

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM S-8

REGISTRATION STATEMENT UNDER THE SECURITIES ACT OF 1933

ISIS PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware
(State of Incorporation)

33-0336973
(I.R.S. Employer Identification No.)

1896 Rutherford Road
Carlsbad, CA 92008
(Address of principal executive offices)

AMENDED & RESTATED 2000 EMPLOYEE STOCK PURCHASE PLAN (Full title of the plans)

B. Lynne Parshall
Chief Operating Officer, Chief Financial Officer and Secretary
ISIS PHARMACEUTICALS, INC.
1896 Rutherford Road
Carlsbad, California 92008
(760) 931-9200
(Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies to:

Grantland E. Bryce, Esq.
Vice President Legal and General Counsel
ISIS PHARMACEUTICALS, INC.
1896 Rutherford Road
Carlsbad, California 92008
(760) 931-9200

CALCULATION OF REGISTRATION FEE

Title of Securities to be Registered	Amount to be Registered(2)	Proposed Maximum Offering Price per Share (3)	Proposed Maximum Aggregate Offering Price (2)	Amount of Registration Fee
Common Stock, par value \$.001per share	1,500,000 shares	\$15.05	\$22,575,000	\$1,259.69

- (1) In accordance with Rule 416 under the Securities Act of 1933, as amended, this registration statement shall be deemed to cover any additional securities that may from time to time be offered or issued to prevent dilution resulting from stock splits, stock dividends or similar transactions.
- (2) Includes 1,500,000 shares issuable pursuant to the Registrant's Amended & Restated 2000 Employee Stock Purchase Plan (the "ESPP"). As of the date of this Registration Statement there were 150,000 shares of Common Stock reserved for issuance under the ESPP. Under the ESPP's "evergreen" provision, this amount will be increased as of each January 1, beginning with January 1, 2010, and continuing through and including January 1, 2019 by one hundred fifty thousand (150,000) shares of Common Stock.
- (3) Estimated solely for the purpose of calculating the amount of the registration fee pursuant to Rule 457(c) and Rule 457(h) of the Securities Act of 1933, as amended, (the "Securities Act"). The price per share and the aggregate offering price are calculated on the basis of \$15.05, the average of the high and low sales prices of Registrant's Common Stock on June 23, 2009, as reported on the Nasdaq Global Market for the remainder of the shares subject to the ESPP.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to “incorporate by reference” certain of our publicly-filed documents into this prospectus, which means that information included in those documents is considered part of this prospectus. Information that we file with the SEC after the effective date of this prospectus will automatically update and supersede this information. We incorporate by reference the documents listed below and any future filings made with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, until all the shares of common stock that are part of this offering are sold.

The following documents filed with the SEC are incorporated by reference in this prospectus:

- our Annual Report on Form 10-K for the year ended December 31, 2008;
- our Quarterly Report on Form 10-Q for the quarter ended March 31, 2009;
- our Current Reports on Form 8-K or 8-K/A, filed with the SEC on March 4, 2009, March 30, 2009, April 15, 2009, April 29, 2009, May 20, 2009, and June 4, 2009 ;
- our Notice of Annual Meeting and Proxy Statement for the 2009 Annual Meeting of Stockholders, filed with the SEC on April 20, 2009; and
- the description of our Preferred Share Purchase Rights Plan contained in our Current Report on Form 8-K filed with the SEC on December 13, 2000, as updated by our Form 8-K filed with the SEC on April 8, 2005; and
- the description of our common stock contained in our Registration Statement on Form 8-A filed with the SEC on April 12, 1991, as updated by our Certificate of Amendment of our Restated Certificate of Incorporation filed with our Quarterly Report on Form 10-Q for the period ended June 30, 2001 and our Certificate of Amendment of our Restated Certificate of Incorporation filed with our Quarterly Report on Form 10-Q for the period ended March 31, 2006.

We will furnish without charge to you, on written or oral request, a copy of any or all of the documents incorporated by reference, other than exhibits to those documents. You should direct any requests for documents to Isis’ Corporate Secretary at its principal executive offices, 1896 Rutherford Road, Carlsbad, California 92008, telephone number (760) 931-9200.

DESCRIPTION OF SECURITIES

Not applicable.

INTERESTS OF NAMED EXPERTS AND COUNSEL

The validity of the issuance of the common stock offered in this prospectus will be passed upon for Isis by Grantland E. Bryce, Vice President and General Counsel of Isis. Mr. Bryce is the beneficial owner of options to purchase 71,550 shares of Isis common stock. As of June 23, 2009, Mr. Bryce will be vested and exercisable as to options to purchase 68,440 shares of Isis common stock issuable upon exercise of options held that are exercisable on or before August 22, 2009.

INDEMNIFICATION OF DIRECTORS AND OFFICERS

Under Section 145 of the Delaware General Corporation Law, we have broad powers to indemnify our directors and officers against liabilities they may incur in such capacities, including liabilities under the Securities Act of 1933.

Our certificate of incorporation and by-laws include provisions to (i) eliminate the personal liability of its directors for monetary damages resulting from breaches of their fiduciary duty to the extent permitted by Section 102(b)(7) of the General Corporation Law of Delaware and (ii) require us to indemnify our directors and officers to the fullest extent permitted by Section 145 of the Delaware Law, including circumstances in which indemnification is otherwise discretionary. Pursuant to Section 145 of the Delaware Law, a corporation generally has the power to indemnify its present and former directors, officers, employees and agents against expenses incurred by them in connection with any suit to which they are, or are threatened to be made, a party by reason of their serving in such positions so long as they acted in good faith and in a manner they reasonably believed to be in, or not opposed to, the best interest of the corporation, and with respect to any criminal action, they had no reasonable cause to believe their conduct was unlawful. We believe that these provisions are necessary to attract and retain qualified persons as directors and officers. These provisions do not eliminate the directors’ duty of care, and, in appropriate circumstances, equitable remedies such as injunctive or other forms of non-monetary relief will remain available under Delaware law. In addition, each director will continue to be subject to liability for breach of the directors’ duty of loyalty to us, for acts or omissions not in good faith or involving intentional misconduct, for knowing violations of law, for acts or omissions that the director believes to be contrary to the best interests of Isis or our stockholders, for any transaction from which the director derived an improper personal benefit, for acts or omissions involving a reckless disregard for the directors’ duty to Isis or our stockholders when the director was aware or should have been aware of a risk of serious injury to Isis or our stockholders, for acts or omissions that constitute an unexcused pattern of inattention that amounts to an abdication of the director’s duty to Isis or our stockholders, for improper transactions between the director and us and for improper distributions to stockholders and loans to directors and officers. The provision also does not affect a director’s responsibilities under any other law, such as the federal securities law or state or federal environmental laws.

We have entered into indemnity agreements with each of our directors and executive officers that require us to indemnify such persons against expenses, judgments, fines, settlements and other amounts incurred (including expenses of a derivative action) in connection with any proceeding, whether actual or threatened, to which any such person may be made a party by reason of the fact that such person is or was a director or an executive officer of Isis or any of our affiliated enterprises, provided such person acted in good faith and in a manner such persons reasonably believed to be in, or not opposed to, the best interests of Isis and, with respect to any criminal proceeding, has no reasonable cause to believe his conduct was unlawful. The indemnification agreements also set forth procedures that will apply in the event of a claim for indemnification thereunder.

We have an insurance policy covering our officers and directors with respect to certain liabilities, including liabilities arising under the Securities Act or otherwise.

EXHIBITS

**Exhibit
Number**

- 5.1 Opinion of Grantland E. Bryce
- 23.1 Consent of Independent Registered Public Accounting Firm
- 23.2 Consent of Grantland E. Bryce. Reference is made to Exhibit 5.1
- 24.1 Power of Attorney is contained on the signature pages
- 99.1 Amended and Restated 2000 Employee Stock Purchase Plan (1)

(1) Filed as an exhibit to the Registrant's Notice of Annual Meeting and Proxy Statement for the 2009 Annual Meeting of Stockholders, filed with the SEC on April 20, 2009, and incorporated herein by reference.

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UNDERTAKINGS

1. The undersigned registrant hereby undertakes:

(a) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:

(i) To include any prospectus required by section 10(a)(3) of the Securities Act;

(ii) To reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20% change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective registration statement.

(iii) To include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement;

Provided, however, that paragraphs (a)(i) and (a)(ii) do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the Commission by the registrant pursuant to section 13 or section 15(d) of the Exchange Act that are incorporated by reference in the registration statement.

(b) That, for the purpose of determining any liability under the Securities Act, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered herein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

(c) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

(d) That, for the purpose of determining liability of the registrant under the Securities Act to any purchaser in the initial distribution of the securities, the undersigned registrant undertakes that in a primary offering of securities of the undersigned registrant pursuant to this registration statement, regardless of the underwriting method used to sell the securities to the purchaser, if the securities are offered or sold to such purchaser by means of any of the following communications, the undersigned registrant will be a seller to the purchaser and will be considered to offer or sell such securities to such purchaser:

(i) Any preliminary prospectus or prospectus of the undersigned registrant relating to the offering required to be filed pursuant to Rule 424;

(ii) Any free writing prospectus relating to the offering prepared by or on behalf of the undersigned registrant or used or referred to by the undersigned registrant;

(iii) The portion of any other free writing prospectus relating to the offering containing material information about the undersigned registrant or its securities provided by or on behalf of the undersigned registrant; and

(iv) Any other communication that is an offer in the offering made by the undersigned registrant to the purchaser.

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2. The undersigned registrant hereby undertakes that, for purposes of determining any liability under the Securities Act, each filing of the registrant's annual report pursuant to Section 13(a) or Section 15(d) of the Exchange Act (and, where applicable, each filing of an employee benefit plan's annual report pursuant to section 15(d) of the Exchange Act) that is incorporated by reference in the Registration Statement shall be deemed to be a new registration statement relating to the securities offered herein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.
3. Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

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 June 23, 2009.

ISIS PHARMACEUTICALS, INC.

By: /s/B. Lynne Parshall
 B. Lynne Parshall
 Chief Operating Officer, 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 and B. Lynne Parshall, and each or any one of them, his true and lawful attorney-in-fact and agent, with full power of substitution and resubstitution, for him and in his 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 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 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.

<u>Signature</u>	<u>Title</u>	<u>Date</u>
<u>/s/Stanley T. Crooke</u> Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, Chief Executive Officer and President (Principal Executive Officer)	June 23, 2009
<u>/s/B. Lynne Parshall</u> B. Lynne Parshall	Chief Operating Officer and Chief Financial Officer (Principal Financial and Accounting Officer)	June 23, 2009
<u>/s/Spencer R. Berthelsen</u> Spencer R. Berthelsen	Director	June 23, 2009
<u>/s/Richard D. DiMarchi</u> Richard D. DiMarchi	Director	June 23, 2009
<u>Joseph Klein, III</u>	Director	June 23, 2009
<u>/s/Frederick T. Muto</u> Frederick T. Muto	Director	June 23, 2009
<u>/s/John C. Reed</u> John C. Reed	Director	June 23, 2009
<u>/s/Joseph H. Wender</u> Joseph H. Wender	Director	June 23, 2009

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June 23, 2009

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008

Ladies and Gentlemen:

You have requested my 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 an aggregate of 1,500,000 shares of the Company's Common Stock, \$.001 par value (the "Shares") issuable pursuant to its Amended & Restated 2000 Employee Stock Purchase Plan (the "ESPP"), as described in the Registration Statement.

In connection with this opinion, I have examined and relied upon the Registration Statement, the Company's Amended and Restated Certificate of Incorporation and Bylaws and the originals or copies certified to my satisfaction, of such records, documents, certificates, memoranda and other instruments as in my judgment are necessary or appropriate to enable me to render the opinion expressed below.

On the basis of the foregoing, and in reliance thereon, I am of the opinion that the Shares, when issued and sold in accordance with the ESPP and related prospectus, will be validly issued, fully paid and nonassessable.

I consent to the reference to myself under the caption "Interests of Named Experts and Counsel" in the Registration Statement and to the filing of this opinion as an exhibit to the Registration Statement.

Very truly yours,

/s/Grantland E. Bryce

Grantland E. Bryce
Vice President, General Counsel

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the Registration Statement (Form S-8) pertaining to the Amended & Restated 2000 Employee Stock Purchase Plan of Isis Pharmaceuticals, Inc. of our reports dated February 23, 2009, with respect to the consolidated financial statements of Isis Pharmaceuticals, Inc. and the effectiveness of internal control over financial reporting of Isis Pharmaceuticals, Inc., included in its Annual Report (Form 10-K) for the year ended December 31, 2008, filed with the Securities and Exchange Commission.

/s/ Ernst & Young LLP

San Diego, California
June 22, 2009
