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, 1998

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	26,907,483 shares
(Class)	(Outstanding at July 31, 1998)

EXHIBIT INDEX: Located at page number 10.

ISIS PHARMACEUTICALS, INC.
FORM 10-Q
INDEX

PAGE

ISIS PHARMACEUTICALS, INC.
CONDENSED BALANCE SHEETS
(in thousands, except share data)

ASSETS

	June 30, 1998	December 31, 1997
	(Unaudited)	(Note)
Current assets:		
Cash and cash equivalents	$ 38,852	$ 38,102
Short-term investments	45,515	48,684
Prepaid expenses and other current assets	2,815	2,364
Total current assets	87,182	89,150
Property, plant and equipment, net	19,787	18,785
Patent costs, net	8,266	7,485
Deposits and other assets	2,400	2,461
	$ 117,635	$ 117,881
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 2,746	$ 2,843
Accrued payroll and related expenses	1,482	2,242
Accrued liabilities	4,066	4,347
Deferred contract revenues	22,558	14,893
Current portion of long term debt and capital lease obligations	2,166	2,252
Total current liabilities	33,018	26,577
Long-term debt and capital lease obligations, less current portion	71,919	56,452
Stockholders' equity:		
Common stock, $.001 par value; 50,000,000 shares authorized, 26,855,000 shares and 26,655,000 shares issued and outstanding at June 30, 1998 and December 31, 1997, respectively	27	27
Additional paid-in capital	191,913	188,793
Unrealized gain on investments	266	165
Accumulated deficit	(179,508)	(154,133)
Total stockholders' equity	12,698	34,852
	$ 117,635	$ 117,881

Note: The balance sheet at December 31, 1997 has been derived from the audited financial statements at that date.

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
CONDENSED STATEMENTS OF OPERATIONS
(in thousands, except for per share amounts)
(UNAUDITED)

	Three months ended June 30,		Six months ended June 30,	
	1998	1997	1998	1997
Revenues:				
Research and development revenue under collaborative agreements	$ 5,832	$ 5,793	$ 11,672	$ 10,419
Interest income	1,216	766	2,271	1,713
	7,048	6,559	13,943	12,132
Expenses:				
Research and development	16,532	13,374	31,391	25,160

General and administrative	2,261	2,054	4,119	3,761
Interest expense	2,102	557	3,806	1,191
	20,895	15,985	39,316	30,112
Net loss	$(13,847)	$ (9,426)	$(25,373)	$(17,980)
Basic and diluted net loss per share	$ (.52)	$ (.36)	$ (.95)	$ (.68)
Shares used in computing basic and diluted net loss per share	26,836	26,381	26,788	26,330

See accompanying notes.

5

ISIS PHARMACEUTICALS, INC.
CONDENSED STATEMENTS OF CASH FLOWS
(in thousands)
(UNAUDITED)

	Six months ended June 30,	
	1998	1997
Cash used in operations:	$(15,112)	$(11,698)
Investing activities:		
Short-term investments	3,169	5,797
Property and equipment	(1,881)	(3,856)
Other assets	(817)	(1,492)
Net cash provided from investing activities	471	449
Financing activities:		
Net proceeds from issuance of common stock	3,120	1,659
Proceeds from long-term borrowings	13,354	11,378
Principal payments on debt and capital lease obligations	(1,083)	(3,019)
Net cash provided from financing activities	15,391	10,018
Net increase (decrease) in cash and cash equivalents	750	(1,231)
Cash and cash equivalents at beginning of period	38,102	37,082
Cash and cash equivalents at end of period	$ 38,852	$ 35,851
SUPPLEMENTAL DISCLOSURES OF CASH FLOW INFORMATION:		
Interest paid	$ 1,599	$ 1,080
SUPPLEMENTAL DISCLOSURES OF NON-CASH INVESTING AND FINANCING ACTIVITIES		
Additions to long-term debt obligations for acquisitions of property, plant and equipment	$ 919	$ 670

See accompanying notes.

6

ISIS PHARMACEUTICALS, INC.

NOTES TO FINANCIAL STATEMENTS

1. BASIS OF PRESENTATION

The unaudited interim financial statements for the three and six month periods ended June 30, 1998 and 1997 have been prepared on the same basis as the Company's audited financial statements for the year ended December 31, 1997. 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, 1997 included in the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission.

2. COMPREHENSIVE INCOME

As of January 1, 1998, the Company adopted Statement of Financial Accounting Standards No. 130, Reporting Comprehensive Income ("SFAS 130"). This statement requires the Company to report in the financial statements, in addition to net income, comprehensive income and its components including foreign currency translation adjustments and unrealized gains and losses on its available-for-sale securities. SFAS 130 also requires the Company to reclassify financial statements for earlier periods provided for comparative purposes. For the three and six month periods ended June 30, 1998 and 1997 comprehensive income was not materially different than net income.

3. SUBSEQUENT EVENT

In August 1998, the Company entered into an agreement to exclusively license its issued patents covering immune stimulation by phosphorothioate oligonucleotides to CpG ImmunoPharmaceuticals, Inc. The agreement grants CpG ImmunoPharmaceuticals, Inc. exclusive worldwide rights to certain applications covered by issued U.S. Patents No. 5,663,153; No. 5,723,335; and related patent applications, not including claims for antisense therapeutics. The terms of the agreement provide that the Company will receive $5 million in cash payments in 1998. In addition, Isis will receive a 5% equity interest in CpG ImmunoPharmaceuticals, Inc. Based on recent cash purchases of equity securities of CpG ImmunoPharmaceuticals, Inc., the value of Isis' equity position will approximate $1.4 million.

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

In addition to historical information contained in this Report, this Report contains forward-looking statements regarding the Company's business and products and their projected prospects and qualities, and the Company's relationships with its corporate partners. Such statements are subject to certain risks and uncertainties, particularly those inherent in both the process of discovering, developing and commercializing safe and effective drugs, and the endeavor of building a business around such potential products. Actual results could differ materially from those projected in this Form 10-Q. As a result, the reader is cautioned not to 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 in Isis' Annual Report on Form 10-K for the year ended December 31, 1997 which is on file with the U.S. Securities and Exchange Commission, a copy of which is available from the Company.

Since its inceptions in January 1989, almost all of the Company's resources have been devoted to its research, drug discovery and drug development programs. The Company is not yet profitable and expects to continue to have operating losses for the next several years. Isis' revenue comes from collaborative research and development agreements with pharmaceutical companies, research grants and interest income. The revenue from the collaboration increases the amount of research and development activity that the Company is able to fund and offsets a portion of its research and development costs. To date, Isis has not received any significant revenue from the sale of products.

RESULTS OF OPERATIONS

The Company's revenue from collaborative research and development agreements was $5.8 million for the second quarter and $11.7 million for the six month period ended June 30, 1998, compared with $5.8 million and $10.4 million, respectively, for the same periods in 1997. The revenue increase was primarily due to the increasing level of development activity supported by our corporate partners. The Company also had interest income totaling $1.2 million for the quarter and $2.3 million for the six month period compared with $0.8 million and $1.7 million for the same periods in 1997. This increase in interest income was primarily due to higher average investment balances in the quarter ended June 30, 1998.

Research and development expenses increased to $16.5 million for the three months and $31.4 million for the six months ended June 30, 1998 from $13.4 million and $25.2 million for the same periods in 1997. This increase was attributable to an increase in preclinical and clinical development activities including compounds advancing into more expensive stages of clinical development. We expect that research and development expenses will continue to increase as compounds continue to advance in clinical development.

General and administrative expenses increased to $2.3 million for the quarter and $4.1 million for the six months ended June 30, 1998, from $2.1 million and $3.8 million for the same periods in 1997. This increase in general and administrative expense is related to additional staffing in general and administrative functions required to support the growth in research and development. We expect that general and administrative expenses will continue to increase in the future to support our growing research and development efforts.

Interest expense increased to $2.1 million for the second quarter and $3.8 million for the six month period ended June 30, 1998, compared with $0.6 million and $1.2 million for the same periods in 1997. This increase in interest expense is due to borrowing $25 million in a private debt financing completed in the fourth quarter of 1997 with an additional $15 million follow-on private debt financing in the second quarter of 1998. Under the terms of these financing arrangements payment of interest is deferred for the first five years. Therefore, of the $2.1 million of interest expense recognized in the second quarter, $1.3 million was accrued under the long-term debt agreements and will not require current cash payment. Similarly, of the $3.8 million interest expense for the six-month period ended June 30, 1998, $2.2 million was accrued under the long-term debt agreements and will not require current cash payment.

During the quarter ended June 30, 1998, the Company recorded a net loss of $13.8 million, or $0.52 per share, compared with $9.4 million, or $0.36 per share, for the same period in 1997. During the six-month period ended June 30, 1998, the Company's net loss amounted to $25.4 million, or $0.95 per share, compared to $18.0 million, or $0.68 per share for the same period in 1997. We expect that operating losses will increase for several more years as research and development activities grow. Operating losses may fluctuate from quarter to quarter because of differences in the timing of revenue and expense recognition.

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

LIQUIDITY AND CAPITAL RESOURCES

Isis 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 its inception through June 30, 1998, Isis has earned approximately $117 million in revenue from contract research and development. The Company has also raised net proceeds of approximately $180 million from the sale of equity securities since it was founded. Since 1996, Isis has borrowed approximately $62.6 million under long-term debt arrangements to finance a portion of its operations.

As of June 30, 1998, the Company had cash, cash equivalents and short-term investments totaling $84.4 million and working capital of $54.2 million. In comparison, the Company had cash, cash equivalents and short-term investments of $86.8 million and working capital of $62.6 million as of December 31, 1997. The decreases in cash and working capital resulted from the funding of operating losses, investments in capital equipment and principal payments on debt and capital lease obligations, offset in part, by an additional $15 million

private debt financing.

The Company's collaborative agreement with Boehringer Ingelheim provides Isis with a $40 million line of credit. This line of credit is available under certain circumstances and is to be used to support the collaboration cell adhesion programs. As of June 30, 1998, the outstanding balance under this line of credit was $22.6 million.

In October 1997, Isis borrowed $25 million in a private transaction. The loan bears interest at 14% per annum and must be repaid on November 1, 2007. No payments of either principal or interest are required during the first five years of the loan. After the first five years, interest must be paid quarterly. No principal payments are required until November 1, 2007. In conjunction with this transaction, Isis issued warrants to purchase 500,000 shares of common stock at a price of $25 per share. On May 1, 1998, the Company completed a follow-on $15 million private debt financing. This financing was a follow-on to the Company's October 1997 $25 million private debt financing and bears the same terms and conditions. Because interest is deferred during the first five years, the combined principal balance of both borrowings will accrue to a total of $78 million on November 1, 2002. In conjunction with this follow-on transaction, Isis issued warrants to purchase 300,000 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. 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, 1998 was $42.4 million.

The Company had long-term debt and capital lease obligations at June 30, 1998 totaling $71.9 million, versus $56.5 million at December 31, 1997. This increase was due to the additional follow-on debt financing and the accrual of interest on the ten-year notes described above, partially offset by principal repayments on existing obligations. We expect that capital lease obligations will increase over time to fund capital equipment acquisitions required for the Company's growing business. We will continue to use lease financing as long as the terms remain commercially attractive. We believe that the Company's existing cash, cash equivalents and short-term investments, combined with interest income and contract revenue will be sufficient to meet its anticipated requirements for at least two years.

Year 2000 Computer Issues

Until recently many computer programs were written to store only 2 digits of date-related information. Thus the programs were unable to distinguish between the year 1900 and the year 2000. As a result, many computer experts have significant concerns regarding how those programs will function after December 31, 1999. This is frequently referred to as the "Year 2000 Problem." The Company is in the process of reviewing its computer systems and other equipment that utilize embedded microprocessors to assess the potential exposure to this problem. Because Isis was founded in 1989 and all of its computer systems and equipment have been purchased or upgraded since that time, we believe the risk of material disruption to the Company's operations as a result of the presence of this defect in its own computer systems and equipment is minimal.

The company has also initiated discussions with its significant suppliers, corporate partners and financial institutions to ensure that those parties have appropriate plans to address Year 2000 issues where their systems could impact Isis' operations. The Company is assessing the extent to which its operations are vulnerable should those organizations fail to properly modify their computer systems.

A team of Isis employees is conducting the Company's Year 2000 initiative. The team's activities are designed to ensure that there is no adverse effect on the Company's core business operations and that transactions with customers, suppliers, corporate partners and financial institutions are fully supported. These efforts are scheduled to be completed by early 1999. While the Company believes its planning and preparations will be adequate to address its Year 2000 concerns, there can be no guarantee that the systems of other companies on which the Company's systems and operations rely will be converted on a timely basis and will not have a material effect on the Company. The Company does not yet have a formal contingency plan. A contingency plan will be finalized as the risk assessment is completed. Based on the information

obtained to date, the cost of identifying and remediating exposures to the Year 2000 Problem is not expected to be material to the Company's results of operations or financial position.

ITEM 1. LEGAL PROCEEDINGS

The Company is not a 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

(a) The Company held its Annual Meeting of Stockholders on May 22, 1998.

(b) Burkhard Blank, M.D., Stanley T. Crooke, M.D. Ph.D. and Mark B. Skaletsky were elected to serve as directors for a three-year term and until their successors are duly elected and qualified.

	Votes in Favor	Votes Withheld
Burkhard Blank	26,104,455	356,894
Stanley T. Crooke	26,111,827	356,772
Mark B. Skaletsky	26,111,427	357,172

Other directors whose terms of office continued after the Annual Meeting were as follows: Christopher F. O. Gabrieli, Daniel L. Kisner, M.D., Alan C. Mendelson, J.D., William R. Miller, Larry Soll, Ph.D., and Joseph H. Wender.

(c) The following items were approved at the Annual Meeting:

(1) An increase in the number of shares authorized for issuance under the Company's 1998 Stock Option Plan from 8,200,000 to 10,200,000, the extension of the term of the 1989 Plan until January 31, 2008 and the amendment to the stockholder approval requirements of the 1989 Plan.

Votes in favor:	14,082,001
Votes withheld:	2,411,387
Abstentions:	151,590
Unvoted:	9,823,621

(2) The selection of Ernst & Young LLP as independent auditors of the Company for its fiscal year ending December 31, 1998.

Votes in favor:	26,336,372
Votes withheld:	68,746
Abstentions:	63,481

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 1999 annual meeting of stockholders must provide specified information to the Company by December 14, 1998 (unless such matters are included in the Company's proxy statement pursuant to Rule 14a-8 under the Securities Exchange Act of 1934, as amended).

ITEM 6. EXHIBITS AND REPORTS ON FORM 8-K

a. Exhibits

The following documents are exhibits to this Form 10-Q:

10.1 First Supplement to Purchase Agreement for 14% Senior Subordinated Discount Notes due November 1, 2007 and Warrants for Common Stock dated May 1, 1998 (with certain confidential information deleted).

10.2 Research Collaboration and License Agreement between Merck & Co., Inc. and Isis Pharmaceuticals, Inc. dated June 1, 1998 (with certain confidential information deleted).

27 Financial Data Schedule

b. Reports on Form 8-K

The Company filed no reports on Form 8-K during the quarter ended June 30, 1998.

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, 1998 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, 1998 By: /S/ B. LYNNE PARSHALL

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

EXHIBIT 10.1

CONFIDENTIAL TREATMENT REQUESTED UNDER 17 C.F.R. SECTIONS 200.80(b)(4), 200.83 AND 240.24B-2. * INDICATES OMITTED MATERIAL THAT IS THE SUBJECT OF A CONFIDENTIAL TREATMENT REQUEST THAT IS FILED SEPARATELY WITH THE COMMISSION

FIRST SUPPLEMENT TO PURCHASE AGREEMENT

THIS FIRST SUPPLEMENT TO PURCHASE AGREEMENT (this "First Supplement"), dated as of May 1, 1998, between ISIS PHARMACEUTICALS, INC., a Delaware corporation (including any corporation succeeding thereto by merger, consolidation or acquisition of all or substantially all of its assets, the "Company"), and the Purchaser listed on Schedule I hereto (the "Purchaser").

WHEREAS, the Company and the Purchaser are parties to a Purchase Agreement (the "Purchase Agreement"), dated as of October 24, 1997 (the "Initial Closing Date"), pursuant to which the Purchaser purchased from the Company ten 14% Senior Subordinated Discount Notes due November 1, 2007, in the aggregate principal amount, at maturity, of $50,000,000 (the "Initial Notes");

WHEREAS, pursuant to the Purchase Agreement, the Company issued ten warrants evidencing the right to purchase, in the aggregate, 500,000 shares of Common Stock, $0.001 par value per share, of the Company (the "Initial Warrants" and, together with the Initial Notes, the "Initial Securities");

WHEREAS, the Company now wishes to sell, and the Purchaser now wishes to purchase, five additional 14% Senior Subordinated Discount Notes due November 1, 2007, in the aggregate principal amount, at maturity, of $27,862,337.93 (the "First Supplement Notes");

WHEREAS, in order to induce the Purchaser to purchase the First Supplement Notes and in connection therewith, the Company has duly authorized the issuance to the Purchaser of six additional warrants evidencing the right to purchase, in the aggregate, 300,000 shares of Common Stock, $0.001 par value per share, of the Company (the "First Supplement Warrants" and, together with the First Supplement Notes, the "First Supplement Securities"); and

WHEREAS, the Company and the Purchaser wish to enter into this First Supplement in order to amend the Purchase Agreement, to provide for the purchase and sale of the First Supplement Notes and to provide for the issuance of the First Supplement Warrants;

NOW, THEREFORE, in consideration of the agreements herein contained, the parties hereto hereby agree that the Purchase Agreement, together with all recitals and Exhibits thereto, is hereby amended and supplemented as follows in accordance with this First Supplement, effective as of the date hereof:

ARTICLE I

INCORPORATION OF PURCHASE AGREEMENT; DEFINITIONS

1.1 INCORPORATION OF PURCHASE AGREEMENT. This First Supplement constitutes a supplement to the Purchase Agreement, and the Purchase Agreement and this First Supplement shall be read together and shall have effect so far as practicable as though all of the provisions thereof and hereof are contained in one instrument.

1.2 DEFINITIONS. Except as otherwise expressly provided or unless the context otherwise requires, all terms used herein that are defined in the Purchase Agreement shall have the meanings assigned to them in the Purchase Agreement.

ARTICLE II

AMENDING AND MODIFYING PROVISIONS

2.1 AMENDMENTS TO DEFINITIONS. (a) Definition in Introductory Paragraph of Purchase Agreement. The following term which is defined in the Introductory Paragraph of the Purchase Agreement is hereby amended so that it will have the meaning set forth below whenever such term is used in the Purchase Agreement, this First Supplement or any other supplement to the Purchase Agreement:

"The term 'Agreement' shall mean the Purchase Agreement, the First Supplement, and, when executed by the Company and the Purchaser, any other supplement to the Purchase Agreement, taken as a whole."

(b) Definitions in Section 1.1 of Purchase Agreement. The following terms which are defined in Section 1.1 of the Purchase Agreement are hereby amended so that they will have the respective meanings set forth below whenever such term is used in the Purchase Agreement , this First Supplement or any other supplement to the Purchase Agreement:

"The term 'Notes' shall mean the Initial Notes, the First Supplement Notes and, when issued to the Purchaser, or another financial institution with the written consent of the Purchaser, any other 14% Senior Subordinated Discount Note due November 1, 2007 of the Company issued pursuant to any other supplement to the Purchase Agreement (including all debt securities issued in exchange or replacement thereto)."

"The term 'Securities' shall mean the Initial Securities, the First Supplement Securities, and, when issued to the Purchaser, or another financial institution with the written consent of the Purchaser, all other Notes and Warrants issued pursuant to any other supplement to the Purchase Agreement."

"The term 'Warrants' shall mean the Initial Warrants, the First Supplement Warrants and, when issued to the Purchaser, or another financial institution with the written consent of the Purchaser, any other warrants of the Company issued pursuant to any other supplement to the Purchase Agreement evidencing the right to purchase, in the aggregate, shares of Common Stock, $0.001 par value per share, of the Company."

(c) Definitions in Section 1.2(b) of Purchase Agreement. The following term which is defined in Section 1.2(b) of the Purchase Agreement is hereby amended so that it will have the meaning set forth below whenever such term is used in the Purchase Agreement, this First Supplement or any other supplement to the Purchase Agreement:

"The term 'Closing Date' shall mean the Initial Closing Date, the First Supplement Closing Date (as defined in Section 3.2(b) of the First Supplement) and any closing date for the purchase from the Company of any Securities by the Purchaser, or another financial institution with the written consent of the Purchaser, pursuant to any supplement to the Purchase Agreement."

(d) Amendment to Section 9.2 of Purchase Agreement. Section 9.2 of the Purchase Agreement is hereby amended to add the following defined terms having the respective meanings set forth below:

"The term 'First Supplement' shall mean that certain First Supplement to Purchase Agreement, dated as of May 1, 1998, between the Company and the Purchaser."

"The term 'First Supplement Closing Date' shall mean May 1, 1998, the date of the purchase and sale of the First Supplement Notes."

"The term 'First Supplement Notes' shall mean the 14% Senior Subordinated Discount Notes due November 1, 2007, in the aggregate principal amount, at maturity, of $27,862,337.93, of the Company, issued to the Purchaser in connection with the First Supplement."

"The term 'First Supplement Securities' shall mean the First Supplement Notes, together with the First Supplement Warrants."

"The term 'First Supplement Warrants' shall mean the warrants evidencing the right to purchase, in the aggregate, 300,000 shares of Common Stock, $0.001 par value per share, of the Company, issued to the Purchaser in connection with the First Supplement."

"The term 'Initial Closing Date' shall mean October 24, 1997, the date of the Purchase and Sale of the Initial Notes."

"The term 'Initial Notes' shall mean the 14% Senior Subordinated Discount Notes due November 1, 2007, in the aggregate principal amount, at maturity, of $50,000,000, of the Company, issued to the Purchaser in connection with the Purchase Agreement."

"The term 'Initial Securities' shall mean the Initial Notes, together with the Initial Warrants."

"The term 'Initial Warrants' shall mean the warrants evidencing the right to purchase, in the aggregate, 500,000 shares of Common Stock, $0.001 par value per share, of the Company, issued to the Purchaser in connection with the Purchase Agreement."

"The term 'Purchase Agreement' shall mean that certain Purchase Agreement, dated as of October 24, 1997, between the Company and the Purchaser."

ARTICLE III

AUTHORIZATION AND ISSUANCE OF FIRST SUPPLEMENT SECURITIES

3.1 AUTHORIZATION OF ISSUE. The Company has duly authorized the issuance of the First Supplement Notes. Each First Supplement Note shall be substantially in the form of the Note attached as Exhibit A to the Purchase Agreement. In order to induce the Purchaser to purchase the First Supplement Notes and in connection therewith, the Company has duly authorized the issuance of the First Supplement Warrants evidencing the right to purchase, in the aggregate, 300,000 shares of Common Stock, $0.001 par value per share, of the Company at the Basic Purchase Price (as defined in the form of Warrant attached as Exhibit B to the Purchase Agreement) of $25.00 per share; such number of shares and such Basic Purchase Price being subject to adjustment as provided in the form of Warrant attached as Exhibit B to the Purchase Agreement. Each First Supplement Warrant shall be substantially in the form of the Warrant attached as Exhibit B to the Purchase Agreement.

3.2 ISSUANCE OF FIRST SUPPLEMENT SECURITIES. (a) Purchase of First Supplement Notes; Delivery of First Supplement Warrants. Subject to the terms hereof, (i) the Company agrees to sell, and the Purchaser agrees to purchase, on the First Supplement Closing Date hereinafter referred to, First Supplement Notes in the aggregate principal amount, at maturity, of $27,862,337.93 at a price equal to $15,000,000, payable in immediately available funds and (ii) the Company agrees to deliver to the Purchaser, and the Purchaser agrees to accept, on the First Supplement Closing Date hereinafter referred to, the First Supplement Warrants evidencing the right to purchase, in the aggregate, 300,000 shares of Common Stock, $.001 par value per share, at the Basic Purchase Price of $25.00 per share,

such number of shares and such Basic Purchase Price being subject to adjustment as provided in the form of Warrant attached as Exhibit B to the Purchase Agreement.

(b) First Supplement Closing Date, Delivery of First Supplement Notes and First Supplement Warrants. The date for the purchase and sale of the First Supplement Notes hereunder (the "First Supplement Closing Date") shall be May 1, 1998 or such other date as may be agreed to by the parties hereto. The purchase and sale of the First Supplement Notes hereunder shall take place at 1:00 P.M., Eastern Time, on the First Supplement Closing Date, at the offices of the Purchaser, (*) or such other place as the parties hereto may designate. On the First Supplement Closing Date, the Company will deliver to the Purchaser against payment of the purchase price therefor, five Notes in the aggregate principal amount, at maturity, of $27,862,337.93, dated the First Supplement Closing Date and registered in the name of the Purchaser's nominee set forth on Schedule I attached hereto, and in connection with the delivery of the First Supplement

Notes to the Purchaser on the First Supplement Closing Date, and simultaneously with such delivery, the Company will deliver to the Purchaser six First Supplement Warrants, registered in the name of the Purchaser's nominee set forth on Schedule I attached hereto, and evidencing the right to purchase an aggregate of 300,000 shares of Common Stock, $.001 par value per share, at the Basic Purchase Price of $25.00 per share, such number of shares and such Basic Purchase Price being subject to adjustment as provided in the form of the Warrant attached as Exhibit B to the Purchase Agreement.

3.3 SECURITIES LAWS. (a) The Company's Representation and Agreements. The Company represents and warrants to the Purchaser that the Company has not, directly or through any agent, offered any of the First Supplement Securities or any similar security for sale to, or solicited any offers to buy any thereof from, or otherwise approached or negotiated in respect thereof with, any Person other than the Purchaser who was offered the First Supplement Securities in a private sale for investment, and the Company agrees that neither the Company nor any agent acting on the Company's behalf has done or caused to be done or will do or cause to be done or omit to do or cause to be done anything which would result in bringing the issuance or sale of the First Supplement Notes and the First Supplement Warrants within the registration requirements of Section 5 of the Securities Act.

(b) The Purchaser's Representations and Agreements. The Purchaser represents and warrants, and in entering into this First Supplement the Company understands and acknowledges, that it is acquiring the First Supplement Securities for its own account for investment purposes and not with a view to, or for sale in connection with, any distribution (as such term is used under Section 2(11) of the Securities Act) thereof. Without limiting the foregoing, the Purchaser acknowledges and agrees that the First Supplement Securities have not and will not be registered under the Securities Act or any applicable state securities laws and it agrees that it will reoffer or resell the First Supplement Securities or the First Supplement Warrant Shares purchased by it under this First Supplement (i) only (A) to the

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* CONFIDENTIAL TREATMENT REQUESTED

Company, (B) pursuant to any transaction under and meeting the requirements of Rule 144A, as amended from time to time, promulgated under the Securities Act, (C) pursuant to an exemption from registration under the Securities Act in accordance with Rule 144, as amended from time to time, promulgated under the Securities Act, or (D) in accordance with any other available exemption from the requirements of Section 5 of the Securities Act and (ii) in accordance with any applicable federal and state securities laws. The Purchaser further agrees to hold the Company harmless from any claim, demand or liability for broker's or finder's placement fees or commissions payable by the Purchaser alleged to have been incurred by Purchaser in connection with this transaction.

ARTICLE IV

RESTATEMENT OF THE COMPANY'S REPRESENTATIONS AND WARRANTIES

4.1 REPRESENTATIONS AND WARRANTIES. Except as described on Schedule 4.1 annexed hereto, the representations and warranties of the Company set forth in Article II of the Purchase Agreement were true and correct as of the Initial Closing Date, were true and correct as if made at all times between the Initial Closing Date and the First Supplement Closing Date, and are true and correct as if made on the First Supplement Closing Date.

ARTICLE V

CLOSING CONDITIONS

The Purchaser's obligation to purchase and pay for the First Supplement Notes and the First Supplement Warrants on the First Supplement Closing Date is subject to the complete satisfaction of the Purchaser, on or before the First

Supplement Closing Date, of the conditions set forth in this Article.

5.1 OPINION OF COMPANY'S COUNSEL. The Purchaser shall have received from Cooley Godward LLP, counsel for the Company, an opinion, dated the First Supplement Closing Date, substantially in the form set forth in Exhibit A hereto.

5.2 REPRESENTATIONS AND WARRANTIES. The Company's representations and warranties contained in Section 3.3(a) and in Article IV of this First Supplement shall be true on and as of the First Supplement Closing Date. There shall exist on the First Supplement Closing Date no Event of Default and no condition or event which, with notice or lapse of time or both, would constitute an Event of Default if the First Supplement Securities had been outstanding at all times from and after the date hereof, and all agreements and conditions to be performed or satisfied by the Company hereunder on or before the First

Supplement Closing Date shall have been duly performed or satisfied. The Company shall have delivered to the Purchaser a certificate, dated the First Supplement Closing Date and signed by its Chief Executive Officer or its President or one of its Vice Presidents and by its Secretary or an Assistant Secretary, to each of the foregoing effects.

5.3 CONSENTS AND APPROVALS. The Company shall have delivered to the Purchaser a certificate, dated the First Supplement Closing Date and signed by its Chief Executive Officer or its President or one of its Vice Presidents, listing any consents, waivers, approvals, authorizations, registrations, filings and notifications of the character referred to in Section 2.11 of the Purchase Agreement which are necessary, to which shall be attached evidence, satisfactory to the Purchaser, that the same that are required to be obtained or made prior to the First Supplement Closing Date have been obtained or made and are in full force and effect, or stating that none is necessary.

5.4 PROCEEDINGS AND DOCUMENTS. All corporate and other proceedings and all documents incident to the transactions contemplated by this First Supplement shall be reasonably satisfactory in form and substance to the Purchaser and the Purchaser shall have received copies of all documents and records relating thereto which the Purchaser may reasonably request.

5.5 LEGALITY OF INVESTMENT. The Purchaser's acquisition of the First Supplement Securities shall be permitted as of the First Supplement Closing Date under the provisions of all applicable laws or governmental regulations, and such acquisition shall not subject the Purchaser to any penalty or other onerous condition in or pursuant to any such law or regulation; and the Purchaser shall have received such certificates or other evidence as the Purchaser may reasonably request to establish compliance with this condition.

5.6 AMENDMENT TO INITIAL WARRANTS. With the consent of the Purchaser, the Company shall have amended each of the Initial Warrants with an amendment substantially in the form of Exhibit B attached hereto (each, a "Warrant Amendment"), and within a reasonable time after the First Supplement Closing Date the Purchaser will cause each Initial Warrant to bear a legend indicating the existence of the Warrant Amendment which amends such Initial Warrant.

ARTICLE VI

COVENANTS

6.1 PRIVATE PLACEMENT NUMBERS. Within two Business Days after the First Supplement Closing Date, the Company shall apply to Standard & Poor's Corporation for assignment of a Private Placement Number for the First Supplement Notes and the First Supplement Warrants.

ARTICLE VII

MISCELLANEOUS

7.1 FULL FORCE AND EFFECT. Except as supplemented and amended hereby, the Purchase Agreement and all Notes and the Warrants issued pursuant thereto are in all respects ratified and confirmed and all the terms and provisions thereof shall remain in full force and effect.

7.2 INTEGRATION AND SEVERABILITY. The Purchase Agreement and this First Supplement embody the entire agreement and understanding between the Purchaser and the Company and supersede all prior agreements and understandings relating to the subject matter hereof. In case any one or more of the provisions contained in the Purchase Agreement or the First Supplement or in any Security, or any application thereof, shall be invalid, illegal or unenforceable in any respect, the validity, legality and enforceability of the remaining provisions contained herein and therein, and any other application thereof, shall not in any way be affected or impaired thereby.

7.3 GOVERNING LAW. The Purchase Agreement, this First Supplement, the Notes and the Warrants shall be construed in accordance with and governed by the laws of the State of New York (without giving effect to the principles of conflict of laws thereof). If any action or proceeding shall be brought by the Purchaser or by any Holder in order to enforce any right or remedy under the Purchase Agreement or this First Supplement or under any Security, the Company hereby consents and will, and the Company will cause each Subsidiary to, submit to the jurisdiction of any state or federal court of competent jurisdiction sitting within the area comprising the Southern District of New York on the date of this First Supplement. Nothing contained in this section shall affect the right of any Holder of Notes to serve legal process in any other manner permitted by law or to bring any action or proceeding in the courts of any jurisdiction against the Company or to enforce a judgment obtained in the courts of any other jurisdiction.

7.4 COUNTERPARTS. This First Supplement may be signed by each party hereto upon a separate copy in which event both of said copies shall constitute a single counterpart of this First Supplement. This First Supplement may be executed in two or more counterparts, each of which shall be deemed an original, and it shall not be necessary in making proof of this First Supplement to produce or account for more than one such counterpart.

IN WITNESS WHEREOF, the Company and the Purchaser have caused this First Supplement to be executed by their respective officers thereunto duly authorized as of the day and year first above written.

ISIS PHARMACEUTICALS, INC.

By: /s/ Stanley T. Crooke

Name: Stanley T. Crooke
Title: Chairman and Chief Executive Officer

(*)

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* CONFIDENTIAL TREATMENT REQUESTED

SCHEDULE I

PURCHASER AND PAYMENT INFORMATION

PURCHASER (NAME AND ADDRESS)	NOTES TO BE PURCHASED

1. (*) $27,862,337.93

Registration Instructions
(*)

Delivery Instructions:
(*)

Wire Instructions:
(*)

Notices:
(*)

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* CONFIDENTIAL TREATMENT REQUESTED

SCHEDULE 4.1 TO FIRST SUPPLEMENT

The authorized Capital Stock of the Company consists solely of (i) 50,000,000 shares of Common Stock, par value $.001 per share, of which 26,820,342 are outstanding as of April 24, 1998, all of which have been duly authorized and validly issued by the Company and are fully paid, nonassessable and free of preemptive rights and (ii) 15,000,000 shares of Preferred Stock, par value $.001 per share, none of which has been issued.

EXHIBIT B

FORM OF AMENDMENT TO WARRANT

To Purchase Common Stock of

ISIS PHARMACEUTICALS, INC.

Expiring November 1, 2004

THIS AMENDMENT (this "Amendment to Warrant WR-1"), dated as of May 1, 1998, to that Warrant WR-1 ("Warrant WR-1"), dated as of October 24, 1997 issued by ISIS PHARMACEUTICALS, INC., a Delaware corporation, to the holder set forth in such Warrant WR-1 (the "Holder").

WHEREAS, the Company is party to a Purchase Agreement, dated as of October 24, 1997, pursuant to which the Company issued ten warrants evidencing the right to purchase, in the aggregate, 500,000 shares of Common Stock, $0.001 par value per share, of the Company;

WHEREAS, the Company is now party to a First Supplement to Purchase Agreement, dated as of May 1, 1998 (the "First Supplement"), pursuant to which the Company issued an additional six warrants evidencing the right to purchase, in the aggregate, 300,000 shares of Common Stock, $0.001 par value per share, of the Company;

WHEREAS, the Company wishes to amend Warrant WR-1, and the Holder wishes to consent to such amendment of Warrant WR-1, so that Warrant WR-1 will reflect the issuance of the additional Warrants pursuant to the First Supplement;

NOW, THEREFORE, Warrant WR-1, together with all recitals and Exhibits thereto, is hereby amended and supplemented as follows in accordance with this Amendment to Warrant WR-1, effective as of the date hereof:

ARTICLE I

INCORPORATION OF WARRANT WR-1; DEFINITIONS

1.1 INCORPORATION OF WARRANT WR-1. This Amendment to Warrant WR-1 constitutes a supplement to Warrant WR-1, and Warrant WR-1 and this Amendment to Warrant WR-1 shall be read together and shall have effect so far as practicable as though all of the provisions thereof and hereof are contained in one

instrument.

13

1.2 DEFINITIONS. Except as otherwise expressly provided or unless the context otherwise requires, all terms used herein that are defined in Warrant WR-1 shall have the meanings assigned to them in Warrant WR-1.

ARTICLE II

AMENDING AND MODIFYING PROVISIONS

2.1 AMENDMENTS TO DEFINITION IN SECTION 1 OF WARRANT WR-1. The following term which is defined in Section 1 of Warrant WR-1 is hereby amended so that it will have the respective meaning set forth below whenever such term is used in Warrant WR-1:

"'Warrants' shall mean all Warrants of the Company (including this Warrant) (i) described in Section 1.1 of the Purchase Agreement, whether issued or issuable, which are identical as to terms and conditions, except as to the names and addresses of the Warrantholders thereunder and the number of shares of the Stock for which they may be exercised, and which evidence the right to purchase an aggregate of not in excess of 500,000 shares of the Stock (prior to making any adjustments of the character provided in Section 6 thereof), including all amendments thereto, and together with all Warrants issued in exchange, transfer or replacement of any thereof, (ii) described in Section 2.1(b) of the First Supplement to Purchase Agreement (the "First Supplement"), dated as of May 1, 1998, between the Company and the Purchaser, whether issued or issuable, which are identical as to terms and conditions, except as to the names and addresses of the Warrantholders thereunder and the number of shares of the Stock for which they may be exercised, and which evidence the right to purchase an aggregate of not in excess of 300,000 shares of the Stock (prior to making any adjustments of the character provided in Section 6 thereof), including all amendments thereto, and together with all Warrants issued in exchange, transfer or replacement of any thereof and (iii) when issued to the purchaser listed on Schedule I to the First Supplement, or another financial institution with the written consent of the purchaser listed on Schedule I to the First Supplement, described in any Supplement to the Purchase Agreement, whether issued or issuable, which are identical as to terms and conditions, except as to the names and addresses of the Warrantholders thereunder and the number of shares of the Stock for which they may be exercised, including all amendments thereto, and together with all Warrants issued in exchange, transfer or replacement of any thereof."

2.1 AMENDMENT AND MODIFICATION TO SECTION 5C. Section 5(C) of Warrant WR-1 is hereby amended and restated in its entirety as follows: :

"C. Registration Requested by Warrantholders.

2

14

(1) At any time and from time to time after the date hereof, the Warrantholders shall have the right to request the Company to effect the registration under the Securities Act of all or part of such Warrantholders' Registrable Securities. Upon receipt by the Company of any such request, the Company shall promptly give notice of such proposed registration to all Warrantholders and thereupon shall, as expeditiously as possible, use its best efforts to effect the registration under the Securities Act of:

(i) all Registrable Securities which the Company has been requested to register pursuant to clause (1) of Section 5C of any Warrant; and

(ii) all other Registrable Securities which Warrantholders have, within 20 days after the Company has given such notice, requested the Company to register;

all to the extent requisite to permit the sale or other disposition by the Warrantholders of the Registrable Securities so to be registered.

(2) If the managing underwriter of the public offering to be effected pursuant to a registration statement filed pursuant to clause (1) of Section 5C of any Warrant shall advise the Company in writing (with a copy to each holder of Registrable Securities requesting registration) that, in its opinion, the number of securities requested to be included in such registration (including securities of the Company which are not Registrable Securities) exceeds the number which can be sold in such offering, the Company will include in such registration to the extent of the number which the Company is so advised can be sold in such offering:

(i) first, Registrable Securities requested to be included in such registration by the Warrantholders pursuant to clauses (i) and (ii) of Section 5C(l) of any Warrant, pro rata among such holders on the basis of the number of Registrable Securities requested to be included by each; and

(ii) second, other securities of the Company proposed to be included in such registration, in accordance with the priorities, if any, then existing among the Company and the holders of such other securities.

(3) The Warrantholders requesting inclusion in a registration statement under this Section 5C and Section 5C of the other Warrants may withdraw from any requested registration pursuant to this Section 5C and Section 5C of the other Warrants by giving written notice to the Company prior to the filing date of such registration statement; provided, however, that for a period of three months after such withdrawal, such Warrantholders may not request any registration pursuant to this Section 5C and Section 5C of the other Warrants.

(4) The Company shall not be required to effect more than a total of three effective registrations under Section 5C of this Warrant and Section 5C of any other Warrant.

(5) The Company shall not be required to effect a registration pursuant to Section 5C of any Warrant unless the offering includes Registrable Securities having a Fair Market Value of at least $4 million in the aggregate.

(6) The Company shall not be required to effect any registration within twelve months of the effective date of any other registration under Section 5C of any Warrant."

ARTICLE III

MISCELLANEOUS

3.1 FULL FORCE AND EFFECT. Except as supplemented and amended hereby, Warrant WR-1 is in all respects ratified and confirmed and all the terms and provisions hereof shall remain in full force and effect.

3.2 GOVERNING LAW; CONSENT TO JURISDICTION. This Amendment to Warrant WR-1 shall be governed by, and construed in accordance with, the laws of the State of New York (without giving effect to the conflict of laws principles thereof).

IN WITNESS WHEREOF, ISIS PHARMACEUTICALS, INC. has caused this Amendment to Warrant WR-1 to be signed by its duly authorized officer under its corporate seal, attested by its duly authorized officer, and to be dated as of May 1, 1998.

ISIS PHARMACEUTICALS, INC.

By:

Stanley T. Crooke
Chairman and Chief Executive Officer

[Corporate Seal]

Attest:

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

CONSENT TO AMENDMENT TO WARRANT WR-1

IN WITNESS WHEREOF, (*), pursuant to Section 13 of Warrant WR-1, hereby consents to this Amendment to Warrant WR-1.

(*)

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* CONFIDENTIAL TREATMENT REQUESTED

1

EXHIBIT 10.2

CONFIDENTIAL TREATMENT REQUESTED UNDER 17 C.F.R. SECTIONS 200.80(b)(4), 200.83 AND 240.24B-2. * INDICATES OMITTED MATERIAL THAT IS THE SUBJECT OF A CONFIDENTIAL TREATMENT REQUEST THAT IS FILED SEPARATELY WITH THE COMMISSION

RESEARCH COLLABORATION AND LICENSE AGREEMENT

by and among

MERCK & CO., INC.

and

ISIS PHARMACEUTICALS, INC.

2

TABLE OF CONTENTS

3

RESEARCH COLLABORATION AND LICENSE AGREEMENT

THIS AGREEMENT effective as of June 1, 1998 (the "Effective Date") between Merck & Co., Inc., a corporation organized and existing under the laws of New Jersey ("Merck") and Isis Pharmaceuticals, Inc., a corporation organized and existing under the laws of Delaware ("Isis") together referred to as the "Parties".

WITNESSETH:

WHEREAS, Isis has expertise in the area of nucleoside and nucleotide chemistry and is willing to utilize that expertise to discover Research Compounds (as hereinafter defined) under the terms of this Agreement; and

WHEREAS, Merck and Isis desire to enter into a research collaboration to discover Research Compounds (as hereinafter defined) upon the terms and conditions set forth herein; and

WHEREAS, Merck desires to obtain a license under Isis Intellectual Property (as hereinafter defined), upon the terms and conditions set forth herein;

NOW, THEREFORE, in consideration of the foregoing premises and the mutual covenants herein contained, the Parties hereby agree as follows:

ARTICLE I

DEFINITIONS

Unless specifically set forth to the contrary herein, the following terms, whether used in the singular or plural, shall have the respective meanings set forth below:

1.1 "Affiliate" shall mean (i) any corporation or business entity of which fifty percent (50%) or more of the securities or other ownership interests representing the equity, the voting stock or general partnership interest are owned, controlled or held, directly or indirectly, by a Party; or (ii) any corporation or business entity which, directly or indirectly, owns, controls or holds fifty percent (50%) (or the maximum ownership interest permitted by law) or more of the securities or other ownership interests representing the equity, the voting stock or, if applicable, the general partnership interest, of a Party.

1.2 "Anti-Viral Animal Product(s)" shall mean Anti-Viral Products for animal use.

1.3 "Anti-Viral Human Product(s)" shall mean Anti-Viral Products for human use.

1.4 "Anti-Viral Product(s)" (*)

1.5 "Calendar Quarter" shall mean the respective periods of three (3) consecutive calendar months ending on March 31, June 30, September 30 and December 31.

1.6 "Calendar Year" shall mean each successive period of twelve (12) months commencing on January 1 and ending on December 31.

1.7 (*)

1.8 "Collection Animal Products" shall mean Collection Products for animal use.

1.9 "Collection Human Products" shall mean Collection Products for human use.

1.10 "Collection Products". (*)

1.11 "Combination Product" shall mean a Royalty Bearing Product which includes one or more therapeutically active ingredients other than Compound, in combination with Compound.

1.12 "Compounds" shall mean Research Compounds and Derived Compounds.

1.13 "Derived Compound(s)" shall mean a chemical entity derived by Merck from a Research Compound after the term of the Research Program or any derivative or analog of any such chemical entity or salt or ester thereof, including but not limited to Oligonucleotides.

*CONFIDENTIAL TREATMENT REQUESTED

1.14 "Effective Date" shall mean the date first set forth above.

1.15 "Extended Research Program Term" shall have the meaning set forth in Section 2.8.

1.16 "FDA" shall mean the United States Food and Drug Administration and any successor agency having substantially the same functions.

1.17 "First Commercial Sale" shall mean, with respect to any Royalty Bearing Product, the first sale for end use or consumption of such Royalty Bearing Product in a country after all required approvals, including marketing and pricing approvals, have been granted by the governing health authority of such country.

1.18 "Full Time Equivalent" or "FTE" shall mean the equivalent of a full-time scientist's work time over a twelve-month period (including normal vacations, sick days and holidays). The portion of an FTE year devoted by a scientist to the Research Program shall be determined by dividing the number of working days during any twelve-month period devoted by such employee to the Research Program by the total number of working days during such twelve-month period.

1.19 "HCV Human Products" shall mean HCV Products for human use.

1.20 HCV Product(s)" shall mean any preparations in final form for sale by prescription, over-the-counter or any other method for any indication, including human or animal use, which contain Compound(s) which (i) are approved as an RMC Development Candidate during the Research Program or within ten (10) years thereafter and (ii) are initially developed for the prevention and/or treatment of infections caused by hepatitis C virus. It is understood that Compounds which are claimed in or covered by Isis Patent Assets or Isis Research Patent Assets and which meet the criteria set forth in (ii) above but do not meet the criteria set forth in (i) above are Compounds included in Article 1.10.

1.21 "Isis Compounds" shall mean nucleoside and/or nucleotide small molecules identified and/or discovered by Isis (i) prior to the commencement of this Agreement or (ii) during the term of the Research Program but outside the course of the Research Program which are, in the sole discretion of Isis, provided by Isis to Merck under the terms of this Agreement.

1.22 "Isis Field" shall mean the use of Research Compounds solely for the purpose of developing Oligonucleotide products for therapeutic indications other than the prevention and/or treatment of infections caused by Hepatitis C virus.

1.23 "Isis Intellectual Property" shall mean (i) Isis Know-How, (ii) Isis Patent Assets, (iii) Isis Research Know-How and (iv) Isis Research Patent Assets to the extent that (iii) and (iv) are owned solely by Isis.

1.24 "Isis Know-How" shall mean all information and materials, including but not limited to, discoveries, processes, formulas, data, non-patented inventions, know-how and trade secrets of Isis conceived prior to the Effective Date or during the term of the Research Program but outside its scope, to the extent Isis is not precluded from licensing such know-how to Merck by the terms of any third party agreement, which are necessary or useful to Merck (a) in the conduct of Merck's activities under the Research Program or (b) to make, have made, use, import or sell Research Compounds and to incorporate Research Compounds into Licensed Products.

1.25 "Isis Patent Assets" shall mean issued patents and patent applications (which shall be deemed to include certificates of invention and applications for certificates of invention), other than Isis Research Patents Assets, which during the Research Program or any Extended Research Program Term are owned by Isis or which Isis through license or otherwise acquires rights, to the extent Isis is not precluded from licensing such Isis Patent Assets to Merck by the terms of any third party agreement, which claim or cover Research Compounds and/or Derived Compounds their uses or a method of their manufacture, including all divisions, continuations, continuations-in-part, reissues, renewals, extensions, supplementary protection certificates or the like of any such patents and patent applications and foreign equivalents thereof; provided, however, that if a patent (other than an Isis Patent Asset) of which Isis is the sole or joint owner issues after the Research Program Term or any Extended Research Program Term which (i) claims or covers a composition of matter or a process and (ii) prevents Merck from making, having made, using, importing and/or selling a Research Compound, then such patent shall be deemed to be part of Isis Patent Assets solely to the extent such patent is necessary to enable Merck to make, have made, use, import and/or sell such, Research Compound (or any Derived Compound claimed in or covered by such patent, other than an Oligonucleotide).

1.26 "Isis Research Know-How" shall mean all information and Materials, including but not limited to, discoveries, processes, formulas, data, non-patented inventions, know-how and trade secrets of Isis conceived in the course of the Research Program, including know-how conceived jointly with Merck. It is understood that, notwithstanding the foregoing, Merck retains its joint ownership of know-how conceived jointly with Isis during the Research Program.

1.27 "Isis Research Patent Assets" shall mean patents and patent applications (which shall be deemed to include certificates of invention and applications for certificates of invention) which claim inventions conceived solely by Isis or jointly by Isis and Merck in the course of the Research Program and all divisions, continuations, continuations-in-part, reissues, renewals, extensions, supplementary protection certificates or the like of any such patents and patent applications and foreign equivalents thereof. It is understood that, notwithstanding the foregoing, Merck

retains its joint ownership of patents and patent applications of inventions conceived in the course of the Research Program jointly with Isis.

1.28 "Joint Research Committee" shall mean the committee described in Section 2.4.

1.29 "Licensed Product" shall mean any preparation, including but not limited to a Royalty Bearing Product, in final form for sale by prescription, over-the-counter or any other method for any indication, including human or animal use, which contains one or more Compound(s), including in combination with a therapeutically active ingredient which is not a Compound.

1.30 "Major Market Country" shall mean Japan, the United Kingdom, France, Germany, Italy or Spain.

1.31 "Merck Know-How" shall mean all information and materials, including but not limited to, discoveries, processes, formulas, data, non-patented inventions, knowhow and trade secrets of Merck, to the extent Merck is not precluded from licensing such know-how to Isis by the terms of any third party agreement, which during the term of the Research Program are not generally known and which are necessary to Isis in the performance of its obligations under the Research Program.

1.32 "Merck Patent Assets" shall mean issued patents and patent applications (which shall be deemed to include certificates of invention and applications for certificates of invention which are owned by Merck and which claim or cover-the manufacture, use or sale of Compounds and all divisions, continuations, continuations in-part, reissues, renewals, extensions, supplementary protection certificates or the like of any such patents and patent applications and foreign equivalents thereof.

1.33 "NDA" shall mean a new drug application filed with the FDA for marketing authorization of a Royalty Bearing Product.

1.34 "Net Sales" shall mean (*)

*CONFIDENTIAL TREATMENT REQUESTED

1.35 "Oligonucleotide" shall mean (*)

1.36 "Proprietary Information" shall mean any and all scientific, clinical, regulatory, marketing, financial and commercial information or data, whether communicated in writing, orally or by any other means, which is provided by one Party to the other Party in connection with this Agreement. Proprietary Information shall include, without limitation, Merck Know-How and Isis Know-How and Isis Research Know-How.

1.37 "RMC Development Candidate" shall mean a Compound which has been approved, in Merck's sole discretion, by the Merck Research Management Committee (or its successor) for initiation of formal development studies, including safety assessment.

1.38 "Research Compounds" shall mean (*)

*CONFIDENTIAL TREATMENT REQUESTED

1.39 "Research Field" shall mean chemistry efforts to design (*) small molecules which inhibit hepatitis C virus polymerase.

1.40 "Research Program" shall mean the collaborative research effort between the parties as described in Attachment 2.1 to identify and discover nucleoside and nucleotide analogs which may be useful in the prevention

and/or treatment of infections caused by Hepatitis C virus and other indications.

1.41 "Research Program Term" shall have the meaning set forth in Section 2.8.

1.42 "Royalty Bearing Products" shall mean HCV Products, Anti-Viral Products and Collection Products.

1.43 "Territory" shall mean all countries of the world.

1.44 "Valid Patent Claim" shall mean a claim of an issued and unexpired patent included within Isis Patent Assets, Isis Research Patent Assets or Merck Patent Assets, which has not been revoked or held unenforceable or invalid by a decision of a court or other governmental agency of competent jurisdiction, unappealable or unappealed within the time allowed for appeal, and which has not been disclaimed, denied or admitted to be invalid or unenforceable through reissue or disclaimer or otherwise.

ARTICLE II

RESEARCH PROGRAM

2.1 General. Isis and Merck shall engage in the Research Program upon the terms and conditions set forth in this Agreement. The activities to be undertaken in the course of the Research Program are set forth in this Article II and in Attachment 2.1 which may be amended from time to time upon the mutual agreement of the parties. Isis shall dedicate the efforts of at least (*) during each year of the Research Program Term.

2.2 Description of Research. Isis and Merck will cooperate in the design, synthesis and evaluation of nucleosides and nucleotides as candidate inhibitors of the (*) hepatitis C virus. Isis and Merck chemists will collaborate in the design of the modular synthesis and purification of the (*) Isis will prepare (*) for screening by Merck. Prodrug and other modifications of selected compounds will also be synthesized by Isis to explore structure-activity relationships. It is understood that Merck, in its sole discretion, may also perform the activities to be carried out by Isis. Merck (*) will provide support for the modular syntheses

*CONFIDENTIAL TREATMENT REQUESTED

at Isis by supplying (as agreed by Isis and Merck) pre-weighed samples, with structures, of various starting materials from the Merck proprietary chemical compound collection. All biochemical and biological studies of (*) prepared by Isis, which will be directed to the identification and optimization of lead compounds, will be performed by Merck. It is understood that Merck's activities under the Research Program may also, in Merck's discretion, be carried out by Merck's Affiliates and at other Merck sites.

2.3 Conduct of Research. Isis and Merck each shall conduct the Research Program in a good scientific manner, and in compliance in all material respects with all requirements of applicable laws, rules and regulations and all applicable standard laboratory practices to attempt to achieve their objectives efficiently and expeditiously. Isis and Merck each shall proceed diligently with the work set out in the Research Program by using their respective good faith efforts.

2.4 Joint Research Committee. The parties hereby establish a joint research committee to direct and monitor the Research Program as follows:

2.4.1 Composition of the Committee. The Research Program shall be conducted under the direction of a joint research committee (the "Joint Research Committee") comprised of three named representatives of Merck and three named representatives of Isis. Each of Merck and Isis shall appoint its respective representatives to the Joint Research Committee, and from time to time may substitute one or more of its representatives, in its sole discretion, effective upon notice to the other Party of

such change. It is anticipated that these representatives shall have appropriate technical credentials and knowledge, and ongoing familiarity with the Research Program. The Merck representatives initially shall be (*) and the Isis representatives initially shall be (*) Additional employees of Isis or Merck (or its Affiliates) may from time to time, by mutual consent of the parties, be invited to attend Joint Research Committee meetings. To the extent a party's representative is unable to attend a Joint Research Committee meeting, his or her vote on any matter coming before the Joint Research Committee may be cast by another representative of that party.

2.4.2 Chairman and Vice Chairman. The Chairman of the Joint Research Committee shall be selected by Merck and the Vice Chairman shall be selected by Isis. The Chairman and the Vice Chairman shall be the primary contacts between the parties with respect to the Research Program. Each Party shall notify the other as soon as practicable upon changing this appointment.

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2.4.3 Meetings and Decisions. The Joint Research Committee shall meet at least once each Calendar Quarter at such locations as shall be determined by the Joint Research Committee. Each Party shall bear its own expenses related to attendance of such meetings by its representatives. At the first such meeting, which shall take place within thirty (30) days after the Effective Date, the Joint Research Committee shall discuss any necessary or recommended changes in the Research Program. The Joint Research Committee may meet by means of teleconference or video conference or other similar communications equipment. The Joint Research Committee shall confer and make decisions regarding the status and direction of the Research Program and the other matters specified in the Research Program and shall also advise on issues regarding any technical, budgetary or economic matters relating to the Research Program, provided that the Joint Research Committee shall not have authority to decide on technical, budgetary or economic matters. Decisions of the Joint Research Committee shall be made by a majority of the members. In the event that the Joint Research Committee cannot or does not, after good faith efforts, achieve a majority on an issue, the Chief Executive Officer of Isis, or his designee, acting as the duly authorized representative of Isis, and the Executive Vice President of Merck Research Laboratories, acting as the duly authorized representative of Merck, shall discuss the matter and attempt, in good faith, to reach agreement with respect to such decision. In the event that the Chief Executive Officer of Isis, or his designee, and the Executive Vice President of Merck Research Laboratories shall be unable to reach agreement, Merck shall, in its sole discretion, make the final decision.

2.4.4 Records. The Joint Research Committee shall maintain accurate records to document the discussions and decisions at each meeting. Meeting minutes or summaries shall be prepared in accordance with procedures established by the Joint Research Committee at its first meeting and shall be distributed to all members of the Joint Research Committee after approval of drafts by the Chairman and Vice Chairman.

2.5 Exchange of Information. Merck and Isis, respectively, shall promptly disclose to each other during the Research Program Term or the Extended Research Program Term all Merck Know-How and Isis Know-How and Isis Research Know-How and any relevant Isis Patent Assets. During the term of the Research Program and for a period of ten (10) years thereafter, Isis agrees that Merck (including any agents or Affiliates of Merck) shall have the freedom to operate under Isis Patent Assets for the purpose of performing any Research Program activities or any other activities necessary or useful for the identification or development of

Compounds and/or Derived Compounds (*)

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2.6 Records and Reports.

2.6.1 Records. Isis shall maintain records in sufficient detail and in good scientific manner appropriate for patent and regulatory purposes, which shall be complete and accurate and shall fully and properly reflect all work done and results achieved in the performance of the Research Program.

2.6.2 Copies and Inspection of Records. Merck shall have the right, during normal business hours and upon reasonable notice, to inspect and copy all such records of Isis referred to in Section 2.6.1. Merck shall maintain such records and the information disclosed therein in confidence in accordance with Section 4.1. Merck shall have the right to arrange for its employees, agents and outside consultants to visit Isis 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 Isis.

2.6.3 Progress Reports. Within sixty (60) days following the end of the Research Program Term (or the Extended Research Program Term if applicable), Isis shall provide to the Joint Research Committee a written final report which shall describe the work performed on the Research Program, evaluate the work performed in relation to the goals of the Research Program and provide such other information required by the Research Program or reasonably requested by Merck relating to the progress of the goals or performance of the Research Program. Upon request, Isis shall provide copies of the records described in Section 2.6.1. above.

2.7 Research information and inventions. All information and inventions conceived or reduced to practice in the course of the Research Program:

(a) solely by employees of Isis shall be owned solely by Isis;

(b) solely by employees of Merck (or its agents or Affiliates) shall be owned solely by Merck;

(c) jointly by employees of Isis and Merck (or its Affiliates) shall be owned jointly by Isis and Merck.

Isis shall promptly disclose to Merck the development, making, conception or reduction to practice of the research information and inventions referred to in subsections (a) and (c) herein.

2.8 Research Program Term. The term of the Research Program shall commence on the Effective Date and continue for a period of three years (the "Research Program Term"). Merck may terminate the Research Program Term upon six (6) months prior written notice given at the completion of the second year of the Research

Program Term. Termination will be within six (6) months of the notice. In such event, Merck will be liable for funding of the Research Program until its termination. It is understood that Merck, in its sole discretion, may reduce its efforts under the Research Program during the six month notice period. Unless the Research Program is terminated, the parties may agree to extend the Research Program Term for (a) one or more additional one-year terms or (b) one additional term of a period of at least six (6) months but less than one (1) year (each an "Extended Research Program Term". Neither party may terminate an Extended Research Program Term, other than a termination for cause as set forth in Article 8.3.1. The parties shall agree to any such extension at least ninety

(90) days prior to the end of the current Research Program Term or Extended Research Program Term and shall negotiate in good faith to complete a mutually acceptable schedule of Research Program activities to be carried out during such Extended Research Program Term. The Schedule shall include the number of FTE's to be devoted to the Research Program by Isis during the Extended Research Program Term.

2.9 Use of Compounds. Research Compounds and Derived Compounds will be incorporated by Merck into Merck's chemical compound collection. It is understood that Merck may utilize Research Compounds and Derived Compounds for any purpose, including the provision of samples of such Compounds to third parties, subject to the license granted to Isis in the Isis Field. It is further understood that, subject to the limitations of paragraph 3.5 hereof, Merck may develop such Research Compounds and Derived Compounds for any purpose subject to any royalty obligations set forth in Article 5. Isis Compounds may be screened by Merck only for activity relative to Hepatitis C polymerase and other anti-viral activity and will be returned to Isis at the end of the Research Program, unless Merck is developing such Isis Compound(s) for any anti-viral indication. It is understood that should Merck thereafter abandon development of such Isis Compound(s), Merck will return such Isis Compound(s) to Isis at that time.

2.10 Exclusive Efforts. During the Research Program Term and any Extended Research Program Term, Isis shall work exclusively with Merck in the Research Field. Upon completion of the Research Program Term or any Extended Research Program Term(s), Isis agrees to refrain from conducting any activities in the Research Field for a period equal to the lesser of (*)

To the extent that, at the end of the period set forth in the prior sentence, Merck has an HCV Product in development, pending regulatory approval or on the market, Isis shall continue to refrain from conducting any activities in the Research Field during the pendency of any such activities for a period not to exceed (*) additional years.

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ARTICLE III

LICENSE; DEVELOPMENT AND COMMERCIALIZATION

3.1 License Grant

(a) Isis hereby grants to Merck an exclusive, sublicensable license in the Territory, subject to the rights retained by Isis in Article 3.2, under Isis Research Know-How and Isis Research Patent Assets, to utilize Isis Research Know-How for any and all purposes and to practice all inventions claimed in Isis Research Patent Assets, including but not limited to the right to make, have made, use, import and/or sell Compounds (*) and Licensed Products.

(b) Isis hereby grants to Merck an exclusive, sublicensable license in the Territory, subject to the rights retained by Isis in Article 3.2, under Isis Know-How, to make, have made, use, import and/or sell Compounds (except for a Derived Compound which is an Oligonucleotide) and Licensed Products.

(c) At the time of the approval of an RMC Development Candidate which is a Research Compound, Isis agrees to grant to Merck an exclusive, sublicensable, license in the Territory, subject to the rights retained by Isis in Article 3.2, under those Isis Patent Assets which are necessary or useful to make, have made, use, import and/or sell such Research Compound and Licensed Products which contain such Research Compound.

(d) At the time of approval of an RMC Development Candidate which is a Derived Compound (*) Isis agrees to grant to Merck a non-exclusive, sublicensable license in the Territory, subject to rights retained by Isis in Article 3.2, under those Isis Patent Assets necessary or useful to make, have made, use and/or sell such-Derived

Compounds.

3.2 Isis Retained Rights. Except as specifically set forth herein, Merck is not granted any other license by implication or otherwise and Isis expressly reserves all rights not granted to Merck hereunder. Notwithstanding the licenses granted in Article 3.1, Isis shall retain the right to use Isis Research Know-How and to practice under Isis Research Patent Assets for the purpose of performing its obligations under the Research Program and in the Isis Field. The rights retained by Isis in the Isis Field under this Article 3.2 shall be exclusive, but for a research license granted to Merck and its Affiliates to conduct research in the Isis Field during the term of this Agreement.

3.3 Merck Retained Rights. Except as specifically set forth herein, Isis is not granted any other license by implication or otherwise and Merck expressly reserves all rights not granted to Isis hereunder.

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3.4 Merck Grant. Merck grants to Isis an exclusive, royalty-free, sublicensable license in the Territory under those Merck Patent Assets or Isis Research Patent Assets which are owned by Merck during the Research Term or any Extended Research Term and Merck Know-How to develop, make, have made, use and sell Research Compounds in the Isis Field, subject to a research license retained by Merck and its Affiliates in the Isis Field. In addition, Merck grants to Isis the right to utilize Merck Know-How solely for the purpose of performing its obligations under the Research Program. To the extent a Merck Patent Asset which is filed within one (1) year of the Research Program (i) claims or covers a composition of matter or a process and (ii) prevents Isis from making, having made, using, importing and/or selling a Research Compound in the Isis Field, Merck shall grant Isis an exclusive, royalty-free, sublicensable license in the Territory under such Merck Patent Assets to make, have made, use and/or sell Research Compounds in the Isis Field.

3.5 Development and Commercialization. Merck shall use reasonable efforts, consistent with the usual practice followed by Merck in pursuing the commercialization and marketing of pharmaceutical products of similar market potential, at its own expense, to develop and commercialize one HCV Product and any Royalty Bearing Product for which Merck has been granted a license under Paragraph 3.1(c) or (d) on a commercially reasonable basis in such countries in the Territory where in Merck's reasonable opinion it is commercially viable to do so. In the event that, at any time during the term of the Agreement Merck, in good faith, determines that the use of Compounds for Hepatitis C polymerase inhibition is not scientifically or commercially viable, Merck will have no further due diligence obligation for HCV Products under this Agreement. In the event that Merck determines that the therapeutic target of a Compound for which it has been granted a license under Paragraph 3.1(c) or (d) is no longer scientifically or commercially viable, the license under paragraph 3.1(c) or (d) for such Compound will terminate. To the extent Merck thereafter requests Isis to regrant such license under the terms and conditions of this Agreement, Isis will do so unless precluded by a third party agreement.

3.6 (*) Merck may not utilize Isis Intellectual Property to develop inhibitors of (*) nor may Merck utilize Research Compounds identified and/or discovered solely by Isis or jointly by Merck and Isis to identify inhibitors of (*) during the time that Isis is precluded from doing so by the terms of its Collaborative Agreement with (*)

*CONFIDENTIAL TREATMENT REQUESTED

ARTICLE IV

CONFIDENTIALITY AND PUBLICATION

4.1 Non-Disclosure and Non-Use Obligations. All Proprietary Information disclosed by one Party to the other Party hereunder shall be maintained in confidence and shall not be disclosed to any non-party or used for any purpose except as expressly permitted herein without the prior written consent of the disclosing Party. The foregoing non-disclosure and non-use obligations shall not apply to the extent that such Proprietary Information:

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

(b) is properly in the public domain;

(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, as documented by written records.

4.2 Permitted Disclosure of Proprietary Information. Notwithstanding Section 4.1, 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 patents subject to this Agreement, or to gain approval to conduct clinical trials or to market Licensed Product pursuant to this Agreement, but such disclosure may be only to the extent reasonably necessary to obtain such patents or authorizations;

(b) by Merck to its permitted sublicensees, agents, consultants, Affiliates and/or other third parties for the research and development, manufacturing and/or marketing of Compound(s) and/or Licensed Product(s) (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 notice is promptly delivered to the non-disclosing Party in order to provide an opportunity to challenge or limit the disclosure obligations.

4.3 Dual Information. It is understood that Isis Research Know-How will be deemed to be Proprietary Information of both Merck and Isis.

4.4 Publication and Public Disclosures. Merck and Isis each acknowledge the other Party's interest in publishing its research results. Each Party also recognizes the mutual interest in obtaining valid patent protection and in protecting business interests and trade secret information. Consequently, either Party wishing to make a publication or to make an oral disclosure regarding any activity of the Research Program shall deliver to the other Party a copy of the proposed written publication or an outline of an oral disclosure at least sixty (60) days prior to submission for publication or presentation. The reviewing Party shall have the right (a) to propose modifications to the publication or oral disclosure for patent reasons, trade secret reasons or business reasons or (b) to request a reasonable delay in publication or oral disclosure in order to protect patentable information. If the reviewing Party requests a delay, the publishing or disclosing Party shall delay submission or presentation for a period of sixty (60) days to enable patent applications protecting each Party's rights in such information to be filed in accordance with Article VII below. Upon expiration of such sixty (60) days, the publishing Party shall be free to proceed with the publication or oral disclosure. If the reviewing Party requests modifications to the publication or oral disclosure, the publishing Party shall edit such publication to prevent disclosure of trade secret

or proprietary business information prior to submission of the publication or prior to oral disclosure.

ARTICLE V

PAYMENTS; ROYALTIES AND REPORTS

5.1 Commitment Fee and Option Payment. In consideration for Isis's commitment to perform its obligations under the Research Program and for access to the Isis Intellectual Property granted hereunder, Merck shall pay to Isis a non-refundable commitment fee of (*) within thirty (30) days after the Effective Date.

5.2 Research Program Funding. In consideration for Isis's performance of its obligations under the Research Program and subject to the terms and conditions contained herein, Merck shall pay Isis:

(a) During the First Three Years of the Research Program Term: an amount equal to (*) per year payable in four quarterly installments of (*) for a minimum of (*) FTE's for each year. The first such annual installment shall be due no later than June 30, 1998. The remaining installments shall be due at the end of each succeeding calendar quarter.

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(b) For any Additional Year(s) of the Research Program Term: If the Research Program Term is extended for one (1) or more subsequent periods in accordance with Section 2.8 above, payments for such additional year or years shall be negotiated annually, based upon an adjusted FTE rate calculated as follows multiplied by the agreed upon number of FTE's. The FTE rate shall be determined for the first extension by applying the percentage change in the Consumer Price Index for urban wage earners and clerical workers - U.S. City Average, from December 1, 1999 to May 30, 2001 to the FTE rate in effect during the Research Program of (*). For any additional extension, the percentage change in the Index for the twelve (12) months preceding the extension shall be applied to the current FTE rate in effect.

5.3 Milestone Payments.

5.3.1 Subject to the terms and conditions contained in this Agreement, Merck shall pay to Isis the following non-refundable milestone payments as set forth in this Article V:

(a) (*) upon approval by Merck's Research Management Committee (or its successors) in its sole discretion, of a Compound as (*)

(b) (*)

(c) (*)

(d) (*)

and

(e) (*)

5.3.2 (*)

5.3.3 (*)

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5.3.4 (*)

5.3.5 (*)

5.3.6 In the event Milestones are paid pursuant to Sections 5.3.1-5.3.5 for a Royalty Bearing Product and the Royalty Bearing Product is thereafter developed for an indication which would have incurred greater Milestones if the product had initially been developed for the additional indication, the greater Milestone payments will apply and the Royalty Bearing Product will be considered to have been developed for the additional indication initially for purposes of the Milestones.

5.3.7 In addition to the milestones set forth above, Merck shall pay Isis (*) in consideration of Isis's efforts in identifying Research Compounds for the prevention and/or treatment of infections caused by Hepatitis C virus, in the event Merck elects to continue efforts to pursue an HCV Product at the conclusion of the Research Program Term or within (3) months thereafter.

5.3.8 Merck shall notify Isis in writing within thirty (30) days after the achievement of each milestone, and such notice shall be accompanied by payment of the appropriate milestone payment.

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5.3.9 (*)

5.4 Royalties.

5.4.1 Royalties Payable By Merck. Subject to the terms and conditions of this Agreement, for each Royalty Bearing Product, Merck shall pay to Isis royalties on a country-by-country basis as follows:

(a) if the sale of an HCV Human Product would, but for the licenses granted under this Agreement, infringe a Valid Patent Claim of an Isis Patent Asset, an Isis Research Patent Asset or a Merck Patent Asset covering the sale of such product in the country of sale, Merck shall pay a royalty of (*) of Net Sales (i) in the case of an Isis Patent Asset or an Isis Research Patent Asset, until the last to expire of such patent(s) or (ii) in the case of a Merck Patent Asset, (*)

(b) for sales of HCV Human Product(s) other than those covered in Subsection 5.4.1(a) above, Merck shall pay a royalty of (*) of Net Sales for a period of (*) from First Commercial Sale in each country;

(c) if the sale of an Anti-Viral Human Product would, but for the licenses granted pursuant to this Agreement, infringe a Valid Patent Claim of an Isis Patent Asset, an Isis Research Patent Asset or a Merck Patent Asset in the country of sale, Merck shall pay a royalty of (*) of Net Sales (i) in the case of an Isis Patent Asset or an Isis Research Patent Asset, until the last to expire of such patent(s) or (ii) in the case of a Merck Patent Asset, (*)

(d) for sales of Anti-Viral Human Products, other than those covered in subsections 5.4.1(c) above, Merck shall pay a royalty of (*) of Net Sales for a period of (*) from First Commercial Sale in each country;

(e) if the sale of a Collection Human Product would, but for the license granted under this Agreement, infringe a Valid Patent Claim of an Isis Patent Asset or an Isis Research Patent Asset covering the sale of such product in the country of sale, Merck shall pay a royalty of (*) of Net Sales until the last to expire of such patent(s);

(f) for sales of Collection Human Products other than those covered in subsection 5.4.1(e) above, Merck shall pay a royalty of (*) of Net Sales for a period of (*) from First Commercial Sale in each country;

(g) for Anti-Viral Animal Products and Collection Animal Products, Merck shall pay (*) of the royalties set forth in this Section 5.4.1 for, respectively, the corresponding Anti-Viral Human Products and Collection Human Products;

(h) in the event a Royalty Bearing Product is initially marketed as an (*) and is thereafter marketed as an (*) the royalties set forth in Section 5.4.1(a) and (b), as the case may be, will apply instead of the royalties set forth in Sections 5.4.1 (c) and (d), as the case may be, in each country where an HCV indication is approved commencing with the approval of the HCV indication in each such country.

Royalties on each Royalty Bearing Product at the rate set forth above shall be effective as of the date of First Commercial Sale of a Royalty Bearing Product in a country and shall continue during the term(s) set forth above subject to the following:

(x) that only one royalty shall be due with respect to the same unit of Royalty Bearing Product;

(y) that no royalties shall be due upon the sale or other transfer among Merck, its Affiliates or sublicensees, but in such cases the royalty shall be due and calculated upon Merck's or its Affiliate's or its sublicensee's Net Sales to the first-independent third party; and

(z) no royalties shall accrue on the disposition of Royalty Bearing Products in reasonable quantities by Merck, its Affiliates or sublicenses as sample(s) (promotion or otherwise) or as donations (for example, to non-profit institutions or government agencies).

5.4.2 No Other Royalties. It is understood that no royalties shall be due and owing to Isis by Merck on sales of Licensed Products which are not Royalty Bearing Products.

5.4.3 Managed Pharmaceutical Contract. Merck may sell Royalty Bearing Products to an independent third party (such as a retailer or wholesaler) and may subsequently perform services relating to Royalty Bearing Products and other products under a managed pharmaceutical benefits contract or other similar contract. In such cases, it is agreed by the parties that Net Sales shall be based on the invoice price to an independent retailer or wholesaler, as set

forth in the definition of Net Sales in Article I hereof, notwithstanding that Merck may receive compensation arising from the performance of such services.

5.4.4 Change in Sales Practices. The parties acknowledge that during

the term of this Agreement, Merck's sales practices for the marketing and distribution of Royalty Bearing Products may change to the extent to which the calculation of the payment for royalties on Net Sales may become impractical or even impossible. In such event the parties agree to meet and discuss in good faith new ways of compensating Isis to the extent currently contemplated under Section 5.4.1.

5.4.5 Royalties for Bulk Compound. In those cases where Merck sells bulk Compound rather than a Royalty Bearing Product in packaged form to an independent third party, the royalty obligations of this Article V shall be applicable to the bulk Compound sold.

5.4.6 Compulsory Licenses. If a compulsory license is granted to a third party with respect to a Royalty Bearing Product in any country in the Territory with a royalty rate lower than the royalty rate provided by Section 5.4.1., then the royalty rate to be paid by Merck on Net Sales in that country under Section 5.4.1 shall be reduced to the rate paid by the compulsory Third Party licensee.

5.4.7 Third Party Licenses. If one or more licenses from a third party or parties are required by Merck, its Affiliates and/or sublicensees in order to develop, make, have made, use, sell or import Royalty Bearing Products, (*) of any royalties actually paid under such third party licenses by Merck for sale of such Royalty Bearing Product shall be creditable against the royalty payments to be paid to Isis by Merck with respect to the sale of such Royalty Bearing Products in such country, provided, however, that the royalties set forth in Article 5.4.1 shall not be reduced to less than (*) of the amounts set forth therein. Unused credits may be carried over into subsequent royalty periods.

5.5 Reports; Payment of Royalty. Following the First Commercial Sale of a Royalty Bearing Product and during the term of the Agreement, Merck shall furnish to Isis a quarterly written report for the Calendar Quarter showing all Net Sales of Royalty Bearing Products subject to royalty payments sold by Merck, its Affiliates and its sublicensees in the Territory during the reporting period and the royalties payable under this Agreement. Reports shall be due on the thirtieth (30th) day following the close of each Calendar Quarter. Royalties shown to have accrued by each royalty report shall be due and payable on the date such royalty report is due. Merck shall keep complete and accurate records in sufficient detail to enable the royalties payable hereunder to be determined.

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5.6 Pass Through Royalties. In the event the licenses granted by Isis under Article 3 would include rights licensed to Isis by a third party, Isis shall inform Merck prior to providing such rights to Merck, and shall advise Merck of any payments that would be due to the third party. In the event that Merck is agreeable to making such payments, Isis will include the third party rights in the license grant to Merck. The parties will discuss in good faith a reasonable apportionment to Merck of fees which are not measured by Net Sales of Compounds or Licensed Products.

5.7 Audits.

(a) Upon the written request of Isis and not more than once in each Calendar Year, Merck shall permit an independent certified public accounting firm of nationally recognized standing selected by Isis and reasonably acceptable to Merck, to have access during normal business hours to such of the records of Merck as may be reasonably

necessary to verify the accuracy of the royalty reports hereunder for any year ending not more than twenty-four (24) months prior to the date of such request. The accounting firm shall disclose to Isis only whether the royalty reports are correct or incorrect and the specific details concerning any discrepancies. Upon the expiration of twenty-four (24) months following the end of any year, the calculation of royalties payable with respect to such year shall be binding and conclusive upon Isis, and Merck and its sublicensees shall be released from any liability or accountability with respect to royalties for such year.

(b) If such accounting firm correctly concludes that additional royalties were owed during such period, Merck shall pay the additional royalties within thirty (30) days of the date Isis delivers to Merck such accounting firm's written report so correctly concluding. The fees charged by such accounting firm shall be paid by Isis unless the additional royalties owed by Merck exceed (*) of the royalties paid for the royalty period subject to the audit, in which case Merck shall pay the reasonable fees of the accounting firm.

(c) Merck shall include in each sublicense granted by it pursuant to this Agreement a provision requiring the sublicensee to make reports to Merck, to keep and maintain records of sales made pursuant to such sublicense and to grant access to such records by Isis's independent accountant to the same extent required of Merck under this Agreement.

(d) Isis shall 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 shall cause its accounting firm to enter into an acceptable confidentiality agreement with Merck obligating it to retain all such financial information in confidence pursuant to such confidentiality agreement.

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5.8 Payment Exchange Rate. All payments to Isis under this Agreement shall 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 Isis from time to time. In the case of sales outside the United States, the rate of exchange to be used in computing the amount of currency equivalent in United States dollars due Isis shall be made at the rate of exchange utilized by Merck in its worldwide accounting system, prevailing on the third to the last business day of the Calendar Quarter to which such payments relate.

5.9 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, Merck shall make such withholding payments as required and subtract such withholding payments from the payments set forth in this Article V. Merck shall submit appropriate proof of payment of the withholding taxes to Isis within a reasonable period of time.

ARTICLE VI

REPRESENTATIONS AND WARRANTIES

6.1 Isis Representations and Warranties. Isis represents and warrants to Merck 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 Program and to grant the licenses granted under Article III hereof,

(b) to the best of its knowledge, Isis has not previously assigned, transferred, conveyed or otherwise encumbered its right, title

and interest in the Isis Intellectual Property so as to interfere with Isis' ability to perform the Research Program activities or grant the licenses contemplated hereunder;

(c) Isis has not taken nor will not take any action which would, in Isis's good faith judgment, interfere with any obligations of Isis set forth in this Agreement, including but not limited to the obligation to grant Merck the licenses described in Paragraphs 3.1(c) and (d).

6.2 Merck Representations and Warranties. Merck represents and warrants to Isis that as of the date of this Agreement it has the full right, power and authority to enter into this Agreement and to perform the Research Program.

ARTICLE VII

PATENT MATTERS

7.1 Filing, Prosecution and Maintenance of Patents. Merck shall have the first right to file, prosecute and maintain the Isis Research Patent Assets upon appropriate consultation with Isis and Isis shall cooperate fully in the filing and prosecution of such patents. In the event that Merck decides not to file, prosecute or maintain the Isis Research Patent Assets, Isis may do so. In each case, the filing party shall consult with the non-filing party with respect thereto, and shall supply the non-filing party with a copy of the application as filed, together with notice of its filing date and serial number. Each party shall keep the other party advised of the status of the actual and prospective patent filings. Isis shall promptly give notice to Merck of the grant, lapse, revocation, surrender, invalidation or abandonment of any Isis Research Patent Asset or Isis Patent Asset licensed or sub-licensed to Merck by Isis for which Isis is responsible and Merck shall give such notice to Isis for Isis Research Patent Assets for which Merck is responsible. The Party that is the filing party under this Section shall be responsible for the payment of all costs and expenses related to such filing.

7.2 Right of Other Parties to Prosecute and Maintain Patents. Any Party having the first right to file, prosecute and maintain the patent applications and patents referred to in Section 7.1 shall give notice to the other Party of any desire to cease prosecution and/or maintenance of such patent and, in such case, shall permit the other Party, at the other Party's sole discretion, to continue prosecution or maintenance at its own expense.

7.3 Interference, Opposition, Reexamination and Reissue.

(a) Each Party, within ten (10) days of learning of such an event, shall inform the other of any request for, or filing or declaration of, any interference, opposition or reexamination relating to Isis Research Patent Assets. Merck and Isis thereafter shall consult and cooperate fully to determine an appropriate course of action with respect to any such proceeding and shall agree upon the Parties' rights of review and approval of submissions relating to such proceeding, provided, that Merck shall have the first right to control any such proceeding.

(b) In connection with any interference, opposition, reissue, or reexamination proceeding relating to Isis Research Patent Assets, Merck and Isis will cooperate fully and will provide each other with any information or assistance that either reasonably may request. Merck shall keep Isis informed of developments in any such action or proceeding, including, to the extent permissible, the status of any settlement negotiations and the terms of any offer related thereto.

(c) Merck shall bear the expense of any interference, opposition, reexamination, or reissue proceeding relating to Isis Research Patent Assets, provided that Merck is prosecuting the interference or opposition or that Merck has prosecuted the application resulting in the re-examination or reissue.

7.4 Enforcement and Defense.

(a) Each Party shall promptly give the other party notice of any infringement of Isis Research Patent Assets, or any misappropriation or misuse of Isis Research Know-How, that comes to such Party's attention. The Parties shall thereafter consult and cooperate fully to determine a course of action, including, without limitation, the commencement of legal action by one or both of the Parties. Merck shall have the first right to initiate and prosecute such legal action at its own expense and in the name of Merck and if necessary, Isis, or to control the defense of any declaratory judgment action relating to Isis Research Patent Assets or Isis Research Know-How. Merck shall promptly inform Isis if it elects not to exercise such first right, and Isis thereafter shall have the right either to initiate and prosecute such action or to control the defense of such declaratory judgment action in the name of Isis.

(b) If Merck elects not to initiate and prosecute an infringement action as provided in Subsection 7.4(a), and Isis elects to do so, the cost of any agreed upon course of action, including the costs of any legal action commenced or the defense of any declaratory judgment, shall be borne solely by Isis.

(c) For any such legal action, in the event that any Party is unable to initiate or prosecute such action solely in its own name, the other Party will join such action voluntarily and will execute and cause its Affiliates under its control to execute all documents necessary for the Party to prosecute and maintain such action. In connection with any such action, the Parties will cooperate fully and will provide each other with any information or assistance that either reasonably may request Each Party shall keep the other informed of developments in any such action or proceeding, including, to the extent permissible by law, the status of any settlement negotiations and the terms of any offer related thereto.

(d) Any recovery obtained by Merck or Isis shall be shared as follows:

(i) the Party that initiated and prosecuted the action shall recoup all of its costs and expenses incurred in connection with the action, whether by settlement or otherwise;

(ii) the other Party shall then, to the extent possible, recover its costs and expenses incurred in connection with the action;

(iii) the remaining recovery shall be allocated between the parties on a pro rata basis under which Isis shall receive a proportion based on the royalties it lost and Merck shall receive a proportion based on its lost profits.

(e) Isis shall inform Merck of any certification regarding any Isis

Research Patent Assets it has received pursuant to either 21 U.S.C. Sections 355(b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) or under Canada's Patented Medicines (Notice of Compliance) Regulations Article 5 and shall provide Merck with a copy of such certification within five (5) business days of receipt. Isis's and Merck's rights with respect to the initiation and prosecution of any legal action as a result of such certification or any recovery obtained as a result of such legal action shall be allocated as defined in Subsections 7.4(a) through (d).

7.5 Patent Term Restoration. The Parties shall cooperate in obtaining patent term restoration or supplemental protection certificates or their equivalents in any country in the Territory where applicable. If elections with respect to obtaining such patent term restoration are to be made, Merck shall have the right to make the election and Isis shall abide by such election.

ARTICLE VIII

TERM AND TERMINATION

8.1 Term and Expiration. This Agreement shall be effective as of the Effective Date and unless terminated earlier pursuant to Sections 8.2 or 8.3 below, the term of-this Agreement shall continue in effect until expiration of all royalty obligations hereunder. Upon expiration of this Agreement due to expiration of all royalty obligations hereunder, Merck's licenses pursuant to Section 3.1 shall become fully paid-up, perpetual licenses.

8.2 Termination by Notice. Notwithstanding anything contained herein to the contrary, after expiration or termination of the initial Research Program Term or any Extended Research Program Term, Merck shall have the right to terminate this Agreement at any time by giving ninety (90) days advance written notice to Isis. In the event of such termination, (i) the rights and obligations hereunder, including any payment obligations not due and owing as of the termination date shall terminate and (ii) Merck shall have no further rights with respect to Isis Intellectual Property, other than the right to utilize Research Compounds and Derived Compounds in its chemical collection for any purpose, subject to the payment by Merck of milestones and royalties set forth in Article 5, including royalties on HCV Products and Anti-Viral Products.

8.3 Termination.

8.3.1 Termination for Cause. Any Party may terminate this Agreement by notice to the other Party at any time during the term of this Agreement:

(a) if the other Party is in breach of its material obligations hereunder by causes and reasons within its control and has not cured such breach within ninety (90) days after notice requesting cure of the breach; or

(b) 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 shall only become effective if the Party consents to the involuntary bankruptcy or such proceeding is not dismissed within ninety (90) days after the filing thereof.

8.3.2 Effect of Termination for Cause on License.

(a) In the event that Merck terminates this Agreement under Section 8.3.1(a), Merck's licenses pursuant to this

Agreement shall become perpetual licenses, and Isis shall, within one month from such termination, return or cause to be returned to Merck all substances or compositions delivered or provided by Merck hereunder, as well as any other materials provided by Merck. It is understood that in the event Merck contends it suffers damages as a result of the breach, Merck may place a portion of the payments to be made by Merck pursuant to Article 5 that would reasonably cover Merck's alleged damages, into an interest-bearing escrow account pending resolution of any dispute between the parties relating to the material breach or termination of the agreement, including a dispute over damages, pursuant to paragraph 9.6.

(b) In the event that Isis terminates this Agreement under Section 8.3.1(a), Merck's exclusive licenses set forth under Article 3 will terminate and become non-exclusive. Merck shall pay to Isis fifty percent (50%) of the royalty payments set forth in Article 5. No milestone payments will be due from Merck.

(c) In the event Merck terminates this Agreement under Section 8.3.1(b) or this Agreement is otherwise terminated under 8.3.1(b), all rights and licenses granted pursuant to this Agreement are, and shall 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 Merck, as a licensee of such rights under this Agreement, shall 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 Isis under the Bankruptcy Code, Merck shall 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 therefore by Merck. Such intellectual property and all embodiments thereof shall be promptly delivered to Merck (i) upon any such commencement of a bankruptcy proceeding upon written request therefore by Merck, unless Isis elects to continue to perform its respective obligations under this Agreement or (ii) if not delivered under (i) above, upon the rejection of this Agreement by or on behalf of Isis, as the case may be, upon written request therefor by Merck.

8.4 Effect of Expiration or Termination. Expiration or termination of this Agreement shall not relieve the parties of any obligation accruing prior to such expiration or termination, and Merck shall be obligated to pay and shall pay to Isis, within thirty (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 IV shall survive the expiration or termination of this Agreement and shall continue in effect for (*) years from the date of expiration or termination. Any expiration or early termination of this Agreement shall be without prejudice to the rights of any Party against the others accrued or accruing under this Agreement prior to termination, including the obligation to pay royalties for Royalty Bearing Product(s) sold prior to such termination.

ARTICLE IX

PUBLICITY

9.1 Public Disclosure. Neither party may make a public announcement or other disclosure of the terms of this Agreement or its existence, except as may be required by law or if the text of such announcement is agreed to in writing by the parties.

ARTICLE X

MISCELLANEOUS

10.1 Force Majeure. No Party shall be held liable or responsible to the other Party nor be deemed to have defaulted under or breached the Agreement for failure or delay

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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. The affected Party shall notify the other Party of such force majeure circumstances as soon as reasonably practical.

10.2 Assignment. The Agreement may not 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 an Affiliate or in connection with the transfer or sale of all or substantially all of its assets related to a Licensed Product or its business, or in the event of its merger or consolidation or change in control or similar transaction. Any permitted assignee shall assume all obligations of its assignor under this Agreement.

10.3 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 shall 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 shall 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.

10.4 Notices. All notices or other communications which are required or permitted hereunder shall be in writing and sufficient if delivered personally, sent by telecopier (and promptly confirmed by personal delivery, registered or certified mail or overnight courier), sent by nationally-recognized overnight courier or sent by registered or certified mail, postage prepaid, return receipt requested, addressed as follows:

if to Isis, to: Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008
Attention: Chief Executive Officer
Telecopier No.: 760-931-0265

with a copy to: Attention: General Counsel
Telecopier No.: 760-431-9448

if to Merck, to: Merck & Co., Inc.
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889-0100
Attention: Office of Secretary
Telecopier No.: 908-735-1246

with a copy to: Attention: Office of Assistant General Counsel Telecopier No.: 908-735-1370

or to such other address as the Party to whom notice is to be given may have furnished to the other Party in writing in accordance herewith. Any such communication shall be deemed to have been given when delivered if personally delivered or sent by telecopier on a business day, on the business day after dispatch if sent by nationally-recognized overnight courier and on the third business day following the date of mailing if sent by mail.

10.5 Applicable Law. The Agreement shall be governed by and construed in accordance with the laws of the State of New York and the United States without reference to any rules of conflict of laws or renvoi.

10.6 Dispute Resolution. The Parties agree to attempt initially to solve all claims, disputes, or controversies arising under, out of, or in connection with this Agreement by conducting good faith negotiations. If the Parties are unable to settle the matter between themselves, the matter shall thereafter be resolved by a final and binding arbitration. Whenever a Party shall decide to institute arbitration proceedings, it shall give written notice to that effect to the other Party. The Party giving such notice shall refrain from instituting the arbitration proceedings for a period of sixty (60) days following such notice. During such period, the Parties shall make good faith efforts to amicably resolve the dispute without arbitration. Any arbitration hereunder shall be conducted under the rules of the American Arbitration Association. Each such arbitration shall be conducted by a panel of three arbitrators: one arbitrator shall be appointed by each of Merck and Isis and the third shall be appointed by the American Arbitration Association. Any such arbitration shall be held in Dallas, Texas. The arbitrators shall have the authority to grant specific performance. Judgment upon the award so rendered may be entered in any court having jurisdiction or application may be made to such court for judicial acceptance of any award and an order of enforcement, as the case may be. In no event shall 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.

10.7 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.

10.8 Headings. The captions to the several 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.

10.9 Independent Contractors. It is expressly agreed that the Parties shall be independent contractors and that the relationship between the Parties shall not constitute a partnership, joint venture or agency. No Party shall have the authority to make any statements, representations or commitments of any kind, or to take any action, which shall be binding on the other Parties, without the prior consent of such other Parties.

10.10 Waiver. The waiver by a Party hereto of any right hereunder or the

failure to perform or of a breach by another Party shall 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.

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

IN WITNESS WHEREOF, the Parties have executed this Agreement as of the date first set forth above.

MERCK & CO., INC.	ISIS PHARMACEUTICALS, INC.
BY: /s/ Raymond V. Gilmartin	BY: /s/ B. Lynne Parshall
Name: Raymond V. Gilmartin	Name: B. Lynne Parshall
Title: Chief Executive Officer	Title: Executive Vice President

Research Program

Discovery of Inhibitors of HCV Polymerase

Isis' Activities

Isis will prepare (*) screening by Merck. SAR studies (*) will be performed on selected compounds. Particular attention will be paid to accelerated synthesis and purification processes. The following compounds will be synthesized:

1. a. A series of (*)
   b. A series of (*)

   C. A series of (*)
   d. A series of (*)

2. (*)

3. (*)

4. (*)

5. (*)

Merck's Activities

A. Merck chemists at (*) will provide support to the modular syntheses at Isis by supplying (as agreed by Isis and Merck) pre-weighed samples, with structures, of various starting materials from the Merck proprietary Sample Collection.

B. All biochemical and biological studies of (*) and its inhibition by (*) prepared by Isis, which will be directed to the identification and optimization of lead compounds, will be performed at (*) in the Department of Antiviral Research.

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Biochemical analyses will include:

1. Purification of the (*) and any related accessory proteins deemed necessary during the course of this collaboration for the catalysis of (*)

2. Characterization of the (*) activity to allow facile design of necessary assay protocols for analyses of inhibition;

3. Any kinetic studies when of interest and if necessary. For example, investigations of (*)

Mechanistic studies will include:

1. Determinations of percentage (%) inhibition of (*) with use of selected (*)

2. Determinations of (*) for selected (*), as determined jointly by (*) and ISIS, with use of (*)

3. Determination of mode of inhibition for selected (*)

4. Counter-screening hits against (*)

Biological studies will include:

1. Determination of antiviral activity using both a (*) (These assays are currently in place and can be scaled up to evaluate large numbers of compounds as necessary.)

2. Characterization of biological activity on (*)

3. Optimization and characterization of the (*)

4. Mechanistic analysis of biological activity including (*)

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Other biological, biochemical and/or enzymatic analyses for the optimization of lead (*) will also be performed as necessary.

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<ARTICLE> 5
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THIS SCHEDULE CONTAINS SUMMARY FINANCIAL INFORMATION DERIVED FROM THE COMPANY'S CONDENSED BALANCE SHEET AS OF JUNE 30, 1998 (UNAUDITED) AND CONDENSED STATEMENTS OF OPERATIONS FOR THE SIX MONTHS ENDED JUNE 30, 1998 (UNAUDITED) AND IS QUALIFIED IN ITS ENTIRETY BY REFERENCE TO SUCH FINANCIAL STATEMENTS.
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