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SECURITIES AND EXCHANGE COMMISSION  
Washington, D.C. 20549

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FORM S-8  
REGISTRATION STATEMENT  
UNDER  
THE SECURITIES ACT OF 1933

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ISIS PHARMACEUTICALS, INC.

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(Exact name of registrant as specified in its charter)

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DELAWARE

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33-0336973

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(State or other jurisdiction of  
incorporation or organization)

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(I.R.S. Employer Identification No.)

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2292 FARADAY AVENUE  
CARLSBAD, CALIFORNIA 92008

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(Address of principal executive offices)

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1989 STOCK OPTION PLAN  
1992 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN

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(Full title of the plans)

B. LYNNE PARSHALL, ESQ.  
EXECUTIVE VICE PRESIDENT, CHIEF FINANCIAL OFFICER AND SECRETARY  
ISIS PHARMACEUTICALS, INC.  
2292 FARADAY AVENUE  
CARLSBAD, CALIFORNIA 92008  
(619) 931-9200

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(Name, address, including zip code, and telephone number,  
including area code, of agent for service)

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Copies to:

D. BRADLEY PECK, ESQ.  
COOLEY GODWARD CASTRO HUDDLESON & TATUM  
4365 EXECUTIVE DRIVE  
SAN DIEGO, CALIFORNIA 92121  
(619) 550-6000

CALCULATION OF REGISTRATION FEE

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TITLE OF SECURITIES TO	AMOUNT TO BE	PROPOSED MAXIMUM OFFERING PRICE PER	PROPOSED MAXIMUM AGGREGATE OFFERING	AMOUNT OF
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BE REGISTERED	REGISTERED	SHARE (1)	PRICE (1)	REGISTRATION FEE
Stock Options and Common Stock (par value \$.001)	2,300,000	\$11.375 - \$19.75	\$40,542,838	\$13,980

(1) Estimated solely for the purpose of calculating the amount of the registration fee pursuant to Rule 457(c) and (h)(1). The price per share and the aggregate offering price are calculated on the basis of (a) the weighted average exercise price of \$13.25 for 656,141 shares subject to outstanding options granted under the Registrant's 1989 Stock Option Plan (the "1989 Plan") and (b) \$19.375, the average of the high and low sales prices of Registrant's Common Stock on June 7, 1996 as reported on the Nasdaq National Market for shares issuable under the 1989 Plan and the 1992 Non-Employee Directors' Stock Option Plan.

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INCORPORATION BY REFERENCE OF CONTENTS OF  
REGISTRATION STATEMENT ON FORM S-8 NO. 33-42356, NO. 33-51236,  
NO. 33-54840, NO. 33-58450, NO. 33-75150 AND NO. 33-90780

The contents of Registration Statements on Form S-8 Nos. 33-42356, 33-51236, 33-54840, 33-58450, 33-75150 and 33-90780 filed with the Securities and Exchange Commission on August 23, 1991, August 25, 1992, November 20, 1992, February 16, 1993, February 4, 1994 and March 30, 1995 are incorporated by reference herein.

EXHIBITS

EXHIBIT  
NUMBER

- 5.1 Opinion of Cooley Godward Castro Huddleson & Tatum
- 23.1 Consent of Ernst & Young LLP
- 23.2 Consent of Cooley Godward Castro Huddleson & Tatum is contained in Exhibit 5.1 to this Registration Statement
- 24.1 Power of Attorney is contained on the signature pages.
- 99.1\* 1989 Stock Option Plan, as amended
- 99.2 1992 Non-Employee Directors' Stock Option Plan, as amended

\* Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1995, and incorporated herein by reference.

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SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, as amended, the Registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-8 and has duly caused this Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Carlsbad, State of California, on May 31, 1996.

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall

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

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Stanley T. Crooke, Daniel L. Kisner and

B. Lynne Parshall and each or any one of them, his or her true and lawful attorney-in-fact and agent, with full power of substitution and resubstitution, for him or her and in his or her name, place and stead, in any and all capacities, to sign any and all amendments (including post-effective amendments) to this Registration Statement, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or any of them, or their or his or her substitutes or substitute, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act of 1933, this Registration Statement has been signed by the following persons in the capacities and on the dates indicated.

SIGNATURE	TITLE	DATE
/s/ Stanley T. Crooke ----- Stanley T. Crooke	Chairman of the Board and Chief Executive Officer (Principal Executive Officer)	May 31, 1996
/s/ B. Lynne Parshall ----- B. Lynne Parshall	Executive Vice President, Chief Financial Officer and Secretary (Principal Financial and Accounting Officer)	May 31, 1996
/s/ Daniel L. Kisner ----- Daniel L. Kisner	President, Chief Operating Officer and Director	May 31, 1996

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/s/ Christopher F.O. Gabrieli ----- Christopher F.O. Gabrieli	Director	May 31, 1996
----- Christoph Hohbach	Director	May 31, 1996
/s/ Alan C. Mendelson ----- Alan C. Mendelson	Director	May 31, 1996
/s/ William R. Miller ----- William R. Miller	Director	May 31, 1996
/s/ Mark B. Skaletsky ----- Mark B. Skaletsky	Director	May 31, 1996
----- Larry Soll	Director	May 31, 1996
/s/ Joseph H. Wender ----- Joseph H. Wender	Director	May 31, 1996

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EXHIBIT INDEX

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99.1*	1989 Stock Option Plan, as amended	--
99.2*	1992 Non-Employee Directors' Stock Option Plan, as amended	9

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\* Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1995, and incorporated herein by reference.

June 12, 1996

ISIS PHARMACEUTICALS, INC.  
2292 Faraday Avenue  
Carlsbad, CA 92008

Ladies and Gentlemen:

You have requested our opinion with respect to certain matters in connection with the filing by Isis Pharmaceuticals, Inc. (the "Company") of a Registration Statement on Form S-8 (the "Registration Statement") with the Securities and Exchange Commission covering the offering of up to 2,200,000 shares of the Company's Common Stock, \$.001 par value pursuant to its 1989 Stock Option Plan (the "1989 Plan") and up to 100,000 shares of the Company's Common Stock, \$.001 par value, pursuant to its 1992 Non-Employee Directors' Stock Option Plan (the "1992 Plan") (collectively referred to herein as the "Shares").

In connection with this opinion, we have examined the 1989 Plan, the 1992 Plan, the Registration Statement, your Certificate of Incorporation and By-laws, as amended, and such other documents, records, certificates, memoranda and other instruments as we deem necessary as a basis for this opinion. We have assumed the genuineness and authenticity of all documents submitted to us as originals, the conformity to originals of all documents submitted to us as copies thereof, and the due execution and delivery of all documents where due execution and delivery are a prerequisite to the effectiveness thereof.

On the basis of the foregoing, and in reliance thereon, we are of the opinion that the Shares, when sold and issued in accordance with the 1989 Plan, the 1992 Plan and the Registration Statement, will be validly issued, fully paid, and nonassessable.

We consent to the filing of this opinion as an exhibit to the Registration Statement.

Very truly yours,

COOLEY GODWARD CASTRO  
HUDDLESON & TATUM

By: /s/ D. BRADLEY PECK

-----  
D. Bradley Peck

## CONSENT OF ERNST &amp; YOUNG LLP, INDEPENDENT AUDITORS

We consent to the incorporation by reference in the Registration Statement (Form S-8) pertaining to the 1989 Stock Option Plan and the 1992 Non-Employee Directors' Stock Option Plan of Isis Pharmaceuticals, Inc. for the registration of 2,200,000 shares and 100,000 shares, respectively, of our report dated January 26, 1996, with respect to the financial statements of Isis Pharmaceuticals, Inc. included in its Annual Report (Form 10-K) for the year ended December 31, 1995 filed with the Securities and Exchange Commission.

/s/ ERNST & YOUNG LLP

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Ernst & Young LLP

San Diego, California  
June 6, 1996

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

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(b) The Board shall 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 shall 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 two (2) members of the Board (the "Committee"). If administration is delegated to a Committee, the Committee shall 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 revest 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 shall not exceed in the aggregate three-hundred thousand (300,000) shares of the Company's common stock. If any option granted under the

Plan shall for any reason expire or otherwise terminate without having been exercised in full, the stock not purchased under such option shall 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.

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4. ELIGIBILITY.

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

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 shall, 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 eighteen-thousand (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 shall be granted an option to purchase four-thousand (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 shall be made on the next business day.

6. OPTION PROVISIONS.

Each option shall contain the following terms and conditions:

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

(b) The exercise price of each option shall be one-hundred percent (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 shall be paid, to the extent permitted by applicable statutes and regulations, either (1) in cash at the time the option is exercised, or (2) 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.

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(d) An option shall not be transferable except by will or by the laws of descent and distribution, and shall be exercisable during the lifetime of the person to whom the option is granted only by such person or by his guardian or legal representative.

(e) An option shall vest with respect to each optionee in four (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 Company, whereupon such option shall 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, shall 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.

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7. COVENANTS OF THE COMPANY.

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

(b) The Company shall 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 shall 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 shall be relieved from any liability for failure to issue and sell stock upon exercise of such options.

8. USE OF PROCEEDS FROM STOCK.

Proceeds from the sale of stock pursuant to options granted under the Plan shall 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) shall 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 shall confer upon any Non-Employee Director any right to continue in the service of the Company or any Affiliate or shall 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, shall have any right, title or

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interest in or to any option reserved for the purposes of the Plan except as to such shares of common stock, if any, as shall have been reserved for him pursuant to an option granted to him.

(d) In connection with each option made pursuant to the Plan, it shall 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 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 fifty percent (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 shall be accelerated to permit the optionee to exercise all such options prior to such merger,

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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 shall 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 shall be effective unless approved by the stockholders of the Company within twelve (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;

(2) Modify the requirements as to eligibility for participation in 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); or

(3) Modify the Plan in any other way if 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 shall not be altered or impaired by such amendment of the Plan unless (i) the Company 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 shall terminate on July 1, 2002. No options may be granted under the Plan while the Plan is suspended or after it is terminated.

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(b) Rights and obligations under any option granted while the Plan is in effect shall 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 shall become effective upon adoption by the Board of Directors, subject to the condition subsequent that the Plan is approved by the

stockholders of the Company.

(b) No option granted under the Plan shall be exercised or exercisable unless and until the condition of subparagraph 13(a) above has been met.