terms and conditions contained in this Agreement, Agouron will pay to Ibis the following non-refundable milestone payments for each Collaboration Product:

(a) [*]

(b) [*]

(c) [*]

(d) [*]

(e) [*]

(f) [*]

(g) [*]

(h) [*]

(i) [*]

(j) [*]

[*]

5.4 ROYALTIES.

Subject to the terms and conditions of this Agreement, for each Collaboration Product, Agouron will pay to Ibis royalties on Net Sales Revenue on a worldwide basis as follows:

5.4.1 ROYALTY RATE.

(i) [*]

(ii) [*]

5.4.2 ROYALTY SCHEDULE.

---

[*]

5.4.3 ROYALTY PERIOD.

Agouron's obligation to pay royalties to Ibis under Section 5.4 will begin upon the date of the First Commercial Sale in a country of a Collaboration Product, and will end based upon the following schedule, as appropriate:

(a) [*]

(b) [*]

5.4.4 METHOD OF CALCULATION.

The calculation of the amount of annual royalties due under the provisions of Section 5.4 will be subject to and in accordance with the following provisions:

(a) FREQUENCY. Royalties will be calculated on a Calendar-Year basis. Royalties will be payable only once with respect to a given unit of Collaboration Product, regardless of the number of Enforceable Claims of the Collaboration Patent Rights pertaining to such Collaboration Product.

(b) COMBINATION PRODUCTS. In calculating royalties with respect to any Combination Product, the Parties will enter into good-faith negotiations regarding the percentage of the Net Sales Revenue of such Combination Product to be used in calculating royalties payable with respect to such Combination Product, on a country-by-country basis. If the Parties are unable to agree upon such percentage of Net Sales Revenue for Combination Products, then such percentage will be equal to a fraction whose numerator is Agouron's, its Affiliates' or Sublicensees' published sales price in such country for equivalent dosages of all active ingredients that are Collaboration Compounds contained in a given Combination Product, and whose denominator is Agouron's, its Affiliates' or Sublicensees' published sale price in such country for equivalent dosages of all active ingredients contained therein. If the numerator and denominator cannot be determined in the manner set forth above, then they will be determined reasonably by Agouron based on the relative contributions to the prophylactic or therapeutic effect of the Combination Product of the active ingredients.

(c) [*]

(d) COMPULSORY LICENSES.

(i) [*]

(ii) [*]

(e) Sales to Third Parties. No sales will be deemed to have occurred as the result of sales between and among Agouron, its Affiliates and Sublicensees; it being understood that sales occur when made to Third-Party purchasers. If Agouron, its Affiliates or Sublicensees intend to use a Collaboration Product rather than resell it, the sales price for such Collaboration Product will be calculated based on the average of the sales prices of Collaboration Product to Third Parties during the period in which such Collaboration Product is used by Agouron, its Affiliate or Sublicensee, and included in Net Sales Revenue as if sold to a Third Party at such price during such period.

(f) SALES UPON INVOICING. A sale of a Collaboration Product will be deemed to have occurred upon the invoicing of such Collaboration Product for value to a Third-Party purchaser; or if not invoiced, then when delivered, shipped, or paid for, whichever is first, provided, however, that if a sale of a Collaboration Product occurs in a country (e.g., Spain or Italy) or to a category of customer (e.g., hospitals) where the customary payment terms exceed ninety (90) days from the date of invoicing, the sale of a

Collaboration Product in such country or to such category of customer will be deemed to have occurred upon the date of receipt of payment for such sale and will be reported as a sale for the calendar quarter in which such date of receipt occurred.

(g) OTHER CONSIDERATION. In the case of a sale or other disposal of a Collaboration Product for value other than in an arm's-length transaction exclusively for money, such as barter or counter-trade, the amount of such sale will be calculated using the fair market value of such Collaboration Product (if higher than the stated sales price) in the country of disposition.

5.5 THIRD-PARTY TECHNOLOGY.

[*]

5.6 REPORTS; PAYMENT OF ROYALTY.

Following the First Commercial Sale of a Collaboration Product and during the term of the Agreement, Agouron will furnish to Ibis a quarterly written report showing all Net Sales Revenue of Collaboration Products sold by Agouron, its Affiliates and its Sublicensees in the Territory during the reporting period and the royalties payable under this Agreement. Reports will be due on the 60th day following the close of each quarterly period. Royalties shown to have accrued by each royalty report will be due and payable on the date such royalty report is due. Agouron will keep complete and accurate records in sufficient detail to enable the royalties payable hereunder to be determined.

5.7 AUDITS.

5.7.1 AUDIT RIGHTS.

Upon the written request of Ibis, and not more than once in each Calendar Year, Agouron will permit an independent certified public accounting firm of nationally recognized standing selected by Ibis and reasonably acceptable to Agouron, to have access during normal business hours to such of the records of Agouron as may be reasonably necessary to verify the accuracy of the royalty reports hereunder for any year ending not more than 24 months prior to the date of such request. The accounting firm will disclose to Ibis only whether the royalty reports are correct or incorrect and the specific details concerning any discrepancies. Upon the expiration of 24 months following the end of any year, the calculation of royalties payable with respect to such year will be binding and conclusive upon Ibis, and Agouron, its Affiliates, and its Sublicensees will be released from any liability or accountability with respect to royalties for such year.

5.7.2 AUDIT FEES.

If such accounting firm concludes that additional royalties were owed during such period, Agouron will pay the additional royalties within 30 days of the date Ibis delivers to Agouron such accounting firm's written report. If Agouron disagrees with the report, then the parties will resolve such disagreement pursuant to the provisions of Section 11.6. The fees charged by such accounting firm will be paid

by Ibis unless the additional royalties owed by Agouron exceed 5% of the royalties paid for the royalty period subject to the audit, in which case Agouron will pay the reasonable fees of the accounting firm.

5.7.3 SUBLICENSEE REPORTS.

Agouron will include in each sublicense granted by it pursuant to this Agreement a provision requiring the Sublicensee to make reports to Agouron, and to keep and maintain records of sales made pursuant to such sublicense. Ibis's independent accountant will be granted access to such reports as part of the above-referenced audit.

5.7.4 CONFIDENTIALITY.

Ibis will treat all financial information subject to review under this Section 5.7 or under any sublicense agreement in accordance with the confidentiality provisions of this Agreement, and will cause its accounting firm to enter into an acceptable confidentiality agreement with Agouron obligating it to retain all such financial information in confidence pursuant to such confidentiality agreement.

5.8 PAYMENT EXCHANGE RATE.

All payments to Ibis under this Agreement will be made in United States dollars by bank wire transfer in immediately available funds to such bank account in the United States designated in writing by Ibis from time to time. Any required conversion of Net Sales Revenue to U.S. dollars will be made using the monthly average of the rates of exchange for each day in the calendar month in which the sale of a Collaboration Product occurred. The rate of exchange to be used will be the rate of exchange used by Agouron in its worldwide accounting system in the quarterly period to which such payments relate. If Agouron has no designated rate, the rate quoted in the Los Angeles edition of the WALL STREET JOURNAL will be used.

5.9 FOREIGN CURRENCY.

When royalties or other payments are due for Net Sales Revenue in a country where, for reasons of currency, tax or other regulations, transfer of foreign currency from such country is prohibited, Agouron will have the right to deposit the royalties owed to Ibis in the applicable country's currency in a bank account in such country in the name of and under the sole control of Ibis; provided, however, that the bank selected is reasonably acceptable to Ibis and Agouron promptly informs Ibis in writing of the location, account number, amount, and currency of the monies deposited therein. After Ibis has been so notified, those monies will be considered as royalties duly paid to Ibis, and will be completely controlled by Ibis, and Agouron will have no further responsibility with respect thereto.

5.10 INCOME TAX WITHHOLDING.

If laws, rules or regulations require withholding of income taxes or other taxes imposed upon payments set forth in this Article V, Agouron will make such withholding payments as required and subtract such withholding payments from the payments set forth in this Article V. Agouron will submit appropriate proof of payment of the withholding taxes to Ibis within a reasonable period of time.

ARTICLE VI
REPRESENTATIONS AND WARRANTIES

6.1 IBIS REPRESENTATIONS AND WARRANTIES.

Ibis represents and warrants to Agouron that as of the date of this Agreement:

(a) it has the full right, power and authority to enter into this Agreement, to perform the Research Plan and to grant the licenses granted under Article IV hereof;

(b) to the best of its knowledge, the licenses granted under Article IV hereof will fully enable the performance of the Research Plan by the Parties, and there are no other licenses required from any Third Party, including from any nonprofit institutions, the U.S. Government, or to any agency thereof, including the U.S. Department of Commerce or the U.S. Department of Defense, to enable Parties to perform the Research Plan activities contemplated hereunder without interference;

(c) to the best of its knowledge, Ibis has not previously assigned, transferred, conveyed or otherwise encumbered its right, title and interest in the [*], including to any nonprofit institutions, the U.S. Government, or to any agency thereof, including the U.S. Department of Commerce or the U.S. Department of Defense, so as to interfere with Ibis's ability to perform the Research Plan activities or grant the licenses contemplated hereunder, or so as to interfere with Agouron's ability to freely develop, manufacture, or commercialize Collaboration Products; and

(d) Ibis has not taken nor will not take any action which would, in Ibis's good faith judgment, interfere with any obligations of Ibis set forth in this Agreement, including but not limited to the obligation to grant Agouron the licenses described in Article IV.

6.2 AGOURON REPRESENTATIONS AND WARRANTIES.

Agouron represents and warrants to Ibis that as of the date of this Agreement it has the full right, power and authority to enter into this Agreement, to perform the Research Plan and to grant to Ibis the licenses described in Article IV.

ARTICLE VII
PATENT MATTERS

7.1 [*]

[*]

7.2 OWNERSHIP OF INVENTIONS.

[*]

7.3 REPORTING AND COOPERATION.

[*]

7.4 FILING, PROSECUTION AND MAINTENANCE OF PATENTS.

7.4.1 [*]

(a) [*]

(b) [*]

7.4.2 RESEARCH PROGRAM TECHNOLOGY PATENT RIGHTS.

(a) [*]

(b) [*]

7.4.3 COLLABORATION PATENT RIGHTS.

(a) [*]

(b) [*]

7.5 PATENT ENFORCEMENT AGAINST THIRD-PARTY INFRINGERS.

7.5.1 IBIS [*] AND IBIS EXISTING PATENT RIGHTS.

(a) [*]

(b) [*]

7.5.2 RESEARCH PROGRAM TECHNOLOGY PATENT RIGHTS.

(a) [*]

(b) [*]

7.5.3 COLLABORATION PATENT RIGHTS.

(a) [*]

(b) [*]

7.5.4 COOPERATION BETWEEN PARTIES.

[*]

7.5.5 [*]

(a) [*]

(i) [*]

(ii) [*]

(b) [*]

(i) [*]

(ii) [*]

7.5.6 SETTLEMENT.

[*]

7.6 INFRINGEMENT OF THIRD-PARTY PATENT RIGHTS.

[*]

ARTICLE VIII
[*]

8.1 [*]

[*]

8.2 [*]

[*]

8.3 [*]

[*]

8.4 [*]

[*]

8.5 [*]

[*]

8.6 [*]

[*]

(a) [*]

(b) [*]

(c) [*]

(d) [*]

ARTICLE IX
TERM AND TERMINATION

9.1 AGREEMENT TERM AND EXPIRATION.

This Agreement will be effective as of the Effective Date and, unless terminated earlier pursuant to Section 9.2, the term of this Agreement will continue in effect until expiration of all licenses and royalty obligations hereunder.

9.2 TERMINATION.

9.2.1 TERMINATION FOR MATERIAL DEFAULT.

(a) This Agreement will be terminable upon the material default of either Party. In the event of such default by a Party ("Defaulting Party"), the other Party ("Non-Defaulting Party") will give the Defaulting Party written notice of the default and its election to terminate this Agreement at the expiration of a cure period ninety (90) days from the date of the notice. If the Defaulting Party fails to resolve the default during the cure period by: (a) curing the default, (b) providing a written explanation satisfactory to the Non-Defaulting Party that a default has not occurred, or (c) entering into a written agreement with the Non-Defaulting Party for the cure or other resolution of the default, then the Non-Defaulting Party may terminate this Agreement by giving fifteen days prior written notice to the Defaulting Party. The termination will be effective fifteen days after Defaulting Party's receipt of such notice. All termination rights will be in addition to and not in substitution for any other remedies that may be available to the Non-Defaulting Party. Termination pursuant to this section will not relieve the Defaulting Party from liability and damages to the Non-Defaulting Party for default. Waiver by either Party of a single default or a succession of defaults will not deprive such Party of any right to terminate this Agreement arising by reason of any subsequent default.

(b) If Agouron or Ibis terminate this Agreement pursuant to Section 9.2.1(a), all rights and licenses granted hereunder will terminate. However, if there is a material breach of this Agreement by Ibis and such breach is not cured by Ibis during the period stipulated in Section 9.2.1(a), but Agouron nevertheless wishes to retain its rights granted by the terms of this Agreement with respect to Collaboration Compounds or Collaboration Products, then Agouron may elect not to terminate this Agreement but may terminate only the licenses granted to Ibis and will not be obligated to make any payments to Ibis to compensate Ibis for performance that was the subject of the material breach. In addition Agouron may pursue an action for damages or other relief arising as a result of such material breach. If there is a material breach of this Agreement by Agouron and such breach is not cured by Agouron during the period stipulated in Section 9.2.1(a), but Ibis nevertheless does not wish to terminate this Agreement, then Ibis will be entitled to pursue an action for damages or other relief arising as a result of such material breach.

9.2.2 TERMINATION UPON BANKRUPTCY.

(a) Any Party may terminate this Agreement by notice to the other Party upon the filing or institution of bankruptcy, reorganization, liquidation or receivership proceedings, or upon an assignment of a substantial portion of the assets for the benefit of creditors by the other Party; provided, however, in the case of any involuntary bankruptcy proceeding such right to terminate will only become effective if the Party consents to the involuntary bankruptcy or such proceeding is not dismissed within 90 days after the filing thereof.

(b) If Agouron terminates this Agreement under Section 9.2.2(a) or this Agreement is otherwise terminated under 9.2.2(a), all rights and licenses granted pursuant to this Agreement are, and will otherwise be deemed to be, for purposes of Section 365(n) of the Bankruptcy Code, licenses of rights to "intellectual property" as defined under Section 101(35A) of the Bankruptcy Code. The Parties agree that Agouron, as a licensee of such rights under this Agreement, will retain and may fully exercise all of its rights and elections under the Bankruptcy Code. The Parties further agree that, in the event of the commencement of a bankruptcy proceeding by or against Ibis under the Bankruptcy Code, Agouron will be entitled to a complete duplicate of (or complete access to, as appropriate) any such intellectual property and all embodiments of such intellectual property upon written request therefor by Agouron. Such intellectual property and all embodiments thereof will be promptly delivered to Agouron (i) upon any such commencement of a bankruptcy proceeding upon written request therefore by Agouron, unless Ibis elects to continue to perform its respective obligations under this Agreement or (it) if not delivered under (i) above, upon the rejection of this Agreement by or on behalf of Ibis, as the case may be, upon written request therefor by Agouron.

9.2.3 TERMINATION BY AGOURON'S NOTICE.

Notwithstanding anything contained herein to the contrary, after expiration of the Research Program Term, Agouron will have the right to terminate this Agreement at any time by giving 90 days advance written notice to Ibis.

9.3. DISPOSITION OF INVENTORY.

If any license rights of Agouron are terminated with respect to a Collaboration Product that is on the market, then Agouron may sell its inventory of such Collaboration Product for up to six months after the date of such termination, provided that required royalty payments, if any, are made to Ibis in connection therewith.

9.4. EFFECT OF EXPIRATION OR TERMINATION.

(a) Expiration or termination of this Agreement will not relieve the Parties of any obligation accruing prior to such expiration or termination, and Agouron will be obligated to pay and will pay to Ibis, within 30 calendar days of such expiration or termination, all payments and royalties due or accrued pursuant to the terms of Article V herein. The provisions of Article X will survive the expiration or termination of this Agreement and will continue in effect for 7 years from the date of expiration or termination. Any other provisions that from their nature are apparently intended to remain in force will also survive the expiration or termination of this Agreement. Any expiration or early termination of this Agreement will be without prejudice to the rights of any Party against the others accrued or accruing under this Agreement prior to termination, including Agouron's obligation to pay royalties to Ibis on Net Sales Revenue for Collaboration Products. If Agouron continues to develop and/or commercialize Collaboration Compounds and/or Collaboration Products after the termination of this Agreement, then such development and/or commercialization will be subject to the provisions of Article V, with the exception of Sections 5.1 and 5.2 thereof.

(b) [*]

ARTICLE X
CONFIDENTIALITY, PUBLICATION AND PUBLICITY

10.1 NON-DISCLOSURE AND NON-USE OBLIGATIONS.

All Proprietary Information disclosed by one Party to the other Party hereunder will be maintained in confidence by the receiving Party and will not be disclosed by it to any Third Party or used for any purpose (except as expressly permitted herein) without the prior written consent of the disclosing Party.

10.2 PERMITTED DISCLOSURE OF PROPRIETARY INFORMATION.

Notwithstanding Section 10.1, a Party receiving Proprietary Information of the other Party may disclose such Proprietary Information:

(a) to governmental or other regulatory agencies in order to obtain Patent Rights as provided for in this Agreement, or to gain approval to conduct clinical trials or to market any Collaboration Product pursuant to this Agreement, provided that receiving Party notifies the disclosing Party of its intent to disclose such Proprietary Information and limits the disclosure to only that Proprietary Information reasonably necessary to obtain such Patent Rights or authorizations;

(b) by Agouron to its permitted sublicensees, agents, consultants, Affiliates and/or other Third Parties for the research and development, manufacturing and/or marketing of any Collaboration Compounds or Collaboration Products (or for such parties to determine their interest in performing such activities) in accordance with this Agreement on the condition that such Third Parties agree to be bound by the confidentiality obligations contained in this Agreement; or

(c) if required to be disclosed by law or court order, provided that advance written notice is delivered to the non-disclosing Party so as to provide such Party a reasonable opportunity to challenge or limit the disclosure obligations.

10.3 NO WRITTEN PUBLICATION AND ORAL DISCLOSURES.

[*]

10.4 PUBLIC DISCLOSURE OF AGREEMENT.

[*]

ARTICLE XI
MISCELLANEOUS

11.1 FORCE MAJEURE.

No Party will be held liable or responsible to the other Party nor be deemed to have defaulted under or breached the Agreement for failure or delay in fulfilling or performing any term of the Agreement (except payment obligations) when such failure or delay is caused by or results from causes beyond the reasonable control of the affected Party including, but not limited to, fire, flood, embargo, war, acts of war (whether war be declared or not), insurrection, riot, civil commotion, strike, lockout or other labor disturbance, act of God or act, omission or delay in acting by any governmental authority or the other Party, provided that for the duration of such force majeure the affected Party continues to use all reasonable efforts to overcome such force majeure. The affected Party will notify the other Party of such force majeure circumstances as soon as reasonably practical.

11.2 ASSIGNMENT.

The Agreement may neither be assigned or otherwise transferred, nor, except as expressly provided hereunder, may any right or obligations hereunder be assigned or transferred, by a Party without the consent of the other Party; provided however, that any Party may, without such consent, assign the Agreement and its rights and obligations hereunder to (a) an Affiliate; (b) in connection with the transfer or sale of all or substantially all of its assets or business, including the applicable Patent Rights and Technology and other assets relating to the subject matter of this Agreement, or (c) in the event of its merger or consolidation or change in control or similar transaction. Any permitted assignee will assume all obligations of its assignor under this Agreement.

11.3 SEVERABILITY.

In the event that any of the provisions contained in this Agreement are held invalid, illegal or unenforceable in any respect, the validity, legality and enforceability of the remaining provisions contained herein will not in any way be affected or impaired thereby, unless the absence of the invalidated provision(s) adversely affect the substantive rights of the Parties. The Parties will replace the invalid, illegal or unenforceable provision(s) with valid, legal and enforceable provision(s), which, insofar as practical, implement the purposes of this Agreement.

11.4 NOTICES.

All notices or other communications which are required or permitted hereunder will be in writing and deemed to be effective (a) on the date of delivery if delivered in person and written confirmation of delivery is provided, (b) on the date of faxing or other electronic transmission, provided such transmission is acknowledged in writing by the Party receiving the transmission, (c) on the day following date of deposit with an overnight courier if a receipt confirming delivery by overnight courier is provided, or (d) three days after mailing if mailed by first-class certified mail, postage paid, to the respective addresses given below, or to another address as it will designate by written notice given to the other Party.

if to Ibis, to:	Isis Pharmaceuticals, Inc. 2292 Faraday Avenue Carlsbad, CA 92008 Attention: Chief Executive Officer Facsimile No.: 760-931-0265
with a copy to:	Attention- CFO Facsimile No.: 760-931-9639
if to Agouron, to:	Agouron Pharmaceuticals, Inc. 10350 North Torrey Pines Road La Jolla, CA 92037 Attention: Director, Business Development Facsimile No.: 858-678-8275

with a copy to: Attention: General Counsel
Facsimile No.: 858-622-3297

11.5 APPLICABLE LAW.

The Agreement will be governed by and construed in accordance with the laws of the State of California, as applied to contracts executed and performed entirely within the state, without reference to any rules of conflict of laws or renvoi, provided, however, that issues concerning the validity and construction of patents, trademarks and other intellectual property rights will be determined in accordance with the laws of the country under which such intellectual property rights were granted.

11.6 DISPUTE RESOLUTION.

(a) PRE-ARBITRATION EFFORTS. In the event of any controversy or claim arising from or relating to any provision of this Agreement, or any term or condition hereof, or the performance by a Party of its obligations hereunder, or its construction or its actual or alleged breach, the Parties will try to settle their differences amicably between themselves. If the representatives of the Parties are unable to reach agreement on any such issue, the issue will be submitted for consideration, in the case of Agouron, to its Corporate Vice President, Head of Research, or its designee, and in the case of Ibis, to its Managing Director, or its designee. If such representatives are unable to agree within fourteen (14) days, then the issue will be submitted for consideration to, in the case of Agouron, to its President, Global Commercial Operations, and, in the case of Ibis, to its Chief Executive Officer. If such representative are unable to agree within fourteen (14) days, then any disputes remaining unresolved between the Parties, except as otherwise provided in this Agreement, will be finally resolved by binding arbitration, as set forth below.

(b) ARBITRATION JURISDICTION. Any dispute or controversy arising out of or relating to this Agreement not able to be resolved between the Parties will be finally decided by arbitration in accordance with the then-current Licensing Agreement Arbitration Rules of the American Arbitration Association; provided, however, that the California Code of Civil Procedure will apply to any such proceeding. Any arbitration proceeding will be conducted in San Diego, California. The Parties agree that any arbitration panel will include members knowledgeable as to evaluation of biopharmaceutical technology.

(c) ARBITRATION PROCEDURES. Whenever a Party decides to institute arbitration proceedings, it will give written notice to the other Party. A single arbitrator mutually chosen by the Parties will conduct the arbitration. If the Parties cannot agree upon a single arbitrator within fifteen (15) days after the institution of the arbitration proceeding, then the arbitration will be conducted by a panel of three arbitrators appointed in accordance with applicable AAA rules; provided, however, that each Party will within thirty (30) days after the institution of the arbitration proceedings appoint one arbitrator, with the third arbitrator being chosen by the other two arbitrators. If only one Party appoints an arbitrator, then

such arbitrator will be entitled to act as the sole arbitrator to resolve the controversy. All arbitrator(s) eligible to conduct the arbitration must agree to render their opinion(s) within thirty (30) days of the final arbitration hearing. The arbitrator(s) will have the authority to grant injunctive relief and specific performance, and to allocate between the Parties the costs of arbitration in an equitable manner; provided, however, that each Party will bear its own costs, attorneys fees and witness fees. Notwithstanding the terms of this Section, a Party will also have the right to obtain, prior to the arbitrator(s) rendering the arbitration decision, provisional remedies, including injunctive relief or specific performance, from a court having jurisdiction thereof. The arbitrator(s) will, upon the request of either Party, issue a written opinion of the findings of fact and conclusions of law and will deliver a copy to each of the Parties. Decisions of the arbitrator(s) will be final and binding on the Parties. Judgment upon the award rendered may be entered in the highest court or forum, state or federal, having jurisdiction; provided, however, that the provisions of this Section will not apply to decisions on the validity of patent claims or to any dispute or controversy as to which any treaty or law prohibits such arbitration. In no event will a demand for arbitration be made after the date when institution of a legal or equitable proceeding based on such claim, dispute or other matter in question would be barred by the applicable statute of limitations.

11.7 REGULATORY APPROVALS.

The expenses for all approvals and licenses sought by Agouron for importation, marketing and selling of Collaboration Products in any country throughout the world will be borne by Agouron. Agouron will have sole title to and ownership of any such approvals and licenses it obtains.

11.8 ENTIRE AGREEMENT.

This Agreement contains the entire understanding of the Parties with respect to the subject matter hereof. All express or implied agreements and understandings, either oral or written, heretofore made are expressly merged in and made a part of this Agreement. This Agreement may be amended, or any term hereof modified, only by a written instrument duly executed by the Parties hereto.

11.9 HEADINGS.

The captions to the Articles and Sections hereof are not a part of the Agreement, but are merely guides or labels to assist in locating and reading the several Articles and Sections hereof.

11.10 INDEPENDENT CONTRACTORS.

It is expressly agreed that the Parties will be independent contractors and that the relationship between the Parties will not constitute a partnership, joint venture or agency. No Party will have the authority to make any statements, representations or commitments

of any kind, or to take any action, which will be binding on the other Party, without the prior consent of such other Party.

11.11 WAIVER.

The waiver by a Party hereto of any right hereunder or the failure to perform or of a breach by another Party will not be deemed a waiver of any other right hereunder or of any other breach or failure by said other Party whether of a similar nature or otherwise.

11.12 COUNTERPARTS.

The Agreement may be executed in two or more counterparts, each of which will be deemed an original, but all of which together will constitute one and the same instrument.

IN WITNESS WHEREOF, the Parties have executed this Agreement on the date set forth below.

AGOURON PHARMACEUTICALS, INC.	ISIS PHARMACEUTICALS, INC.
BY:_____	BY:_____
Name: Barry D. Quart, Pharm.D.	Name: B. Lynne Parshall
Title: President, Agouron Research and Development	Title: Executive Vice President
Date:_____	Date:_____

EXHIBIT A

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EXHIBIT B

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

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JAN-01-2000
JUN-30-2000
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