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As filed with the Securities and Exchange Commission on May 7, 2013

Registration No. 333-

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM S-3
REGISTRATION STATEMENT
Under
THE SECURITIES ACT OF 1933

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 Number)

2855 Gazelle Court
Carlsbad, California 92010
(760) 931-9200

(Address, including zip code, and telephone number, including area code, of Registrant's principal executive offices)

B. Lynne Parshall, J.D.
Chief Operating Officer
Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, California 92010
Tel: (760) 931-9200
Fax: (760) 918-3592

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

Copies to:
Patrick R. O'Neil, Esq.
SVP Legal & General Counsel
Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, California 92010
Tel: (760) 931-9200
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Approximate date of commencement of proposed sale to the public:
From time to time after the effective date of this Registration Statement.

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box.

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box.

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer

Accelerated filer

Non-accelerated filer
(Do not check if a
smaller reporting company)

Smaller reporting company

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	Amount to be Registered	Proposed Maximum Offering Per Price Unit	Proposed Maximum Aggregate Offering Price	Amount of Registration Fee
Common Stock, par value \$0.001 per share	(1)	(1)	(1)	(2)

(1) Omitted pursuant to Form S-3 General Instruction II.E. Such indeterminate number or amount of common stock is being registered as may from time to time be offered at indeterminate prices pursuant to this registration statement.

(2) In accordance with Rules 456(b) and 457(r) under the Securities Act, the registrant is deferring payment of all of the registration fee and is omitting this information.



Common Stock

We may from time to time offer and sell common stock in amounts, at prices and on terms described in one or more supplements to this prospectus.

This prospectus describes some of the general terms that may apply to an offering of our common stock. The specific terms and any other information relating to a specific offering will be set forth in a post-effective amendment to the registration statement of which this prospectus is a part or in a supplement to this prospectus or may be set forth in one or more documents incorporated by reference in this prospectus.

Our securities may be offered and sold in the same offering or in separate offerings; to or through underwriters, dealers, and agents; or directly to purchasers. The names of any underwriter, dealer or agents involved in the sale of our securities and their compensation will be described in an applicable prospectus supplement. See "Plan of Distribution." You should read this prospectus and the applicable prospectus supplement before you invest in our common stock.

Our common stock is currently traded on The NASDAQ Global Select Market under the symbol "ISIS."

Investing in our common stock involves risks.

See "Risk Factors" on page 3 of this prospectus, in the applicable prospectus supplement and similar headings in documents incorporated by reference herein and therein before investing in our common stock.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or the SEC, using the "shelf" registration process as a "well-known seasoned issuer," as defined in Rule 405 under the Securities Act of 1933, as amended, or the Securities Act. By using a shelf registration statement, we may offer and sell from time to time in one or more offerings the common stock described in this prospectus. No limit exists on the aggregate number of shares of common stock we may sell pursuant to the registration statement.

Neither we nor any underwriters named in any prospectus supplement have authorized anyone to provide you with information different from that contained in or incorporated by reference into this prospectus or any applicable prospectus supplement. We take no responsibility for, and can provide no assurance as to the reliability of, any information that others may give you. This document may only be used where it is legal to sell these securities. You should not assume that the information contained in this prospectus, any prospectus supplement or any free writing prospectus prepared by or on behalf of us to which we have referred you, is accurate as of any date other than their respective dates regardless of the time of delivery or any sale of the common stock. Our business, financial condition, results of operations and prospects may have changed since that date.

This prospectus and the information incorporated herein by reference include trademarks, service marks and trade names owned by us or other companies. All trademarks, service marks and trade names included or incorporated by reference in this prospectus are the property of their respective owners.

We urge you to read carefully both this prospectus and any prospectus supplement accompanying this prospectus, together with the information incorporated herein by reference as described under the heading "Where You Can Find More Information," before deciding whether to invest in any of the securities being offered.

PROSPECTUS SUMMARY

The following summary does not contain all of the information that may be important to purchasers of our securities. Prospective purchasers of securities should carefully review the detailed information and financial statements, including the notes thereto, appearing elsewhere in or incorporated by reference into this prospectus and any prospectus supplement.

We are exploiting our leadership position in antisense technology to discover and develop novel drugs for our product pipeline and for our partners. Our broad pipeline consists of 28 drugs in various stages of development to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, and cancer. Our partner, Genzyme, is commercializing our lead product, KYNAMRO™, in the United States for the treatment of patients with homozygous familial hypercholesterolemia, or HoFH. Genzyme is also pursuing marketing approval of KYNAMRO in other markets. We maintain a website at www.isispharm.com. The reference to our website does not constitute incorporation by reference into this prospectus of any of the information contained on or accessible through our website.

Our principal executive offices are located at 2855 Gazelle Court, Carlsbad, CA 92010, and our telephone number is (760) 931-9200. We incorporated in California in 1989, and in January 1991 we changed our state of incorporation to Delaware.

In this prospectus, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals, Inc. and its consolidated subsidiaries.

Isis Pharmaceuticals® is a registered trademark of Isis Pharmaceuticals, Inc.

KYNAMRO™ is a trademark of Genzyme Corporation.

RISK FACTORS

Investing in our securities involves risks. Please see the risk factors described under the caption "Risk Factors" in our most recent Annual Report on Form 10-K and in our most recent Quarterly Report on Form 10-Q filed with the SEC, as well as any amendments thereto reflected in subsequent filings with the SEC, which are incorporated by reference in this prospectus and in any accompanying prospectus supplement. Before making an investment decision, you should carefully consider these risks as well as information we include or incorporate by reference in this prospectus and in any accompanying prospectus supplement. The risks and uncertainties we have described are not the only ones that we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our business or operations.

FORWARD-LOOKING STATEMENTS

This prospectus, each prospectus supplement and the documents incorporated herein and therein by reference contain forward-looking statements regarding our business, the therapeutic and commercial potential of our technologies and products in development, and our financial position. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of KYNAMRO, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors known by us at the times the statements are made. As a result, you are cautioned not to rely on these forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in the section entitled "Risk Factors", as well as in our most recent Annual Report on Form 10-K and in our most recent Quarterly Report on Form 10-Q filed with the SEC.

We claim the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995 for all forward-looking statements.

USE OF PROCEEDS

Unless otherwise indicated in an applicable prospectus supplement, we will use the net proceeds from the sale of the securities for general corporate purposes and to fund our capital expenditures and working capital requirements. Pending the application of the net proceeds, we intend to invest the net proceeds in investment-grade, interest-bearing securities.

DESCRIPTION OF CAPITAL STOCK

Our authorized capital stock consists of:

- Series B Convertible Exchangeable 5% Preferred Stock, 4,605 shares of which were authorized and none of which was issued and outstanding as of March 31, 2013;
- Series C Junior Participating Preferred Stock, 1,000,000 shares of which were authorized and none of which was issued and outstanding as of March 31, 2013; and
- Common stock, 200,000,000 shares of which were authorized and 102,695,200 shares of which were outstanding as of March 31, 2013.

Preferred Stock

Blank Check Preferred Stock

We are authorized to issue up to 15,000,000 shares of "blank check" preferred stock. Our board of directors has the authority to fix the rights and preferences of and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

Series B Convertible Exchangeable 5% Preferred Stock

As of March 31, 2013, there were no Series B Convertible Exchangeable 5% Preferred Stock shares outstanding. We do not intend to issue any of the remaining authorized but unissued Series B Convertible Exchangeable 5% Preferred Stock.

Series C Junior Participating Preferred Stock

Series C Junior Participating Preferred Stock is designated but not outstanding. Each one one-hundredth of a share of the Series C Preferred Stock has designations and powers, preferences and rights, and qualifications, limitations and restrictions that make its value approximately equal to the value of a share of our common stock.

Common Stock

As of March 31, 2013, we had 200,000,000 shares of common stock authorized, of which 102,695,200 were issued and outstanding. As of March 31, 2013, total common shares reserved for future issuance upon the exercise or conversion of outstanding securities that are exercisable or convertible into shares of our common stock was approximately 23,560,141.

Voting Rights

Holders of our common stock are entitled to one vote per share on all matters to be voted upon by stockholders.

Dividend Rights

Subject to preferences that may apply to shares of preferred stock outstanding at the time, the holders of outstanding shares of common stock are entitled to receive dividends out of assets legally available at the times and in the amounts that our board of directors may determine from time to time.

No Preemptive or Redemption Rights; Right to Receive Liquidation Distributions

Our common stock is not entitled to preemptive rights and is not subject to redemption or sinking fund provisions. Upon our liquidation, dissolution or winding-up, the holders of common stock are entitled to share equally in all of our assets remaining after payment of all liabilities and the liquidation preferences of any outstanding preferred stock.

Classified Board of Directors

Our certificate of incorporation provides for classified terms for the members of our board of directors. The board of directors is divided into three classes. Presently, the board of directors has six members with one class consisting of three directors, one class consisting of two directors, and one class consisting of one director. Each class serves a three-year term.

Size of the Board of Directors; Removal of Directors; Vacancies

Our certificate of incorporation and bylaws authorize our board of directors to fix the number of directors from time to time without stockholder approval. The board of directors is currently comprised of six members. Directors may be removed with cause by a majority of the outstanding shares entitled to vote or without cause upon the approval of at least $66\frac{2}{3}$ percent of the outstanding shares entitled to vote. All vacancies on the board of directors are to be filled by the directors then in office.

Power to Call Special Stockholder Meetings; Stockholder Action by Written Consent; Advance Notice of Stockholder Business and Nominees

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. Only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. In addition, our certificate of incorporation and bylaws require advance notice for nominations for election to our board of directors or for proposing matters that can be acted upon by stockholders at a stockholder meeting.

Amendment of Bylaws

Our board of directors is authorized to adopt, alter or repeal our bylaws, while our bylaws may be adopted, amended or repealed by stockholders only through the approval of at least $66\frac{2}{3}$ percent of the outstanding shares entitled to vote.

Fair Price Provision; Anti-takeover Effects of Delaware Law

Our certificate of incorporation includes a provision that requires at least $66\frac{2}{3}$ percent of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15 percent or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

In addition, we are subject to Section 203 of the Delaware General Corporation Law (the "DGCL"), which prohibits a Delaware corporation from engaging in any business combination with any

interested stockholder for a period of three years after the date that such stockholder became an interested stockholder, unless:

- the transaction is approved by the board before the date the interested stockholder attained that status;
- upon consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced; or
- on or after the date the business combination is approved by the board and authorized at a meeting of stockholders by at least two-thirds of the outstanding voting stock that is not owned by the interested stockholder.

A "business combination" is defined to include mergers, asset sales and other transactions resulting in financial benefit to a stockholder. In general, an "interested stockholder" is a person who, together with affiliates and associates, owns (or within three years prior to the determination of interested stockholder status, did own) 15% or more of a corporation's voting stock.

The fair price provision and Section 203 of the DGCL could prohibit or delay mergers or other takeover or change in control attempts with respect to us and, accordingly, may discourage attempts to acquire us even though such a transaction may offer our stockholders the opportunity to sell their stock at a price above the prevailing market price.

Limitation of Liability and Indemnification Matters

Our certificate of incorporation and bylaws include provisions to eliminate the personal liability of our directors for monetary damages resulting from breaches of their fiduciary duty to the extent permitted under Delaware law. Delaware law provides that directors of a company will not be personally liable for monetary damages for breach of their fiduciary duty as directors, except for liabilities:

- for any breach of their duty of loyalty to us or our stockholders;
- for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law;
- for unlawful payment of dividend or unlawful stock repurchase or redemption, as provided under Section 174 of the DGCL; or
- for any transaction from which the director derived an improper personal benefit.

In addition, our bylaws provide that we will indemnify our directors and executive officers to the fullest extent not prohibited by Delaware law or any other applicable law, except that we will generally not be required to indemnify a director or executive officer in connection with any proceeding initiated by such director or executive officer. In addition, we have entered into indemnity agreements with each of our executive officers and directors and certain non-executive officers which provide, among other things, that we will indemnify such officer or director, under the circumstances and to the extent provided for therein, for expenses, damages, judgments, fines and settlements he or she may be required to pay in actions or proceedings which he or she is or may be made a party by reason of his or her position as a director, officer or other agent of Isis, and otherwise to the fullest extent permitted under Delaware law and our bylaws.

Equity Incentive Plans

1989 Stock Option Plan

In March 2004, our board of directors adopted, and our stockholders subsequently approved an amendment and restatement of our 1989 Stock Option Plan that provides for the issuance of non-qualified and incentive stock options for the purchase of up to 20,000,000 shares of common stock to our employees, directors, and consultants. In 2012 our board of directors adopted, and our stockholders subsequently approved an amendment to the 1989 Stock Option Plan such that the plan expires in January 2024. The 1989 Plan does not allow us to grant stock bonuses or restricted stock awards and prohibits us from repricing any options outstanding under the plan unless our stockholders approve the repricing. Options generally vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options we granted after May 26, 2004 have a term of seven years while options we granted before May 26, 2004 have a term of ten years. As of March 31, 2013, a total of 8,739,799 options were outstanding under the 1989 Stock Option Plan, of which options to purchase 4,829,078 shares were exercisable, and 321,295 shares were available for future grant under the 1989 plan.

2000 Broad Based Equity Incentive Plan

In January 2000, we adopted the 2000 Broad-Based Equity Incentive Plan (the "2000 Plan"), which, as amended, provided for the issuance of non-qualified stock options for the purchase of up to 5,990,000 shares of common stock to our employees, directors, and consultants. Typically options expire seven or ten years from the date of grant. Options granted under this plan generally vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. As of March 31, 2013, a total of 1,839,046 options were outstanding, of which 1,823,793 shares were exercisable, and no shares were available for future grant under the 2000 Plan. The 2000 Plan expired on January 5, 2010, so we may no longer grant new options under the 2000 Plan.

Change of Control Under 1989 Plan and 2000 Plan

With respect to both the 1989 Plan and 2000 Plan, in the event of:

- a sale, lease or other disposition of all or substantially all of our assets;
- a merger or consolidation in which we are not the surviving corporation; or
- reverse merger in which we are the surviving corporation but the shares of 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 any surviving corporation or acquiring corporation will assume any stock awards outstanding under the 1989 Plan and the 2000 Plan or will substitute similar stock awards (including an award to acquire the same consideration paid to the stockholders in the transaction for those outstanding under the 1989 Plan and the 2000 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar stock awards for those outstanding under the 1989 Plan and the 2000 Plan, then with respect to stock awards held by participants whose continuous service has not terminated, such stock awards automatically vest in full and the stock awards will terminate if not exercised (if applicable) at or prior to such event.

2011 Equity Incentive Plan

In March 2011, our board of directors adopted, and our stockholders subsequently approved, a stock option plan that provides for the issuance of stock options, stock appreciation rights, restricted

stock awards, restricted stock unit awards, and performance cash awards. The plan provides for the purchase of up to 2,000,000 shares of common stock for issuance to our employees, directors, and consultants. The plan expires in June 2021. The 2011 Plan does not allow us to reduce the exercise price of any outstanding stock options or stock appreciation rights or cancel any outstanding stock options or stock appreciation rights that have an exercise price or strike price greater than the current fair market value of the common stock in exchange for cash or other stock awards unless our stockholders approve such action. Currently we anticipate awarding only options and restricted stock units awards to our employees, directors and consultants. Under the 2011 Plan, stock options generally cannot vest in a period of less than two years and restricted stock unit awards cannot vest in a period of less than three years, subject to certain exceptions. Starting in 2012, we also grant restricted stock unit awards to our employees under the 2011 Plan which vest annually over a four year period. As of March 31, 2013, no options were outstanding or exercisable, 383,765 restricted stock unit awards were outstanding, and 1,577,858 shares were available for future grant under the 2011 Plan. As part of our Proxy Statement for our 2013 Annual Meeting of Stockholders, we included a proposal recommending our stockholders approve an amendment to the 2011 Plan to increase the shares available for issuance under the 2011 Plan to a total of 5,500,000 shares.

Under the 2011 Plan, we may issue a stock award with additional acceleration of vesting and exercisability upon or after a change in control. In the absence of such provisions, no such acceleration will occur. The stock options and restricted stock unit awards we issue to our chief executive officer and chief operating officer will accelerate upon a change of control, as defined in the 2011 Plan.

Corporate Transactions and Change in Control under 2011 Plan

In the event of certain significant corporate transactions, our board of directors has the discretion to take one or more of the following actions with respect to outstanding stock awards under the 2011 Plan:

- arrange for assumption, continuation, or substitution of a stock award by a surviving or acquiring entity (or its parent company);
- arrange for the assignment of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award to the surviving or acquiring corporation (or its parent company);
- accelerate the vesting and exercisability of a stock award followed by the termination of the stock award;
- arrange for the lapse of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award;
- cancel or arrange for the cancellation of a stock award, to the extent not vested or not exercised prior to the effective date of the corporate transaction, in exchange for cash consideration, if any, as the Board, in its sole discretion, may consider appropriate; and
- arrange for the surrender of a stock award in exchange for a payment equal to the excess of (a) the value of the property the holder of the stock award would have received upon the exercise of the stock award, over (b) any exercise price payable by such holder in connection with such exercise.

2002 Non-Employee Directors' Stock Option Plan

In March 2012, our board of directors adopted, and our stockholders subsequently approved, an amendment and restatement of the 2002 Non-Employee Directors' Stock Option Plan (the "2002

Plan"). The 2002 Plan provides for the issuance of stock options and restricted stock unit awards to our non-employee directors for the purchase of up to 1,200,000 shares of our common stock.

Options under this plan expire ten years from the date of grant. Options granted become exercisable, and restricted stock unit awards vest in four equal annual installments beginning one year after the date of grant. As of March 31, 2013, a total of 490,000 options were outstanding, of which 355,000 shares issued were exercisable, 5,000 restricted stock unit awards were outstanding, and 402,000 shares were available for future grant under the 2002 Plan.

Corporate Transactions and Change of Control Under 2002 Plan

With respect to the 2002 Plan, in the event of:

- a sale or other disposition of all or substantially all of our assets;
- a sale or other disposition of at least 90% of our outstanding securities;
- a merger or consolidation in which we are not the surviving corporation; or
- a reverse merger in which we are the surviving corporation but the shares of 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 any surviving corporation or acquiring corporation will assume any stock awards outstanding under the 2002 Plan or will substitute similar awards (including an award to acquire the same consideration paid to the stockholders in the transaction for those outstanding under the 2002 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar awards for those outstanding under the 2002 Plan, then with respect to awards held by participants whose continuous service has not terminated, such awards automatically vest in full and the awards will terminate if not exercised (if applicable) at or prior to such event.

In addition, in the event (other than a dissolution or liquidation):

- any person becomes the owner of our securities representing more than 50% of the combined voting power of our outstanding securities other than by virtue of a merger;
- consolidation or similar transaction and other than by a purchase of securities directly from us;
- of a merger or consolidation in which our stockholders immediately prior to the merger or consolidation no longer own outstanding voting securities representing 50% of the combined voting power of the entity surviving the merger or consolidation;
- of a sale, lease or other disposition of all or substantially all of our assets; or
- a majority of our board of directors is replaced by individuals who are not nominated by members of our current board of directors or members nominated by our current board of directors or their nominees,

then notwithstanding the assumption or substitution of awards, the vesting and exercisability of awards held by participants whose continuous service has not terminated automatically accelerate in full.

Employee Stock Purchase Plan

In June 2009, our board of directors adopted, and our stockholders subsequently approved, the amendment and restatement of the 2000 ESPP and we reserved an additional 150,000 shares of common stock for issuance thereunder. In each of the subsequent years, we reserved an additional 150,000 shares of common stock for the ESPP resulting in a total of 317,286 shares authorized in the plan as of March 31, 2013. The ESPP permits full-time employees to purchase common stock through

payroll deductions (which cannot exceed 10 percent of each employee's compensation) at the lower of 85 percent of fair market value at the beginning of the purchase period or the end of each six-month purchase period. Under the amended and restated ESPP, employees must hold the stock they purchase for a minimum of six months from the date of purchase beginning with the offering ending in January 1, 2010. During 2012, employees purchased and we issued to employees 124,001 shares under the ESPP at \$6.13 per share. As of March 31, 2013, a total of 317,286 shares were available for purchase under the ESPP.

Listing

Our common stock is listed on The NASDAQ Global Select Market under the symbol "ISIS."

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer and Trust. Its address is 59 Maiden Lane, Plaza Level, New York, New York 10038 and its telephone number is (718) 921-8124.

DESCRIPTION OF CONVERTIBLE SENIOR NOTES

In August 2012, we completed a \$201.3 million convertible debt offering. The \$201.3 million of convertible senior notes mature in 2019 and bear interest at $2\frac{3}{4}$ percent, which is payable semi-annually. The $2\frac{3}{4}$ percent notes are convertible under certain conditions, at the option of the note holders, into approximately 12.1 million shares of our common stock at a conversion price of \$16.63 per share. We will settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both. We can redeem the $2\frac{3}{4}$ percent notes at our option, in whole or in part, on or after October 5, 2016 if the last reported sale price of our common stock for at least 20 trading days (whether or not consecutive) during the period of 30 consecutive trading days ending on the trading day immediately preceding the date we provide the redemption notice exceeds 130 percent of the applicable conversion price for the $2\frac{3}{4}$ percent notes on each such day. The redemption price for the $2\frac{3}{4}$ percent notes will equal 100 percent of the principal amount being redeemed, plus accrued and unpaid interest, plus \$90 per each \$1,000 principal amount being redeemed. Holders of the $2\frac{3}{4}$ percent notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indenture governing the $2\frac{3}{4}$ percent notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest.

PLAN OF DISTRIBUTION

We may sell the offered securities in one or more of the following ways, or any manner specified in a prospectus supplement:

- to or through an underwriter or underwriters;
- through dealers;
- through agents;
- directly to one or more purchasers, including affiliates of ours; or
- through a combination of any of these methods of sale.

The applicable prospectus supplement will contain the terms of the offerings of any securities. The public offering price and any discount or concessions allowed or reallocated to dealers may be changed from time to time. The applicable prospectus supplement will contain the expected time of delivery of the securities for which this prospectus is delivered.

Unless otherwise indicated in the applicable prospectus supplement, if underwriters are used in the sale of the securities, the underwriting agreement will provide that the obligations of the underwriters are subject to certain conditions precedent and that the underwriters will be obligated to purchase all of the securities if any are purchased. In connection with the sale of securities, underwriters may receive compensation from us or purchasers of securities for whom they may act as agents in the form of discounts, concessions or commissions. Underwriters may sell securities to or through dealers, and dealers may receive compensation in the form of discounts, concessions or commissions from the underwriters and/or commissions from the purchasers for whom they may act as agent.

Underwriters, agents or dealers participating in the distribution of securities may be deemed to be underwriters, and any discounts and commissions received by them and any profit realized by them on resale of the securities may be deemed to be underwriting discounts and commissions under the Securities Act. The securities may be sold in one or more transactions either at a fixed price or at prices which may be changed based on market prices prevailing at the time of sale, at prices related to the prevailing market prices or at negotiated prices. Any underwriter, dealer or agent will be acting on a best efforts basis or, if indicated in the applicable prospectus supplement, on a firm commitment basis.

We may indemnify the underwriters, agents or dealers who participate in the distribution of securities against certain liabilities, including liabilities under the Securities Act. We may also contribute to payments that the underwriters, dealers or agents or any of their controlling persons may be required to make in respect of such liabilities. Underwriters, agents or dealers may be customers of, engage in transactions with or perform services for us or our subsidiaries in the ordinary course of business.

If so indicated in a prospectus supplement, we will authorize underwriters, dealers and agents to solicit offers by certain institutions to purchase securities from us pursuant to delayed delivery contracts providing for payment and delivery on the date stated in the prospectus supplement. These contracts will be subject only to those conditions contained in the prospectus supplement. The prospectus supplement will also contain the commission payable for solicitation of any of these contracts.

Offers to purchase securities may be solicited directly by us and sales of securities may be made by us directly to institutional investors or others who may be deemed to be underwriters within the meaning of the Securities Act, with respect to any resale of the securities. The terms of any such sales will be described in the prospectus supplement relating to the securities. Except as contained in the applicable prospectus supplement, no director, officer or employee of ours will solicit or receive a commission in connection with the direct sales by us of the securities, although these persons may respond to inquiries by potential purchasers and perform ministerial and clerical work in connection with any such direct sales.

LEGAL MATTERS

The validity of the issuance of the common stock offered hereby will be passed upon for us by Patrick R. O'Neil, our Senior Vice President, Legal and General Counsel.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2012, and the effectiveness of our internal control over financial reporting as of December 31, 2012, as set forth in their reports, which are incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements and our management's assessment of the effectiveness of internal control over financial reporting as of December 31, 2012 are incorporated by reference in reliance on Ernst & Young LLP's reports, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND ADDITIONAL INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's web site at www.sec.gov. You may also read and copy any document we file at the SEC's public reference room at 100 F Street, N.E., Washington, D.C. 20549. You may obtain information on the operation of the SEC's public reference room in Washington, D.C. by calling the SEC at 1-800-SEC-0330.

We have filed with the SEC a registration statement under the Securities Act relating to the offering of these securities. The registration statement, including the attached exhibits, contains additional relevant information about us and the securities. This prospectus does not contain all of the information set forth in the registration statement. You can obtain a copy of the registration statement (including the exhibits and schedules thereto), at prescribed rates, from the SEC at the address listed above or from the SEC's website.

The registration statement and the documents referred to below under "Incorporation by Reference" are also available on our corporate website, www.isispharm.com. We have not incorporated by reference into this prospectus the information on our website, and you should not consider it to be a part of this prospectus.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" in this prospectus the information that we file with it. This means that we can disclose important information to you in this document by referring you to other filings we have made with the SEC. The information incorporated by reference is considered to be part of this prospectus. The information incorporated by reference in this prospectus is accurate only as of the date of the information on the front cover of the applicable document, or such earlier date as is expressly stated or otherwise apparent with respect to such incorporated information in the applicable document, regardless of the time of delivery of this prospectus or any sale of securities.

This prospectus incorporates by reference the documents listed below, which we have filed with the SEC:

- our Annual Report on Form 10-K for our fiscal year ended December 31, 2012, filed on February 28, 2013;
- our Quarterly Report on Form 10-Q for our quarter ended March 31, 2013, filed on May 7, 2013;
- portions of our Definitive Proxy Statement on Schedule 14A filed on April 26, 2013 incorporated by reference into the Annual Report on Form 10-K for our fiscal year ended December 31, 2012;
- our Current Reports on Form 8-K filed on January 2, 2013, January 30, 2013, February 13, 2013 and April 8, 2013; 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 quarter ended March 31, 2006.

We incorporate by reference any additional documents that we may file with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Exchange Act (other than the portions of those made pursuant to Item 2.02 or Item 7.01 of Form 8-K or other information "furnished" to the SEC) prior to the termination of the offering of the securities. These documents may include periodic reports, like

Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q and Current Reports on Form 8-K, as well as Proxy Statements. Any material that we subsequently file with the SEC will automatically update and replace the information previously filed with the SEC.

This prospectus may contain information that updates, modifies or is contrary to information in one or more of the documents incorporated by reference in this prospectus. You should rely only on the information incorporated by reference or provided in this prospectus. We have not authorized anyone else to provide you with different information. You should not assume that the information in this prospectus is accurate as of any date other than the date of this prospectus or the date of the documents incorporated by reference in this prospectus.

We will provide to each person, including any beneficial owner, to whom this prospectus is delivered, upon written or oral request, at no cost, a copy of any and all of the information that is incorporated by reference in this prospectus.

Requests for such documents should be directed to:

Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, California 92010
(760) 931-9200
Attention: General Counsel

In addition, copies of our filings are available through our corporate website at www.isispharm.com as soon as reasonably practicable after we electronically file such material with the SEC.

Part II**INFORMATION NOT REQUIRED IN PROSPECTUS****Item 14. Other Expenses of Issuance and Distribution**

The following table sets forth all expenses payable by the Registrant in connection with the sale of the securities being registered. All the amounts shown are estimates except for the registration fee.

SEC registration fee	*
Nasdaq Global Market Listing Fee	**
Printing Fees	**
Legal fees and expenses	**
Accounting fees and expenses	**
Miscellaneous	**
Total	**

* In accordance with Rule 456(b) and 457(r) we are deferring payment of the registration fee for the securities offered by this prospectus.

** Since an indeterminate amount of securities is covered by this registration statement, the expenses in connection with the issuance and distribution of the securities are not currently determinable.

Item 15. Indemnification of Officers and Directors

Under Section 145 of the Delaware General Corporation Law, the Registrant has broad powers to indemnify its Directors and officers against liabilities they may incur in such capacities, including liabilities under the Securities Act of 1933.

The Registrant's Certificate of Incorporation and Bylaws 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 (the "Delaware Law") and (ii) require the Registrant to indemnify its 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. The Registrant believes 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 the Registrant, 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 the Registrant or its 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 the Registrant or its stockholders when the Director was aware or should have been aware of a risk of serious injury to the Registrant or its stockholders, for acts or omissions that constitute an unexcused pattern of inattention that amounts to an abdication of the Director's duty to the Registrant or its stockholders, for improper transactions between the Director and the Registrant 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.

The Registrant has entered into indemnity agreements with each of its Directors and executive officers that require the Registrant 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 the Registrant or any of its 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 the Registrant and, with respect to any criminal proceeding, has no reasonable cause to believe his conduct was unlawful. The indemnification agreements also set forth certain procedures that will apply in the event of a claim for indemnification thereunder.

At present, there is no pending litigation or proceeding involving a Director or officer of the Registrant as to which indemnification is being sought, nor is the Registrant aware of any threatened litigation that may result in claims for indemnification by any officer or Director.

The Registrant has an insurance policy covering the officers and Directors of the Registrant with respect to certain liabilities, including liabilities arising under the Securities Act or otherwise.

Item 16. Exhibits

(a) The following exhibits are filed as part of this Registration Statement:

<u>Exhibit Number</u>	<u>Description of Document</u>
1.1	Form of Underwriting Agreement*
3.1	Amended and Restated Certificate of Incorporation filed June 19, 1991.(1)
3.2	Certificate of Amendment to Restated Certificate of Incorporation filed on May 3, 2006.(2)
3.3	Amended and Restated Bylaws.(3)
4.1	Specimen Common Stock Certificate.(1)
5.1	Opinion of Patrick R. O'Neil
23.1	Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm.
23.2	Consent of Patrick R. O'Neil is contained in Exhibit 5.1 to this Registration Statement.
24.1	Power of Attorney is contained on the signature pages hereto.

* To be filed by amendment or as an exhibit to a document to be incorporated by reference herein.

- (1) Filed as an exhibit to the Registrant's Registration Statement on Form S-1 (No. 33-39640) or amendments thereto and incorporated herein by reference.
- (2) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2006 and incorporated herein by reference.
- (3) Filed as an exhibit to Registrant's report on Form 10-Q as amended for the quarter ended June 30, 2001 and incorporated herein by reference.

Item 17. Undertakings

(a) The undersigned registrant hereby undertakes:

- (1) 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 of 1933;
 - (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 Securities and Exchange Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20 percent change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective registration statement; and
 - (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 the undertakings set forth in paragraphs (1)(i), (1)(ii) and (1)(iii) above 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 Securities and Exchange Commission by the registrant pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 that are incorporated by reference in the registration statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is a part of the registration statement.

- (2) That, for the purpose of determining any liability under the Securities Act of 1933, 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.
- (3) 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.
- (4) That, for the purpose of determining liability under the Securities Act of 1933 to any purchaser:

(A) Each prospectus filed by the registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the registration statement as of the date the filed prospectus was deemed part of and included in the registration statement; and

(B) Each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5), or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii), or (x) for the purpose of providing the information required by Section 10(a) of the Securities Act of 1933 shall be deemed to be part of and included in the registration statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in the prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a

new effective date of the registration statement relating to the securities in the registration statement to which that prospectus relates, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof. Provided, however, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date.

- (5) That, for the purpose of determining liability of the registrant under the Securities Act of 1933 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.

(b) The undersigned registrant hereby undertakes that, for purposes of determining any liability under the Securities Act of 1933, each filing of the registrant's annual report pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934 (and, where applicable, each filing of an employee benefit plan's annual report pursuant to Section 15(d) of the Securities Exchange Act of 1934) that is incorporated by reference in the registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

(c) Insofar as indemnification for liabilities arising under the Securities Act of 1933 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 of 1933 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.

(d) (1) For purposes of determining any liability under the Securities Act of 1933, the information omitted from the form of prospectus filed as part of this registration statement in reliance upon Rule 430A and contained in a form of prospectus filed by the registrant pursuant to Rule 424(b)(1) or

(4) or 497(h) under the Securities Act shall be deemed to be part of this registration statement as of the time it was declared effective.

(2) For purposes of determining any liability under the Securities Act of 1933, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

<u>Signatures</u>	<u>Title</u>	<u>Date</u>
<hr/> <i>/s/ SPENCER R. BERTHELSEN</i> <hr/>		
Spencer R. Berthelsen	Director	May 7, 2013
<hr/> <i>/s/ FREDERICK T. MUTO</i> <hr/>		
Frederick T. Muto	Director	May 7, 2013
<hr/> <i>/s/ JOSEPH KLEIN III</i> <hr/>		
Joseph Klein III	Director	May 7, 2013
<hr/> <i>/s/ JOSEPH H. WENDER</i> <hr/>		
Joseph H. Wender	Director	May 7, 2013

EXHIBIT INDEX

Exhibit Number	Description of Document
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3.3	Amended and Restated Bylaws.(3)
4.1	Specimen Common Stock Certificate.(1)
5.1	Opinion of Patrick R. O'Neil
23.1	Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm.
23.2	Consent of Patrick R. O'Neil is contained in Exhibit 5.1 to this Registration Statement.
24.1	Power of Attorney is contained on the signature pages hereto.

* To be filed by amendment or as an exhibit to a document to be incorporated by reference herein.

- (1) Filed as an exhibit to the Registrant's Registration Statement on Form S-1 (No. 33-39640) or amendments thereto and incorporated herein by reference.
 - (2) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2006 and incorporated herein by reference.
 - (3) Filed as an exhibit to Registrant's report on Form 10-Q as amended for the quarter ended June 30, 2001 and incorporated herein by reference.
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OPINION OF PATRICK R. O'NEIL

May 7, 2013

Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

Ladies and Gentlemen:

I have acted as counsel to Isis Pharmaceuticals, Inc., a Delaware corporation (the "**Company**"), in connection with a Registration Statement on Form S-3 (the "**Registration Statement**") to be filed by the Company under the Securities Act of 1933, as amended (the "**Securities Act**"). The Company has provided me with a prospectus (the "**Prospectus**"), which forms part of the Registration Statement. The Prospectus provides that it will be supplemented in the future by one or more prospectus supplements (each, a "**Prospectus Supplement**"). The Registration Statement, including the Prospectus as supplemented from time to time by one or more Prospectus Supplements, will provide for the registration by the Company of shares of common stock, par value \$0.001 per share, of the Company (the "**Common Stock**").

The Common Stock is being registered for offer and sale from time to time pursuant to Rule 415 under the Securities Act.

In connection with this opinion, I have examined and relied upon originals, or copies certified to my satisfaction, of such records, documents, certificates, opinions, memoranda and other instruments as in my judgment are necessary or appropriate to enable me to render the opinion expressed below. As to certain factual matters, I have relied upon certificates of officers of the Company and have not independently sought to verify such matters.

In rendering this opinion, I have assumed the genuineness and authenticity of all signatures on original documents; the authenticity of all documents submitted to me as originals; the conformity to originals of all documents submitted to me as copies; the accuracy, completeness and authenticity of certificates of public officials; and the due authorization, execution and delivery of all documents where authorization, execution and delivery are prerequisites to the effectiveness of such documents. With respect to my opinion as to the Common Stock, I have assumed that, at the time of issuance and sale, a sufficient number of shares of Common Stock are authorized and available for issuance and that the consideration for the issuance and sale of the Common Stock is in an amount that is not less than the par value of the Common Stock.

My opinion herein is expressed solely with respect to the federal laws of the United States and the Delaware General Corporation Law. My opinion is based on these laws as in effect on the date hereof. I express no opinion as to whether the laws of any jurisdiction are applicable to the subject matter hereof. I am not rendering any opinion as to compliance with any federal or state law, rule or regulation relating to securities, or to the sale or issuance thereof.

On the basis of the foregoing and in reliance thereon, and subject to the qualifications herein stated, I am of the opinion that, with respect to the Common Stock offered under the Registration Statement, provided that (i) the Registration Statement and any required post-effective amendment thereto have all become effective under the Securities Act and the Prospectus and any and all Prospectus Supplement(s) required by applicable laws and any and all free-writing prospectus(es) related to the offer and sale of the Common Stock have been delivered and filed as required by such laws; (ii) the issuance of the Common Stock has been duly authorized by all necessary corporate action on the part of the Company; (iii) the issuance and sale of the Common Stock do not violate any applicable law, are in conformity with the Company's then operative Amended and Restated Certificate of Incorporation (the "**Certificate of Incorporation**") and Bylaws, as amended (the "**Bylaws**"), do not result in a default under or breach of any agreement or instrument binding upon the Company and comply with any applicable requirement or restriction imposed by any court or governmental body having jurisdiction

over the Company; and (iv) the certificates for the Common Stock have been duly executed by the Company, countersigned by the transfer agent therefor and duly delivered to the purchasers thereof against payment therefor, then the Common Stock, when issued and sold as contemplated in the Registration Statement, the Prospectus and the related Prospectus Supplement(s) and any related free-writing prospectus(es) and in accordance with any applicable duly authorized, executed and delivered purchase, underwriting or similar agreement, will be duly authorized, validly issued, fully paid and nonassessable.

I hereby consent to the filing of this opinion as an exhibit to the Registration Statement and to the reference to me under the caption "Legal Matters" in the Prospectus included in the Registration Statement. In giving this consent, I do not admit that I am in the category of persons whose consent is required under Section 7 of the Securities Act. This opinion is expressed as of the date hereof, and I disclaim any undertaking to advise you of any subsequent changes in the facts stated or assumed herein or of any subsequent changes in applicable law.

Very truly yours,

Sincerely,

/s/ PATRICK R. O'NEIL

Patrick R. O'Neil
*Senior Vice President, Legal and
General Counsel*

QuickLinks

[EXHIBIT 5.1](#)

[OPINION OF PATRICK R. O'NEIL](#)

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the reference to our firm under the caption "Experts" in this Registration Statement (Form S-3) and related Prospectus of Isis Pharmaceuticals, Inc. for the registration of common stock and to the incorporation by reference therein of our reports dated February 28, 2013, 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, 2012, filed with the Securities and Exchange Commission.

/s/ ERNST &
YOUNG LLP

San Diego, California
May 7, 2013

QuickLinks

[EXHIBIT 23.1](#)

[CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM](#)