

SECURITIES AND EXCHANGE COMMISSION  
WASHINGTON, DC 20549

FORM 10-Q

(MARK ONE)

/X/ QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(D) OF THE SECURITIES  
EXCHANGE ACT OF 1934

For the quarterly period ended September 30, 1996  
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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  
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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)

(619) 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

25,703,602 shares

-----  
(Class)

-----  
(Outstanding at October 24, 1996)

EXHIBIT INDEX: Located at page number 11.

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

ASSETS

	September 30, 1996	December 31, 1995
	----- (Unaudited)	----- (Note)
Current assets:		
Cash and cash equivalents	\$ 25,784	\$ 46,463
Short-term investments	35,749	30,944
Prepaid expenses and other current assets	1,170	1,638
	-----	-----
Total current assets	62,703	79,045
Property, plant and equipment, net	15,698	14,631
Patent costs, net	5,664	4,773
Deposits and other assets	796	1,120
	-----	-----
	\$ 84,861	\$ 99,569
	=====	=====

LIABILITIES AND STOCKHOLDERS' EQUITY

Current liabilities:		
Accounts payable	\$ 940	\$ 997
Accrued payroll and related expenses	1,380	1,249
Accrued liabilities	3,648	2,838
Deferred contract revenues	8,877	8,913
Current portion of long term debt and capital lease obligations	5,061	5,008
	-----	-----
Total current liabilities	19,906	19,005
Long-term debt and capital lease obligations, less current portion	4,951	4,714
Stockholders' equity:		
Common stock, \$.001 par value; 50,000,000 shares authorized, 25,687,000 shares and 25,249,000 shares issued and outstanding at September 30, 1996 and December 31, 1995, respectively	26	25
Additional paid-in capital	174,780	172,253
Unrealized gain on investments	102	118
Accumulated deficit	(114,904)	(96,546)
	-----	-----
Total stockholders' equity	60,004	75,850
	-----	-----
	\$ 84,861	\$ 99,569
	=====	=====

Note: The balance sheet at December 31, 1995 has been derived from the audited financial statements at that date.

See accompanying notes.

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

	Three months ended September 30,		Nine months ended September 30,	
	1996	1995	1996	1995
	-----	-----	-----	-----
Revenues:				
Research and development revenue under collaborative agreements	\$ 5,142	\$ 3,710	\$ 15,220	\$ 9,578
Interest income	944	778	3,005	1,780
	-----	-----	-----	-----
	6,086	4,488	18,225	11,358

## Expenses:

Research and development	10,219	9,841	31,247	25,200
General and administrative	1,572	1,270	4,571	3,964
Interest expense	280	266	766	843
	-----	-----	-----	-----
	12,071	11,377	36,584	30,007
	-----	-----	-----	-----
Net loss	\$ (5,985)	\$ (6,889)	\$ (18,359)	\$ (18,649)
	=====	=====	=====	=====
Net loss per share	\$ (.23)	\$ (.32)	\$ (.72)	\$ (.91)
	=====	=====	=====	=====
Weighted average common shares	25,671	21,728	25,494	20,447
	=====	=====	=====	=====

See accompanying notes.

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

	Nine months ended September 30,	
	1996	1995
	-----	-----
Cash used in operations:	\$ (15,110)	\$ (8,152)
Investing activities:		
Short-term investments	(4,805)	(2,740)
Property and equipment	(853)	(352)
Other assets	(691)	(326)
	-----	-----
Net cash used in investing activities	(6,349)	(3,418)
	-----	-----
Financing activities:		
Net proceeds from issuance of common stock	2,528	25,456
Principal payments on debt and capital lease obligations	(1,748)	(1,981)
	-----	-----
Net cash provided from financing activities	780	23,475
	-----	-----
Net increase (decrease) in cash and cash equivalents	(20,679)	11,905
Cash and cash equivalents at beginning of period	46,463	12,926
	-----	-----
Cash and cash equivalents at end of period	\$ 25,784	\$ 24,831
	=====	=====
SUPPLEMENTAL DISCLOSURES OF CASH FLOW INFORMATION:		
Interest paid	\$ 760	\$ 803
SUPPLEMENTAL DISCLOSURES OF NON-CASH INVESTING AND FINANCING ACTIVITIES		
Additions to capital lease obligations for acquisitions of property, plant and equipment	\$ 2,038	\$ 143

See accompanying notes.

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ISIS PHARMACEUTICALS, INC.

NOTES TO FINANCIAL STATEMENTS

1. BASIS OF PRESENTATION

The unaudited interim financial statements for the three and nine month periods ended September 30, 1996 and 1995 have been prepared on the same basis as the Company's audited financial statements for the year ended December 31, 1995. 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, 1995 included in the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission.

2. SUBSEQUENT EVENT

In October 1996, the Company borrowed \$8.3 million under a line of credit made available under the terms of its collaborative agreement with Boehringer Ingelheim. The funds will be used to support Isis' share of the collaboration expenses. Borrowings under the line of credit bear interest at the seven year U.S. interbanking rate plus 2.0%. Interest payments are due twice per year with principal repayment due in seven years. The principal may be repaid in cash or stock, at the Company's option.

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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. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that can be proven to be safe and effective for use as human therapeutics, and the endeavor of building a business around such potential products. Actual results could differ materially from those projected in this Form 10-Q. As a result, the reader is cautioned not to rely on these forward-looking statements. These and other risks are described in additional detail in Isis' Annual Report on Form 10-K for the year ended December 31, 1995 filed with the Securities and Exchange Commission, and available from the Company.

Since its inception in January 1989, the Company has devoted substantially all of its resources to its research, drug discovery and development programs. The Company has been unprofitable since its inception and expects to incur additional operating losses for the next several years. The Company has entered into collaborative research and development agreements with pharmaceutical companies that generate cash and revenue to augment the level of research and development activity and to offset portions of its research and development costs. To date, the Company has not received any significant revenue from the sale of products.

RESULTS OF OPERATIONS

The Company had contract revenue of \$5.1 million for the third quarter and \$15.2 million for the nine-month period ended September 30, 1996, compared with \$3.7 million and \$9.6 million, respectively, for the same periods in 1995. The revenue increase was primarily due to revenue received under an expanded collaborative agreement with Ciba-Geigy Limited for the development of two drug

candidates identified through the collaborative research program between Ciba and Isis. Additional revenue from a collaborative agreement with Boehringer Ingelheim International GmbH also contributed to the increase. The Company also had interest income totaling \$0.9 million for the quarter and \$3.0 million for the nine month period, compared with \$0.8 million and \$1.8 million for the same periods in 1995. The increase in interest income was primarily due to higher investment balances in 1996.

Research and development expenses increased to \$10.2 million for the three months and \$31.2 million for the nine months ended September 30, 1996 from \$9.8 million and \$25.2 million during the same periods in 1995. These increases are primarily attributable to an increase in clinical development activities. The Company expects that its research and development expenses will continue to increase as its current preclinical and clinical activities continue and additional preclinical and clinical studies are undertaken.

General and administrative expenses increased to \$1.6 million for the quarter and \$4.6 million for the nine months ended September 30, 1996 from \$1.3 million and \$4.0 million for the same periods in 1995. The Company expects that its general and administrative expenses will increase in the future in support of its expanding operations.

During the quarter ended September 30, 1996, the Company recorded a net loss of \$6.0 million, or \$0.23 per share, compared with \$6.9 million, or \$0.32 per share, for the same period in 1995. During the nine-month period ended September 30, 1996, the Company's net loss amounted to \$18.4 million, or \$0.72 per share, compared to \$18.6 million, or \$0.91 per share for the same period in 1995. The changes in net loss per share from 1995 to 1996 include the effect of increases in the weighted average number of shares outstanding due to the issuance of stock in the second half of 1995 in conjunction with an equity offering and corporate collaborations. The Company expects its operating losses will increase for the remainder of the fiscal year and beyond as its activities grow, and may fluctuate from quarter to quarter as a result of differences in the timing and composition of revenue earned and expenses incurred.

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

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#### LIQUIDITY AND CAPITAL RESOURCES

Since its inception, the Company has financed its operations primarily through the sale of equity securities, raising to date a net aggregate of \$169 million, as of September 30, 1996, from the private and public sale of such securities. The Company has also financed a portion of its operations through contract research revenue, portions of which were paid in advance of work being performed, offsetting the Company's cash usage for operations.

As of September 30, 1996, the Company had cash, cash equivalents and short-term investments totaling \$61.5 million and working capital of \$42.8 million, compared with \$77.4 million and \$60.0 million, respectively, as of December 31, 1995. The decreases in cash and working capital resulted from funding operating losses and making principal repayments on debt and capital lease obligations.

The Company had long-term debt and capital lease obligations at September 30, 1996 totaling \$10.0 million, versus \$9.7 million at December 31, 1995. This increase, which was partially offset by principal repayments on existing obligations, was due to additional capital lease financing. The Company expects that its capital lease obligations will increase over time to fund capital equipment acquisitions required for its expanding business. Lease lines will continue to be used by the Company to the extent that the terms thereof remain commercially attractive. Subsequent to the end of the quarter, the Company borrowed \$8.3 million under a line of credit from Boehringer Ingelheim (see Note 2 to the financial statements). The funds will be used to support Isis' share of the collaboration expenses.

The Company expects to incur substantial additional research and development costs, related primarily to preclinical testing, clinical trials and manufacturing process development and expects losses to continue to increase as the Company's preclinical testing and clinical trial efforts expand. It is the Company's intention to seek additional collaborative research and development relationships with suitable potential corporate partners. There can be no assurance that any agreements resulting from these discussions will successfully reduce the Company's funding requirements, and arrangements with collaborative partners or others may require the Company to relinquish rights to certain of its technologies, product candidates or products. Additional equity or debt financings may be required, and there can be no assurance that these funds will

be available on favorable terms, if at all. If additional funds are raised by issuing equity securities, further dilution to then existing stockholders may result.

The Company believes that its existing available cash, cash equivalents and short-term investments, combined with anticipated interest income, contract revenue and funds available under the line of credit from Boehringer Ingelheim, will be sufficient to meet its anticipated requirements for approximately two years. The Company's future capital requirements will depend on many factors, including continued scientific progress in its research, drug discovery and development programs, the magnitude of these programs and progress with preclinical and clinical trials; the time and costs involved in obtaining regulatory approvals; the costs involved in filing, prosecuting and enforcing patent claims; competing technological and market developments; changes in the existing collaborative research and development relationships; the ability of the Company to establish additional research and development arrangements; and the cost of manufacturing scale-up and effective commercialization activities and arrangements. If adequate funds are not available, the Company may be required to significantly curtail one or more of its research, drug discovery or development programs.

Uncertainties associated with the length and expense of preclinical and clinical testing of any of the Company's products could greatly increase the cost of development of such product and affect the timing of anticipated revenue from product sales, and failure by the Company to obtain regulatory approval for any product will preclude its commercialization. In addition, the failure by the Company to obtain patent protection for its products may make certain of its products commercially unattractive.

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#### PART II - OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

The Company is not party to any legal proceedings.

ITEM 2. CHANGES IN SECURITIES

Not applicable.

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable.

ITEM 4. SUBMISSION OF MATTERS TO A VOTE OF SECURITY HOLDERS

Not applicable.

ITEM 5. OTHER INFORMATION

Not applicable.

ITEM 6. EXHIBITS AND REPORTS ON FORM 8-K

a. Exhibits

The following are exhibits to this Form 10-Q:

- 10.2 Registrant's 1989 Stock Option Plan, as amended.
- 10.3 Revised form of Incentive Stock Option Agreement under the Plan.
- 10.4 Revised form of Supplemental Stock Option Agreement under the Plan.
- 10.7 Registrant's 1992 Non-Employee Directors' Stock Option Plan, as amended.
- 27.1 Financial Data Schedule

b. Reports on Form 8-K

The Company filed no reports on Form 8-K during the quarter ended September 30, 1996.

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ISIS PHARMACEUTICALS, INC.

SIGNATURES

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

ISIS PHARMACEUTICALS, INC.

-----  
(Registrant)

Date: November 11, 1996  
-----

By: /S/ STANLEY T. CROOKE  
-----

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

Date: November 11, 1996  
-----

By: /S/ B. LYNNE PARSHALL  
-----

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

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ISIS PHARMACEUTICALS, INC.

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Registrant's 1989 Stock Option Plan, as amended.

ISIS PHARMACEUTICALS, INC.  
1989 STOCK OPTION PLAN

As Amended September 5, 1991  
As Amended September 4, 1992  
As Amended January 4, 1993  
As Amended December 2, 1993 and January 20, 1994  
As Amended December 7, 1994  
As Amended February 27, 1995 and Amended December 14, 1995  
As Amended September 6, 1996

1. PURPOSE.

(a) The purpose of the Plan is to provide a means by which selected employees and directors (if declared eligible under paragraph 4) of and consultants to Isis Pharmaceuticals, Inc., a Delaware corporation (the "Company"), and its Affiliates, as defined in subparagraph 1(b), may be given an opportunity to benefit from increases in value of the stock of the Company through the granting of (i) incentive stock options, (ii) supplemental stock options, (iii) stock bonuses, and (iv) rights to purchase stock, all as defined below.

(b) The word "Affiliate" as used in the Plan means any parent corporation or subsidiary corporation of the Company, as those terms are defined in Sections 424(e) and (f), respectively, of the Internal Revenue Code of 1986, as amended (the "Code").

(c) The Company, by means of the Plan, seeks to retain the services of persons now employed by or serving as consultants or directors to the Company, to secure and retain the services of new employees/persons capable of filling such positions, and to provide incentives for such persons to exert maximum efforts for the success of the Company.

(d) The Company intends that the rights issued under the Plan ("Stock Awards") will, in the discretion of the Board of Directors of the Company (the "Board") or any committee to which responsibility for administration of the Plan has been delegated pursuant to subparagraph 2(c), be either (i) stock options granted pursuant to paragraph 5 hereof, including incentive stock options as that term is used in Section 422 of the Code ("Incentive Stock Options"), or options which do not qualify as Incentive Stock Options ("Supplemental Stock Options") (together hereinafter referred to as "Options"), or (ii) stock bonuses or rights to purchase restricted stock granted pursuant to paragraph 6 hereof. All Options will be separately designated Incentive Stock Options or Supplemental Stock Options at the time of grant, and in such form as issued pursuant to paragraph 5, and a separate certificate or certificates will be issued for shares purchased on exercise of each type of Option. An Option designated as a Supplemental Stock Option will not be treated as an Incentive Stock Option.

2. ADMINISTRATION.

(a) The Plan will be administered by the Board unless and until the Board delegates administration to a committee, as provided in subparagraph 2(c).

(b) The Board will have the power, subject to, and within the limitations of, the express provisions of the Plan:

(1) To determine from time to time which of the persons

eligible under the Plan will be granted Stock Awards; when and how Stock Awards will be granted; whether a Stock Award will be an Incentive Stock Option, a Supplemental Stock Option, a stock bonus, a right to purchase restricted stock, or a combination of the foregoing; the provisions of each Stock Award granted (which need not be identical), including the time or times when a person will be permitted to purchase or receive stock pursuant to a Stock Award; and the number of shares with respect to which Stock Awards will be granted to each such person.

(2) To construe and interpret the Plan and Stock Awards granted under it, and to establish, amend and revoke rules and regulations for its administration. The Board, in the exercise of this power, may correct any defect, omission or inconsistency in the Plan or in any Stock Award, in a manner and to the extent it will deem necessary or expedient to make the Plan fully effective.

(3) To amend the Plan as provided in paragraph 12.

(4) Generally, to exercise such powers and to perform such acts as the Board deems necessary or expedient to promote the best interests of the Company.

(c) The Board may delegate administration of the Plan to one or more committees, each committee composed of not fewer than 2 members (each, a "Committee"). If administration is delegated to a Committee, that Committee will have, in connection with the administration of the Plan, the powers theretofore possessed by the Board, subject, however, to such resolutions, not inconsistent with the provisions of the Plan, as may be adopted from time to time by the Board. The Board may abolish a Committee at any time and revest in the Board the administration of the Plan. Additionally, and notwithstanding anything to the contrary contained herein, the Board or Committee may delegate to a committee of one or more members of the Board the authority to grant options to certain eligible persons in accordance with guidelines approved by the Board or Committee.

### 3. SHARES SUBJECT TO THE PLAN.

(a) Subject to the provisions of paragraph 11 relating to adjustments upon changes in stock, the stock that may be issued pursuant to Stock Awards granted

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under the Plan will not exceed in the aggregate 8,200,000 shares of the Company's common stock. If any Stock Award granted under the Plan will for any reason expire or otherwise terminate without having been exercised in full, the stock not purchased under such Stock Award will again become available for the Plan.

(b) The stock subject to the Plan may be unissued shares or reacquired shares, bought on the market or otherwise.

(c) An Incentive Stock Option may be granted to an eligible person under the Plan only if the aggregate fair market value (determined at the time the Option is granted) of the stock with respect to which incentive stock options (as defined in the Code) granted after 1986 are exercisable for the first time by such optionee during any calendar year under all Incentive Stock Option plans of the Company and its Affiliates does not exceed \$100,000. If it is determined that an entire Option or any portion thereof does not qualify for treatment as an Incentive Stock Option by reason of exceeding such maximum, such Option or the applicable portion will be considered a Supplemental Stock Option.

### 4. ELIGIBILITY.

(a) Incentive Stock Options may be granted only to employees (including officers) of the Company or its Affiliates. A director of the Company will not be eligible to receive Incentive Stock Options unless such director is also an employee (including an officer) of the Company or any Affiliate. Stock Awards other than Incentive Stock Options may be granted only to employees (including officers) of, directors of or consultants to the Company or its Affiliates.

(b) No person will be eligible for the grant of an Option

under the Plan if, at the time of grant, such person owns (or is deemed to own pursuant to Section 424(d) of the Code) stock possessing more than 10% of the total combined voting power of all classes of stock of the Company or of any of its Affiliates unless the exercise price of such Option is at least 110% of the fair market value of such stock at the date of grant and the term of the Option does not exceed 5 years from the date of grant.

(c) No person will be eligible to be granted Options covering more than 294,873 shares of the Company's common stock in any 12 month period.

5. OPTION PROVISIONS.

Each Option will be in such form and will contain such terms and conditions as the Board or the Committee will deem appropriate. The provisions of separate Options need not be identical, but each Option will include (through incorporation of provisions hereof by reference in the Option or otherwise) the substance of each of the following provisions:

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(a) No Option will be exercisable after the expiration of 10 years from the date it was granted.

(b) The exercise price of each Incentive Stock Option will be not less than 100% of the fair market value of the stock subject to the Option on the date the Option is granted. The exercise price of each Supplemental Stock Option will be not less than 85% of the fair market value of the stock subject to the Option on the date the Option is granted. Notwithstanding the foregoing, an Option (whether an Incentive Stock Option or Supplemental Stock Option) may be granted with an exercise price lower than set forth in the preceding sentences if such Option is granted pursuant to an assumption or substitution for another option in a manner satisfying the provisions of Section 424(a) of the Code.

(c) The purchase price of stock acquired pursuant to an Option will be paid, to the extent permitted by applicable statutes and regulations, either (i) in cash at the time the Option is exercised, or (ii) at the discretion of the Board or the Committee, either at the time of the grant or exercise of the Option, (A) by delivery to the Company of other common stock of the Company, (B) according to a deferred payment or other arrangement (which may include, without limiting the generality of the foregoing, the use of other common stock of the Company) with the person to whom the Option is granted or to whom the Option is transferred pursuant to subparagraph 5(d), or (C) in any other form of legal consideration that may be acceptable to the Board or the Committee.

In the case of any deferred payment arrangement, interest will be payable at least annually and will be charged at the minimum rate of interest necessary to avoid the treatment as interest, under any applicable provisions of the Code, of any amounts other than amounts stated to be interest under the deferred payment arrangement.

(d) An Incentive Option will not be transferable except by will or by the laws of descent and distribution, and will be exercisable during the lifetime of the person to whom the Option is granted only by such person. A Supplemental Stock Option may be transferable at the discretion of the Board or the Committee.

(e) The total number of shares of stock subject to an Option may, but need not, be allotted in periodic installments (which may, but need not, be equal). From time to time during each of such installment periods, the Option may become exercisable ("vest") with respect to some or all of the shares allotted to that period, and may be exercised with respect to some or all of the shares allotted to such period and/or any prior period as to which the Option was not fully exercised. During the remainder of the term of the Option (if its term extends beyond the end of the installment periods), the Option may be exercised from time to time with respect to any shares then remaining subject to the Option. The provisions of this subparagraph 5(e) are subject to any Option provisions governing the minimum number of shares as to which an Option may be exercised.

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(f) The Company may require any optionee, or any person to whom an Option is transferred under subparagraph 5(d), as a condition of exercising any such Option, (1) to give written assurances satisfactory to the Company as to the optionee's knowledge and experience in financial and business matters and/or to employ a purchaser representative reasonably satisfactory to the Company who is knowledgeable and experienced in financial and business matters, and that he or she is capable of evaluating, alone or together with the purchaser representative, the merits and risks of exercising the Option; and (2) to give written assurances satisfactory to the Company stating that such person is acquiring the stock subject to the Option for such person's own account and not with any present intention of selling or otherwise distributing the stock. These requirements, and any assurances given pursuant to such requirements, will be inoperative as to any particular requirement, a determination is made by counsel for the Company that such requirement need not be met in the circumstances under the then applicable securities laws.

(g) An Option will terminate 3 months after termination of the optionee's employment or relationship as a consultant or director with the Company or an Affiliate, unless (i) such termination is due to such person's permanent and total disability, within the meaning of Section 422(c)(6) of the Code, in which case the Option may, but need not, provide that it may be exercised at any time within 1 year following such termination of employment or relationship as a consultant or director; or (ii) the optionee dies while in the employ of or while serving as a consultant or director to the Company or an Affiliate, or within not more than 3 months after termination of such relationship, in which case the Option may, but need not, provide that it may be exercised at any time within 18 months following the death of the optionee by the person or persons to whom the optionee's rights under such Option pass by will or by the laws of descent and distribution; or (iii) the Option by its terms specifies either (a) that it will terminate sooner than 3 months after termination of the optionee's employment or relationship as a consultant or director or (b) that it may be exercised more than 3 months after termination of the relationship with the Company or an Affiliate. This subparagraph 5(g) will not be construed to extend the term of any Option or to permit anyone to exercise the Option after expiration of its term, nor will it be construed to increase the number of shares as to which any Option is exercisable from the amount exercisable on the date of termination of the optionee's employment or relationship as a consultant or director.

(h) The Option may, but need not, include a provision whereby the optionee may elect at any time during the term of his or her employment or relationship as a consultant or director with the Company or any Affiliate to exercise the Option as to any part or all of the shares subject to the Option prior to the stated vesting date of the Option or of any installment or installments specified in the Option. Any shares so purchased from any unvested installment or Option may be subject to a repurchase right in favor of the Company or to any other restriction the Board or the Committee determines to be appropriate.

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(i) To the extent provided by the terms of an Option, the optionee may satisfy any federal, state or local tax withholding obligation relating to the exercise of such Option by any of the following means or by a combination of such means: (1) tendering a cash payment; (2) authorizing the Company to withhold from the shares of the common stock otherwise issuable to the participant as a result of the exercise of the Option a number of shares having a fair market value less than or equal to the amount of the withholding tax obligation; or (3) delivering to the Company owned and unencumbered shares of the common stock having a fair market value less than or equal to the amount of the withholding tax obligation.

#### 6. TERMS OF STOCK BONUSES AND PURCHASES OF RESTRICTED STOCK.

Each stock bonus or restricted stock purchase agreement will be in such form and will contain such terms and conditions as the Board or the Committee will deem appropriate. The terms and conditions of stock bonus or restricted stock purchase agreements may change from time to time, and the terms and conditions of separate agreements need not be identical, but each stock

bonus or restricted stock purchase agreement will include (through incorporation of provisions hereof by reference in the agreement or otherwise) the substance of each of the following provisions as appropriate:

(a) The purchase price under each stock purchase agreement will be such amount as the Board or Committee will determine and designate in such agreement. Notwithstanding the foregoing, the Board or the Committee may determine that eligible participants in the Plan may be awarded stock pursuant to a stock bonus agreement in consideration for past services actually rendered to the Company or for its benefit.

(b) No rights under a stock bonus or restricted stock purchase agreement will be assignable by any participant under the Plan, either voluntarily or by operation of law, except where such assignment is required by law or expressly authorized by the terms of the applicable stock bonus or restricted stock purchase agreement.

(c) The purchase price of stock acquired pursuant to a stock purchase agreement will be paid either: (i) in cash at the time of purchase; (ii) at the discretion of the Board or the Committee, according to a deferred payment or other arrangement with the person to whom the stock is sold; or (iii) in any other form of legal consideration that may be acceptable to the Board or the Committee in their discretion. Notwithstanding the foregoing, the Board or the Committee to which administration of the Plan has been delegated may award stock pursuant to a stock bonus agreement in consideration for past services actually rendered to the Company or for its benefit.

(d) Shares of stock sold or awarded under the Plan may, but need not, be subject to a repurchase option in favor of the Company in accordance with a vesting schedule to be determined by the Board or the Committee.

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(e) In the event a person ceases to be an employee of or ceases to serve as a consultant to the Company or an Affiliate, the Company may repurchase or otherwise reacquire any or all of the shares of stock held by that person which have not vested as of the date of termination under the terms of the stock bonus or restricted stock purchase agreement between the Company and such person.

7. COVENANTS OF THE COMPANY.

(a) During the terms of the Stock Awards granted under the Plan, the Company will keep available at all times the number of shares of stock required to satisfy such Stock Awards.

(b) The Company will seek to obtain from each regulatory commission or agency having jurisdiction over the Plan such authority as may be required to issue and sell shares of stock under the Stock Awards granted under the Plan; provided, however, that this undertaking will not require the Company to register under the Securities Act either the Plan, any Stock Award granted under the Plan or any stock issued or issuable pursuant to any such Stock Award. If, after reasonable efforts, the Company is unable to obtain from any such regulatory commission or agency the authority which counsel for the Company deems necessary for the lawful issuance and sale of stock under the Plan, the Company will be relieved from any liability for failure to issue and sell stock upon exercise of such Stock Awards unless and until such authority is obtained.

8. USE OF PROCEEDS FROM STOCK.

Proceeds from the sale of stock pursuant to Stock Awards granted under the Plan will constitute general funds of the Company.

9. MISCELLANEOUS.

(a) The Board or the Committee will have the power to accelerate the time during which a Stock Award may be exercised or the time during which a Stock Award or any part thereof will vest, notwithstanding the provisions in the Stock Award stating the time during which it may be exercised or the time during which it will vest.

(b) Neither an optionee nor any person to whom an Option is transferred under subparagraph 5(d) will be deemed to be the holder of, or to have any of the rights of a holder with respect to, any shares subject to such Option unless and until such person has satisfied all requirements for exercise of the Option pursuant to its terms.

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(c) Throughout the term of any Option granted pursuant to the Plan, the Company will make available to the holder of such Option, not later than 120 days after the close of each of the Company's fiscal years during the Option term, upon request, such financial and other information regarding the Company as comprises the annual report to the stockholders of the Company provided for in the bylaws of the Company.

(d) Nothing in the Plan or any instrument executed or Stock Award granted pursuant thereto will confer upon any eligible employee, consultant, director or holder of Stock Awards under the Plan any right to continue in the employ of the Company or any Affiliate (or to continue acting as a consultant or director) or will affect the right of the Company or any Affiliate to terminate the employment or consulting relationship or directorship of any eligible employee, consultant, director or holder of Stock Awards under the Plan with or without cause. In the event that a holder of Stock Awards is permitted or otherwise entitled to take a leave of absence, the Company will have the unilateral right to (i) determine whether such leave of absence will be treated as a termination of employment or relationship as consultant or director for purposes of paragraphs 5(g) or 6(e) hereof and corresponding provisions of any outstanding Stock Awards, and (ii) suspend or otherwise delay the time or times at which exercisability or vesting would otherwise occur with respect to any outstanding Stock Awards under the Plan.

#### 10. CANCELLATION AND RE-GRANT OF OPTIONS.

The Board or the Committee will have the authority to effect, at any time and from time to time, with the consent of the affected optionees, (i) the repricing of any or all outstanding Options under the Plan and/or (ii) the cancellation of any or all outstanding Options under the Plan and the grant in substitution therefor of new Options under the Plan covering the same or different numbers of shares of common stock, but having an exercise price per share not less than 85% of the fair market value (100% of the fair market value in the case of an Incentive Stock Option or, in the case of a 10% stockholder (as defined in subparagraph 4(c)), not less than 110% of the fair market value) per share of common stock on the new grant date. Notwithstanding the foregoing, an Option (whether an Incentive stock Option or Supplemental Stock Option) may be granted with an exercise price lower than set forth in the preceding sentence if such Option is granted pursuant to an assumption or substitution for another option in a manner satisfying the provisions of Section 424(a) of the Code.

#### 11. ADJUSTMENTS UPON CHANGES IN STOCK.

(a) If any change is made in the stock subject to the Plan, or subject to any Stock Award granted under the Plan (through merger, consolidation, reorganization, recapitalization, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or otherwise), the Plan and outstanding Stock Awards will be

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appropriately adjusted in the class(es) and maximum number of shares subject to the Plan or an Option under paragraph 4(c) and the class(es) and number of shares and price per share of stock subject to outstanding Stock Awards.

(b) In the event of: (1) a dissolution or liquidation of the Company; (2) a merger or consolidation in which the Company is not the surviving corporation; or (3) a reverse merger in which the Company is the surviving corporation but the shares of the Company's common stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise then to the extent

permitted by applicable law: (i) any surviving corporation will assume any Stock Awards outstanding under the Plan or will substitute similar Stock Awards for those outstanding under the Plan, or (ii) such Stock Awards will continue in full force and effect. In the event any surviving corporation refuses to assume or continue such Stock Awards, or to substitute similar Stock Awards for those outstanding under the Plan, then, with respect to Stock Awards held by persons then performing services as employees or as consultants or directors for the Company, as the case may be, the time during which such Stock Awards become vested or may be exercised will be accelerated and the Stock Awards terminated if not exercised prior to such event.

12. AMENDMENT OF THE PLAN.

(a) The Board at any time, and from time to time, may amend the Plan. However, except as provided in paragraph 11 relating to adjustments upon changes in stock, no amendment will be effective unless approved by the stockholders of the Company within 12 months before or after the adoption of the amendment, where the amendment will:

(i) Increase the number of shares reserved for Stock Awards under the Plan; or

(ii) Modify the requirements as to eligibility for participation in the Plan or the terms of the Plan itself to the extent such modification requires stockholder approval in order for the Plan to satisfy the requirements of Section 422 of the Code.

(b) It is expressly contemplated that the Board may amend the Plan in any respect the Board deems necessary or advisable to provide optionees with the maximum benefits provided or to be provided under the provisions of the Code and the regulations promulgated thereunder relating to employee Incentive Stock Options and/or to bring the Plan and/or Incentive Stock Options granted under it into compliance therewith.

(c) Rights and obligations under any Stock Award granted before amendment of the Plan will not be altered or impaired by any amendment of the Plan

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unless (i) the Company requests the consent of the person to whom the Stock Award was granted and (ii) such person consents in writing.

13. TERMINATION OR SUSPENSION OF THE PLAN.

(a) The Board may suspend or terminate the Plan at any time. Unless sooner terminated, the Plan will terminate on December 31, 2000. No Stock Awards may be granted under the Plan while the Plan is suspended or after it is terminated.

(b) Rights and obligations under any Stock Award granted while the Plan is in effect will not be altered or impaired by suspension or termination of the Plan, except with the consent of the person to whom the Stock Award was granted.

14. EFFECTIVE DATE OF PLAN.

The Plan is effective April 19, 1991.

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EXHIBIT 10.3

Revised form of Incentive Stock Option Agreement under the Plan.

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Optionee: \_\_\_\_\_ Date: \_\_\_\_\_

ISIS PHARMACEUTICALS, INC.  
INCENTIVE STOCK OPTION AGREEMENT

Isis Pharmaceuticals, Inc. (the "Company"), pursuant to its 1989 Stock Option Plan (the "Plan") has this day granted to the undersigned optionee, an option to purchase shares of the common stock of the Company ("Common Stock") as described herein. This option is intended to qualify as an "incentive stock option" within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended from time to time (the "Code"). This option is subject to all of the terms and conditions as set forth herein and on Attachment I hereto, which is incorporated herein in its entirety.

Number of Shares Subject to Option: \_\_\_\_\_

VESTING SCHEDULE:

Number of Shares (installment)	Date of Earliest Exercise (vesting) (1)
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-----	-----
-----	-----

Exercise Price Per Share: \_\_\_\_\_ (2)      Expiration Date: \_\_\_\_\_ (3)  
-----  
Percentage of Full-Time Work: \_\_\_\_\_

Isis Pharmaceuticals, Inc.

By: \_\_\_\_\_      Optionee: \_\_\_\_\_  
Duly authorized on behalf of  
the Board of Directors      Address: \_\_\_\_\_

OPTIONEE:

Acknowledges receipt of the option as described herein and the attachments referenced therein and understands that all rights and liabilities with respect to this option are set forth in the option and the Plan; and acknowledges that as of the date of grant of this option, it sets forth the entire understanding between the optionee and the Company regarding the acquisition of stock in the Company and supersedes all prior oral and written agreements on that subject.

(1) After the first year, the option will vest monthly with 2.08% of the total grant vesting each month; provided, however, that during any period in which the undersigned provides service at less than the Percentage of Full-Time Work set forth above, a reduced number of shares will vest as follows: the percentage of shares which will vest during such period of reduced service will equal (a) the percentage of shares that would vest as set forth on this schedule, multiplied by (b) the percentage of full-time work furnished during the period of reduced service divided by the Percentage of Full Time Work as set forth above. Increases of work percentage up to but not in excess of the Percentage of Full Time Work specified above will result in a corresponding increase in the percentage of shares vesting. This reduction in vesting will not apply during any period of paid leave or the first 20 weeks of a period of unpaid leave. No shares will vest during unpaid leave after the first 20 weeks of such leave. Shares which do not vest because of reductions in work percentage or unpaid leave will be canceled and no longer subject to this option.

(2) Not less than 100% of the fair market value of the Common Stock on the date of grant of this option.

(3) Less than 10 years from the date of grant of this option.

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ATTACHMENT I

TERMS OF INCENTIVE STOCK OPTION

The grant hereunder is in connection with and in furtherance of the Company's compensatory benefit plan for participation of the Company's employees (including officers) and is intended to comply with the provisions of Rule 701 promulgated by the Securities and Exchange Commission under the Securities Act of 1933, as amended (the "Act").

The details of your option are as follows:

1. The total number of shares of Common Stock subject to this option is set forth on the first page of the Incentive Stock Option Agreement. Subject to the limitations contained herein, this option will be exercisable with respect to each installment indicated in the Vesting Schedule set forth on the first page of the Incentive Stock Option Agreement on or after the date of vesting applicable to such installment.

2. (a) The Exercise Price of this option is set forth on the first page of the Incentive Stock Option Agreement and is not less than the fair market value of the Common Stock on the date of this option.

(b) Payment of the exercise price per share is due in full in cash (including check) upon exercise of all or any part of each installment which has become exercisable by you; provided, however, that, if at the time of exercise the Company's Common Stock is publicly traded and quoted regularly in the Wall Street Journal, payment of the exercise price, to the extent permitted by applicable statutes and regulations, may be made by delivery of already-owned shares of Common Stock, or a combination of cash and already-owned Common Stock. Such Common Stock (i) will be valued at its fair market value on the date of exercise, (ii) if originally acquired from the Company, must have been owned by you for at least 6 months and (iii) must be owned free and clear of any liens, claims, encumbrances or security interests. Notwithstanding the foregoing, this option may be exercised pursuant to a program developed under Regulation T as promulgated by the Federal Reserve Board which results in the receipt of cash (or check) by the Company prior to the issuance of Common Stock.

3. The minimum number of shares with respect to which this option may be exercised at any one time is 1,000, unless the number of shares available for exercise (that is, the remaining vested shares pursuant to paragraph 1) equals less than 1,000 shares, in which case the minimum number of shares exercised must equal the number of shares then vested.

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4. Notwithstanding anything to the contrary contained herein, this option may not be exercised unless the shares issuable upon exercise of this option are then registered under the Act or, if such shares are not then so registered, the Company has determined that such exercise and issuance would be exempt from the registration requirements of the Act.

5. The term of this option commences on the date hereof and, unless sooner terminated as set forth below or in the Plan, terminates on the Expiration Date (which date will be no more than 10 years from the date this option is granted). This option will terminate prior to the expiration of its term as follows: 3 months after the termination of your employment with the Company or an affiliate of the Company (as defined in the Plan) for any reason or for no reason unless:

(a) such termination of employment is due to your permanent and total disability (within the meaning of Section 422(c)(6) of the Code), in

which event the option will terminate on the earlier of the termination date set forth above or 1 year following such termination of employment; or

(b) such termination of employment is due to your death, in which event the option will terminate on the earlier of the termination date set forth above or 18 months after your death; or

(c) during any part of such 3 month period the option is not exercisable solely because of the condition set forth in paragraph 4 above, in which event the option will not terminate until the earlier of the termination date set forth above or until it will have been exercisable for an aggregate period of 3 months after the termination of employment; or

(d) exercise of the option within 3 months after termination of your employment with the Company or with an affiliate would result in liability under section 16(b) of the Securities Exchange Act of 1934, in which case the option will terminate on the earlier of the termination date set forth above, the 10th day after the last date upon which exercise would result in such liability or 6 months and 10 days after the termination of your employment with the Company or an affiliate.

However, this option may be exercised following termination of employment only as to that number of shares as to which it was exercisable on the date of termination of employment under the provision of paragraph 1 of this option.

6. (a) This option may be exercised, to the extent specified above, by delivering a notice of exercise (in a form designated by the Company) together with the exercise price to the Secretary of the Company, or to such other person as the Company may designate, during regular business hours, together with such additional

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5 documents as the Company may then require pursuant to subparagraph 5(f) of the Plan.

(b) By exercising this option you agree that:

(i) the Company may require you to enter to arrangement providing for the cash payment by you to the Company of any tax withholding obligation of the Company arising by reason of: the exercise of this option; the lapse of any substantial risk of forfeiture to which the shares are subject at the time of exercise; or the disposition of shares acquired upon such exercise; and

(ii) you will notify the Company in writing within 15 days after the date of any disposition of any of the shares of the Common Stock issued upon exercise of this option that occurs within 2 years after the date of this option grant or within 1 year after such shares of Common Stock are transferred upon exercise of this option.

7. This option is not transferable, except by will or by the laws of descent and distribution, and is exercisable during your life only by you.

8. This option is not an employment contract and nothing in this option will be deemed to create in any way whatsoever any obligation on your part to continue in the employ of the Company, or of the Company to continue your employment with the Company.

9. Any notices provided for in this option or the Plan will be given in writing and will be deemed effectively given upon receipt or, in the case of notices delivered by the Company to you, 5 days after deposit in the United States mail, postage prepaid, addressed to you at the address specified below or at such other address as you hereafter designate by written notice to the Company.

10. This option is subject to all the provisions of the Plan, a copy of which is attached hereto and its provisions are hereby made a part of this option, including without limitation the provisions of paragraph 5 of the Plan relating to option provisions, and is further subject to all interpretations, amendments, rules and regulations which may from time to time be promulgated and adopted pursuant to the Plan. In the event of any conflict between the

provisions of this option and those of the Plan, the provisions of the Plan will control.

Attachments:

1989 Stock Option Plan  
Notice of Exercise

Revised form of Supplemental Stock Option Agreement under the Plan.

Optionee: \_\_\_\_\_ Date: \_\_\_\_\_

ISIS PHARMACEUTICALS, INC.  
SUPPLEMENTAL STOCK OPTION AGREEMENT

Isis Pharmaceuticals, Inc. (the "Company"), pursuant to its 1989 Stock Option Plan (the "Plan") has this day granted to the undersigned optionee, an option to purchase shares of the common stock of the Company ("Common Stock") as described herein. This option is not intended to qualify and will not be treated as an "incentive stock option" within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended from time to time (the "Code"). This option is subject to all of the terms and conditions as set forth herein and on Attachment I hereto, which is incorporated herein in its entirety.

Number of Shares Subject to Option: \_\_\_\_\_

VESTING SCHEDULE:

Number of Shares (installment)	Date of Earliest Exercise (vesting) (1)
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Exercise Price Per Share: (2) \_\_\_\_\_ Expiration Date: (3) \_\_\_\_\_

Percentage of Full-Time Work: \_\_\_\_\_

Isis Pharmaceuticals, Inc.

By: \_\_\_\_\_  
Duly authorized on behalf of  
the Board of Directors

Optionee: \_\_\_\_\_  
Address: \_\_\_\_\_

OPTIONEE:

Acknowledges receipt of the option as described herein and the attachments referenced therein and understands that all rights and liabilities with respect to this option are set forth in the option and the Plan; and acknowledges that as of the date of grant of this option, it sets forth the entire understanding between the optionee and the Company regarding the acquisition of stock in the Company and supersedes all prior oral and written agreements on that subject.

(1)After the first year, the option will vest monthly with 2.08% of the total grant vesting each month; provided, however, that during any period in which the undersigned provides service at less than the Percentage of Full-Time Work set forth above, a reduced number of shares will vest as follows: the percentage of shares which will vest during such period of reduced service will equal (a) the percentage of shares that would vest as set forth on this schedule, multiplied by (b) the percentage of full-time work furnished during the period of reduced service divided by the Percentage of Full Time Work as set forth above. Increases of work percentage up to but not in excess of the Percentage of Full Time Work specified above will result in a corresponding increase in the percentage of shares vesting. This reduction in vesting will not apply during any period of paid leave or the first 20 weeks of a period of unpaid leave. No shares will vest during unpaid leave after the first 20 weeks of such leave. Shares which do not vest because of reductions in work percentage or unpaid leave will be canceled and no longer subject to this option.

(2)Not less than 85% of the fair market value of the Common Stock on the date of grant of this option.

(3) Less than 10 years from the date of grant of this option.

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ATTACHMENT I

TERMS OF SUPPLEMENTAL STOCK OPTION

The grant hereunder is in connection with and in furtherance of the Company's compensatory benefit plan for participation of the Company's employees (including officers), directors or consultants and is intended to comply with the provisions of Rule 701 promulgated by the Securities and Exchange Commission under the Securities Act of 1933, as amended (the "Act").

The details of your option are as follows:

1. The total number of shares of Common Stock subject to this option is set forth on the first page of the Supplemental Stock Option Agreement. Subject to the limitations contained herein, this option shall be exercisable with respect to each installment indicated in the Vesting Schedule set forth on the first page of the Supplemental Stock Option Agreement on or after the date of vesting applicable to such installment.

2. (a) The Exercise Price of this option is set forth on the first page of the Supplemental Stock Option Agreement.

(b) Payment of the exercise price per share is due in full in cash (including check) upon exercise of all or any part of each installment which has become exercisable by you.

3. The minimum number of shares with respect to which this option may be exercised at any one time is 1,000, unless the number of shares available for exercise (that is, the remaining vested shares pursuant to paragraph 1) equals less than 1,000 shares, in which case the minimum number of shares exercised must equal the number of shares then vested.

4. Notwithstanding anything to the contrary contained herein, this option may not be exercised unless the shares issuable upon exercise of this option are then registered under the Act or, if such shares are not then so registered, the Company has determined that such exercise and issuance would be exempt from the registration requirements of the Act.

5. The term of this option commences on the date hereof and, unless sooner terminated as set forth below or in the Plan, terminates on the Expiration Date. This option shall terminate prior to the expiration of its term as follows: 3 months after the termination of your employment with the Company or an affiliate of the Company (as defined in the Plan) for any reason or for no reason unless:

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(a) such termination of employment is due to your permanent and total disability (within the meaning of Section 422(c)(6) of the Code), in which event the option shall terminate on the earlier of the termination date set forth above or one 1 year following such termination of employment;

(b) such termination of employment is due to your death, in which event the option shall terminate on the earlier of the termination date set forth above or 18 months after your death; or

(c) during any part of such 3 month period the option is not exercisable solely because of the condition set forth in paragraph 4 above, in which event the option shall not terminate until the earlier of the termination date set forth above or until it shall have been exercisable for an aggregate period of 3 months after the termination of employment; or

(d) exercise of the option within 3 months after termination of your employment with the Company or with an affiliate would result in liability under section 16(b) of the Securities Exchange Act of 1934, in which case the option will terminate on the earlier of the termination date set forth

above, the 10th day after the last date upon which exercise would result in such liability or 6 months and 10 days after the termination of your employment with the Company or an affiliate.

However, this option may be exercised following termination of employment only as to that number of shares as to which it was exercisable on the date of termination of employment under the provision of paragraph 1 of this option.

6. (a) This option may be exercised, to the extent specified above, by delivering a notice of exercise (in a form designated by the Company) together with the exercise price to the Secretary of the Company, or to such other person as the Company may designate, during regular business hours, together with such additional documents as the Company may then require pursuant to subparagraph 5(f) of the Plan.

(b) By exercising this option you agree that:

(i) the Company may require you to enter to arrangement providing for the cash payment by you to the Company of any tax withholding obligation of the Company arising by reason of: the exercise of this option; the lapse of any substantial risk of forfeiture to which the shares are subject at the time of exercise; or the disposition of shares acquired upon such exercise.

7. This option is not transferable except by will or by the laws of descent and distribution, and is exercisable during your lifetime only by you; notwithstanding the foregoing, you may transfer part or all of this option to any of the following:

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(i) your spouse, children (by birth or adoption), stepchildren, grandchildren, or parents;

(ii) a trust or other entity established solely for your benefit or the benefit of your spouse, children (by birth or adoption), stepchildren, grandchildren, or parents for estate planning purposes; or,

(iii) an organization which is exempt from taxation under Section 501(c)(3) of the Code or to which tax-deductible charitable contributions may be made under Section 170 of the Code.

Furthermore, you may, by delivering written notice to the Company, in a form satisfactory to the Company, designate a third party who, in the event of your death, will thereafter be entitled to exercise the option.

8. This option is not an employment contract and nothing in this option shall be deemed to create in any way whatsoever any obligation on your part to continue in the employ of the Company, or of the Company to continue your employment with the Company. In the event that this option is granted to you in connection with the performance of services as a consultant or director, references to employment, employee and similar terms shall be deemed to include the performance of services as a consultant or a director, as the case may be, provided, however, that no rights as an employee shall arise by reason of the use of such terms.

9. Any notices provided for in this option or the Plan shall be given in writing and shall be deemed effectively given upon receipt or, in the case of notices delivered by the Company to you, five 5 days after deposit in the United States mail, postage prepaid, addressed to you at the address specified below or at such other address as you hereafter designate by written notice to the Company.

10. This option is subject to all the provisions of the Plan, a copy of which is attached hereto and its provisions are hereby made a part of this option, including without limitation the provisions of paragraph 5 of the Plan relating to option provisions, and is further subject to all interpretations, amendments, rules and regulations which may from time to time be promulgated and adopted pursuant to the Plan. In the event of any conflict between the provisions of this option and those of the Plan, the provisions of the Plan shall control.

Attachments:

1989 Stock Option Plan  
Notice of Exercise

Registrant's 1992 Non-Employee Directors' Stock Option Plan, as amended.

ISIS PHARMACEUTICALS, INC.  
1992 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN  
Adopted on July 20, 1992  
Amended March 4, 1993  
Amended February 28, 1996  
Amended September 6, 1996

1. PURPOSE.

(a) The purpose of the 1992 Non-Employee Directors' Stock Option Plan (the "Plan") is to provide a means by which each director of Isis Pharmaceuticals, Inc., a Delaware corporation (the "Company"), who is not otherwise an employee of the Company or of any Affiliate of the Company (each such person being hereafter referred to as a "Non-Employee Director") will be given an opportunity to purchase stock of the Company.

(b) The word "Affiliate" as used in the Plan means any parent corporation or subsidiary corporation of the Company as those terms are defined in Sections 424(e) and (f), respectively, of the Internal Revenue Code of 1986, as amended (the "Code").

(c) The Company, by means of the Plan, seeks to retain the services of persons now serving as Non-Employee Directors of the Company, to secure and retain the services of persons capable of serving in such capacity, and to provide incentives for such persons to exert maximum efforts for the success of the Company.

(d) The Company intends that the options issued under the Plan not be incentive stock options as that term is used in Section 422 of the Code.

2. ADMINISTRATION.

(a) The Plan will be administered by the Board of Directors of the Company (the "Board") unless and until the Board delegates administration to a committee, as provided in subparagraph 2(c).

(b) The Board will have the power, subject to, and within the limitations of, the express provisions of the Plan:

(1) To construe and interpret the Plan and options granted under it, and to establish, amend and revoke rules and regulations for its administration. The Board, in the exercise of this power, may correct any defect, omission or inconsistency in the Plan or in any option agreement, in a manner and to the extent it will deem necessary or expedient to make the Plan fully effective.

(2) To amend the Plan as provided in paragraph 11.

(3) Generally, to exercise such powers and to perform such acts as the Board deems necessary or expedient to promote the best interests of the Company.

(c) The Board may delegate administration of the Plan to a committee composed of not fewer than 2 members of the Board (the "Committee"). If administration is delegated to a Committee, the Committee will have, in connection with the administration of the Plan, the powers theretofore possessed by the Board, subject, however, to such resolutions, not inconsistent with the provisions of the Plan, as may be adopted from time to time by the Board. The

Board may abolish the Committee at any time and reconstitute in the Board the administration of the Plan.

3. SHARES SUBJECT TO THE PLAN.

(a) Subject to the provisions of paragraph 10 relating to adjustments upon changes in stock, the stock that may be sold pursuant to options granted under the Plan will not exceed in the aggregate 300,000 shares of the Company's common stock. If any option granted under the Plan will for any reason expire or otherwise terminate without having been exercised in full, the stock not purchased under such option will again become available for the Plan.

(b) The stock subject to the Plan may be unissued shares or reacquired shares, bought on the market or otherwise.

4. ELIGIBILITY.

Options will be granted only to Non-Employee Directors of the Company.

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5. NON-DISCRETIONARY GRANTS.

(a) Each person who is, after the Adoption Date, elected for the first time to be a Non-Employee Director of the Company will, upon the date of his initial election to be a Non-Employee Director by the Board or stockholders of the Company, be granted an option to purchase 18,000 shares of common stock of the Company on the terms and conditions set forth herein.

(b) On July 1 of each year, commencing July 1, 1996, each person who is then a Non-Employee Director of the Company will be granted an option to purchase 4,000 shares of common stock of the Company on the terms and conditions set forth herein. Should the date of grant set forth above be a legal holiday, such grant will be made on the next business day.

6. OPTION PROVISIONS.

Each option will contain the following terms and conditions:

(a) No option will be exercisable after the expiration of 10 years from the date it was granted.

(b) The exercise price of each option will be 100% of the fair market value of the stock subject to such option on the date such option is granted.

(c) The purchase price of stock acquired pursuant to an option will be paid, to the extent permitted by applicable statutes and regulations, either in cash at the time the option is exercised, or by delivery to the Company of shares of common stock of the Company that have been held for the requisite period necessary to avoid a charge to the Company's reported earnings and valued at the fair market value on the date of exercise, or (3) by a combination of such methods of payment.

(d) An option will not be transferable except as determined by the Board.

(e) An option will vest with respect to each optionee in 4 equal annual installments commencing on the date one year after the date of grant of the option, provided that the optionee has, during the entire year prior to such vesting date, continuously served as a Non-Employee Director or as an employee of or consultant to the Company or any Affiliate of the

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Company, whereupon such option will become fully exercisable in accordance with its terms with respect to that portion of the shares represented by that installment.

(f) The Company may require any optionee, or any person to whom an option is transferred under subparagraph 6(d), as a condition of exercising any such option: (1) to give written assurances satisfactory to the Company as to the

optionee's knowledge and experience in financial and business matters; and (2) to give written assurances satisfactory to the Company stating that such person is acquiring the stock subject to the option for such person's own account and not with any present intention of selling or otherwise distributing the stock. These requirements, and any assurances given pursuant to such requirements, will be inoperative if (I) the issuance of the shares upon the exercise of the option has been registered under a then-currently-effective registration statement under the Securities Act of 1933, as amended (the "Securities Act"), or (ii), as to any particular requirement, a determination is made by counsel for the Company that such requirement need not be met in the circumstances under the then-applicable securities laws.

(g) Notwithstanding anything to the contrary contained herein, an option may not be exercised unless the shares issuable upon exercise of such option are then registered under the Securities Act or, if such shares are not then so registered, the Company has determined that such exercise and issuance would be exempt from the registration requirements of the Securities Act.

#### 7. COVENANTS OF THE COMPANY.

(a) During the terms of the options granted under the Plan, the Company will keep available at all times the number of shares of stock required to satisfy such options.

(b) The Company will seek to obtain from each regulatory commission or agency having jurisdiction over the Plan such authority as may be required to issue and sell shares of stock upon exercise of the options granted under the Plan; provided, however, that this undertaking will not require the Company to register under the Securities Act either the Plan, any option granted under the Plan, or any stock issued or issuable pursuant to any such option. If the Company is unable to obtain from any such regulatory commission or agency the authority which counsel for the Company deems necessary for the lawful issuance and sale of stock under the Plan, the Company will be relieved from any liability for failure to issue and sell stock upon exercise of such options.

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#### 8. USE OF PROCEEDS FROM STOCK.

Proceeds from the sale of stock pursuant to options granted under the Plan will constitute general funds of the Company.

#### 9. MISCELLANEOUS.

(a) Neither an optionee nor any person to whom an option is transferred under subparagraph 6(d) will be deemed to be the holder of, or to have any of the rights of a holder with respect to, any shares subject to such option unless and until such person has satisfied all requirements for exercise of the option pursuant to its terms.

(b) Nothing in the Plan or in any instrument executed pursuant thereto will confer upon any Non-Employee Director any right to continue in the service of the Company or any Affiliate or will affect any right of the Company, its Board or stockholders or any Affiliate to terminate the service of any Non-Employee Director with or without cause.

(c) No Non-Employee Director, individually or as a member of a group, and no beneficiary or other person claiming under or through him, will have any right, title or interest in or to any option reserved for the purposes of the Plan except as to such shares of common stock, if any, as will have been reserved for him pursuant to an option granted to him.

(d) In connection with each option made pursuant to the Plan, it will be a condition precedent to the Company's obligation to issue or transfer shares to a Non-Employee Director, or an affiliate of such Non-Employee Director, or to evidence the removal of any restrictions on transfer, that such Non-Employee Director make arrangements satisfactory to the Company to insure that the amount of any federal or other withholding tax required to be withheld with respect to such sale or transfer, or such removal or lapse, is made available to the Company for timely payment of such tax.

10. ADJUSTMENTS UPON CHANGES IN STOCK.

(a) If any change is made in the stock subject to the Plan, or subject to any option granted under the Plan (through merger, consolidation, reorganization, recapitalization, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination

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of shares, exchange of shares, change in corporate structure or otherwise), the Plan and outstanding options will be appropriately adjusted in the class(es) and maximum number of shares subject to the Plan and the class(es) and number of shares and price per share of stock subject to outstanding options.

(b) In the event of: (i) a dissolution or liquidation of the Company; (ii) a merger or consolidation in which the Company is not the surviving corporation; (iii) a reverse merger in which the Company is the surviving corporation but the shares of the Company's common stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise; or (iv) any other capital reorganization in which more than 50% of the shares of the Company entitled to vote are exchanged, then, to the extent permitted by applicable law, the time during which outstanding options may be exercised will be accelerated to permit the optionee to exercise all such options prior to such merger, consolidation, reverse merger or reorganization, and the options terminated if not exercised prior to such event.

11. AMENDMENT OF THE PLAN.

(a) The Board at any time, and from time to time, may amend the Plan, provided, however, that the Board will not amend the plan more than once every six months, with respect to the provisions of the plan which relate to the amount, price and timing of grants, other than to comport with changes in the Code, the Employee Retirement Income Security Act, or the rules thereunder. Except as provided in paragraph 10 relating to adjustments upon changes in stock, no amendment will be effective unless approved by the stockholders of the Company within 12 months before or after the adoption of the amendment, where the amendment will:

(1) Increase the number of shares reserved for options under the Plan;

or

(2) Modify the requirements as to eligibility for participation in the Plan or modify any other term of the Plan (to the extent such modification requires stockholder approval in order for the Plan to comply with the requirements of Rule 16b-3 promulgated under the Exchange Act).

(b) Rights and obligations under any option granted before any amendment of the Plan will not be altered or impaired by such amendment of the Plan unless (i) the Company

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requests the consent of the person to whom the option was granted and (ii) such person consents in writing.

12. TERMINATION OR SUSPENSION OF THE PLAN.

(a) The Board may suspend or terminate the Plan at any time. Unless sooner terminated, the Plan will terminate on July 1, 2002. No options may be granted under the Plan while the Plan is suspended or after it is terminated.

(b) Rights and obligations under any option granted while the Plan is in effect will not be altered or impaired by suspension or termination of the Plan, except with the consent of the person to whom the option was granted.

13. EFFECTIVE DATE OF PLAN; CONDITIONS OF EXERCISE.

(a) The Plan will become effective on July 20, 1992.

(b) No option granted under the Plan will be exercised or exercisable

unless and until the condition of subparagraph 13(a) above has been met.

Optionee: \_\_\_\_\_ Date: \_\_\_\_\_

ISIS PHARMACEUTICALS, INC.  
SUPPLEMENTAL STOCK OPTION AGREEMENT

Isis Pharmaceuticals, Inc. (the "Company"), pursuant to its 1992 Non-Employee Directors' Stock Option Plan (the "Plan") has this day granted to the undersigned optionee, an option to purchase shares of the common stock of the Company ("Common Stock") as described herein. This option is not intended to qualify and will not be treated as an "incentive stock option" within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended from time to time (the "Code"). This option is subject to all of the terms and conditions as set forth herein and on Attachment I hereto, which is incorporated herein in its entirety.

Number of Shares Subject to Option: \_\_\_\_\_

VESTING SCHEDULE:

Number of Shares (installment)	Date of Earliest Exercise (vesting)
-----	-----
-----	-----
-----	-----
-----	-----

Exercise Price Per Share: \_\_\_\_\_ (1)      Expiration Date: \_\_\_\_\_ (2)

Isis Pharmaceuticals, Inc.

By: \_\_\_\_\_  
Duly authorized on behalf of  
the Board of Directors

Optionee: \_\_\_\_\_  
Address: \_\_\_\_\_

OPTIONEE:

Acknowledges receipt of the option as described herein and the attachments referenced therein and understands that all rights and liabilities with respect to this option are set forth in the option and the Plan; and acknowledges that as of the date of grant of this option, it sets forth the entire understanding between the optionee and the Company regarding the acquisition of stock in the Company and supersedes all prior oral and written agreements on that subject.

(1) Not less than 100% of the fair market value of the Common Stock on the date of grant of this option.

(2) Less than 10 years from the date of grant of this option.

ATTACHMENT I

TERMS OF SUPPLEMENTAL STOCK OPTION

The details of your option are as follows:

1. The total number of shares of Common Stock subject to this option is set forth on the first page of the Supplemental Stock Option Agreement. Subject to the limitations contained herein, this option shall be exercisable with respect to each installment indicated in the Vesting Schedule set forth on the

first page of the Supplemental Stock Option Agreement on or after the date of vesting applicable to such installment.

2. (i) The Exercise Price of this option is set forth on the first page of the Supplemental Stock Option Agreement.

(ii) Upon exercise of all or any part of each installment which has become exercisable by you, payment of the exercise price per share is due, in full, either (a) in cash (including check), or (b) by delivery of shares of Common Stock that have been held for the requisite period necessary to avoid a charge to the Company's reported earnings and valued at the fair market value on the date of exercise, or (c) by a combination of such methods of payment.

3. The minimum number of shares with respect to which this option may be exercised at any one time is 1,000, unless the number of shares available for exercise (that is, the remaining vested shares pursuant to paragraph 1) equals less than 1,000 shares, in which case the minimum number of shares exercised must equal the number of shares then vested.

4. Notwithstanding anything to the contrary contained herein, this option may not be exercised unless the shares issuable upon exercise of this option are then registered under the Securities Act of 1933, as amended (the "Act"), or, if such shares are not then so registered, the Company has determined that such exercise and issuance would be exempt from the registration requirements of the Act.

5. The term of this option commences on the date hereof and terminates on the Expiration Date (which date shall be no more than 10 years from the date this option is granted). However, this option may be exercised following termination of your service as a non-employee director, or as an employee of or consultant to the Company or an affiliate of the Company (as defined in the Plan) only as to that number of shares as to which it was exercisable on the date of termination under the provisions of paragraph 1 of this option.

6. (i) This option may be exercised, to the extent specified above, by delivering a notice of exercise (in a form designated by the Company) together with the exercise price to the Secretary of the Company, or to such other person as the Company may designate, during regular business hours, together with such additional documents as the Company may then require pursuant to subparagraph 6(f) of the Plan.

(ii) By exercising this option you agree that the Company may require you to enter an arrangement providing for the cash payment by you to the Company of any tax withholding obligation of the Company arising by reason of: the exercise of this option; the

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lapse of any substantial risk of forfeiture to which the shares are subject at the time of exercise; or the disposition of shares acquired upon such exercise.

7. This option is not transferable except by will or by the laws of descent and distribution, and is exercisable during your lifetime only by you; notwithstanding the foregoing, you may transfer part or all of this option to any of the following:

(i) your spouse, children (by birth or adoption), stepchildren, grandchildren, or parents;

(ii) a trust or other entity established solely for your benefit or the benefit of your spouse, children (by birth or adoption), stepchildren, grandchildren, or parents for estate planning purposes; or,

(iii) an organization which is exempt from taxation under Section 501(c)(3) of the Code or to which tax-deductible charitable contributions may be made under Section 170 of the Code.

Furthermore, you may, by delivering written notice to the Company, in a form satisfactory to the Company, designate a third party who, in the event of your death, will thereafter be entitled to exercise the option.

8. This option is not an employment contract and nothing in this option

shall be deemed to create in any way whatsoever any obligation on your part to continue as a director of the Company.

9. Any notices provided for in this option or the Plan shall be given in writing and shall be deemed effectively given upon receipt or, in the case of notices delivered by the Company to you, 5 days after deposit in the United States mail, postage prepaid, addressed to you at the address specified below or at such other address as you hereafter designate by written notice to the Company.

10. This option is subject to all the provisions of the Plan, a copy of which is attached hereto and its provisions are hereby made a part of this option, including without limitation the provisions of paragraph 6 of the Plan relating to option provisions, and is further subject to all interpretations, amendments, rules and regulations which may from time to time be promulgated and adopted pursuant to the Plan. In the event of any conflict between the provisions of this option and those of the Plan, the provisions of the Plan shall control.

Attachments:

1992 Non-Employee Directors' Stock Option Plan  
Notice of Exercise

<ARTICLE> 5

<LEGEND>

This schedule contains summary financial information derived from the Company's Condensed Balance Sheet as of September 30, 1986 (Unaudited) and Condensed Statements of Operations for the Nine Months Ended September 30, 1996 (Unaudited) and is qualified in its entirety by the reference to such financial statements.

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