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# SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

## FORM 8-K

### CURRENT REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

Date of report (Date of earliest event reported): **August 22, 2005**

## ISIS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Charter)

**Delaware**

(State or Other Jurisdiction of Incorporation)

**000-19125**

(Commission File No.)

**33-0336973**

(IRS Employer Identification No.)

**1896 Rutherford Road**

**Carlsbad, CA 92008**

(Address of Principal Executive Offices and Zip Code)

Registrant's telephone number, including area code: **(760) 931-9200**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
  - Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
  - Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
  - Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))
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#### Item 1.01. Entry into a Material Definitive Agreement.

On August 22, 2005, Isis Pharmaceuticals, Inc. (the "Company"), entered into a Securities Purchase Agreement with the purchasers set forth on Exhibit A thereto (the "Securities Purchase Agreement"), pursuant to which the Company sold, at the closing on August 24, 2005, 12,000,000 shares of its common stock (the "Shares") and warrants to purchase up to 2,999,998 shares of its common stock (the "Warrants") resulting in aggregate gross proceeds to the Company of \$51 million (the "Private Placement"). The Warrants have an exercise price of \$5.2395 per share, become exercisable 180 days after the closing of the Private Placement and expire on August 24, 2010, unless earlier redeemed by the Company. Under the terms of the Securities Purchase Agreement, the Company has agreed to file, within 15 days after the closing of the Private Placement, a registration statement with the United States Securities and Exchange Commission (the "SEC") to register for resale the Shares and the shares of the Company's common stock issuable upon the exercise of the Warrants, and the Company has agreed to cause such registration statement to be declared effective by the SEC within (i) 60 days following such closing if the registration statement is not reviewed by the SEC, or (ii) 90 days following such closing if the registration statement is reviewed by the SEC.

Federated Kaufman Fund, a portfolio of Federated Equity Funds, which, together with its affiliates, held more than 5% of the Company's outstanding capital stock immediately prior to the closing of the Private Placement, purchased approximately \$20 million of the Shares and Warrants in the Private Placement.

The foregoing is a summary of the terms of the Securities Purchase Agreement, does not purport to be complete and is qualified in its entirety by reference to the full text of the Securities Purchase Agreement, a copy of which is attached hereto as Exhibit 99.1 and incorporated herein by reference, and the Warrants, a form of which is attached hereto as Exhibit 99.2 and incorporated herein by reference.

#### Item 3.02. Unregistered Sales of Equity Securities.

On August 24, 2005, the Company completed a private placement of the Shares and Warrants. Pursuant to the terms of the Securities Purchase Agreement, the Company sold 12,000,000 shares of its common stock and warrants to purchase up to 2,999,998 shares of its common stock. The exercise price of the Warrants is \$5.2395 per share. The Securities Purchase Agreement is attached hereto as Exhibit 99.1 and incorporated herein by reference. The form of Warrant and the other exhibits thereto is attached hereto as Exhibit 99.2 and incorporated herein by reference.

The aggregate offering price of the shares of Common Stock sold was \$51 million and the aggregate placement agent commissions were approximately \$3 million. Needham & Company, LLC and Fortis Securities LLC acted as the Company's placement agents for the Shares and Warrants issued in the Private Placement.

The offering was made only to accredited investors, as such term is defined in Rule 501 of Regulation D promulgated under the Securities Act of 1933, as amended (the "Securities Act"). The Shares and the Warrants issued to the purchasers have not been registered under the

Securities Act or any state securities laws. The Company relied on the exemption from the registration requirements of the Securities Act set forth in Section 4(2) thereof and the rules and regulations promulgated thereunder. As described in Item 1.01 of this current report, the Company has agreed to file a registration statement for the resale of the Shares and the shares of common stock underlying the Warrants. Neither this current report on Form 8-K nor any of the exhibits attached hereto is an offer to sell or the solicitation of an offer to buy shares of common stock or other securities of the Company.

**Item 8.01. Other Events.**

The press release, dated August 22, 2005, announcing the Private Placement is attached hereto as Exhibit 99.3 and is incorporated herein by reference.

**Item 9.01. Financial Statements and Exhibits.**

(c) Exhibits.

- 99.1 Securities Purchase Agreement, dated August 19, 2005, by and among the Company and the purchases listed on Exhibit A thereto.
- 99.2 Form of Warrant.
- 99.3 Press Release dated August 22, 2005.

**SIGNATURE**

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

**ISIS PHARMACEUTICALS, INC.**

Dated: August 24, 2005

By: /s/ B. Lynne Parshall  
**B. LYNNE PARSHALL**  
Executive Vice President,  
Chief Financial Officer and Director

**INDEX TO EXHIBITS**

- 99.1 Securities Purchase Agreement, dated August 19, 2005, by and among the Company and the purchases listed on Exhibit A thereto.
- 99.2 Form of Warrant.
- 99.3 Press Release dated August 22, 2005.

## SECURITIES PURCHASE AGREEMENT

This **SECURITIES PURCHASE AGREEMENT** (this “**Agreement**”), dated as of August 19, 2005, is made by and among **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation (the “**Company**”), and the Purchasers listed on **Exhibit A** hereto, together with their permitted transferees (each, a “**Purchaser**” and collectively, the “**Purchasers**”).

### RECITALS:

- A.** The Company and the Purchasers are executing and delivering this Agreement in reliance upon the exemption from securities registration afforded by Section 4(2) of the Securities Act.
- B.** The Purchasers desire to purchase and the Company desires to sell, upon the terms and conditions stated in this Agreement, (i) \$51,000,000 of Common Stock and (ii) warrants to purchase Common Stock of the Company.
- C.** The capitalized terms used herein and not otherwise defined have the meanings given them in Article 7.

### AGREEMENT

In consideration of the premises and the mutual covenants contained herein and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Company and the Purchasers (severally and not jointly) hereby agree as follows:

### ARTICLE 1

#### PURCHASE AND SALE OF SECURITIES

##### 1.1 Purchase and Sale of Securities.

**(a)** Upon confirmation that the other conditions to closing specified herein have been satisfied or duly waived by the Purchasers, the Company shall deliver to the custodian designated on such Purchaser’s signature page hereto, in trust, a certificate or certificates, registered in such name or names as the Purchasers may designate, representing the Shares and Warrants, with instructions that such certificates are to be held for release to the Purchasers only upon payment in full of the Purchase Price to the Company by all the Purchasers. Upon (i) confirmation that the conditions to closing specified under Section 5.2 have been satisfied or duly waived by the Purchasers and (ii) such receipt by such custodian of the certificates, each Purchaser shall promptly, but no more than one Business Day thereafter, cause a wire transfer in same day funds to be sent to the account of the Company as instructed in writing by the Company, in an amount representing such Purchaser’s pro rata portion of the Purchase Price as set forth on the signature pages to this Agreement. On the date (the “Closing Date”) the Company receives the Purchase Price, the certificates evidencing the Shares and Warrants shall be released to the Purchasers (the “Closing”).

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**(b)** At the Closing, the Company will issue and sell to each Purchaser, and each Purchaser will, severally and not jointly, purchase from the Company, the number of shares of Common Stock (the “**Shares**”) and a warrant (the “**Warrants**”) to purchase the number of shares of Common Stock set forth opposite such Purchaser’s name on **Exhibit A** hereto (the Shares and Warrants referred to collectively as the “**Securities**”). Each Purchaser shall receive a Warrant substantially in the form attached as **Exhibit B** hereto to purchase the number of shares of Common Stock equal to 25% of the number of Shares purchased by such Purchaser. Each Security shall consist of one Share and that portion of the Warrant exercisable for 25% of a share of Common Stock. The purchase price for each Security shall be \$4.25 (the “**Purchase Price**”), consisting of the sum of \$4.225 for the Share comprising the Security and \$0.025 for the portion of the Warrant comprising the Security. The Warrants shall bear an initial exercise price per share equal to \$5.2395.

**1.2 Payment.** At the Closing, each Purchaser will pay the aggregate Purchase Price set forth opposite its name on **Exhibit A** hereto by wire transfer of immediately available funds in accordance with wire instructions provided by the Company to the Purchasers prior to the Closing. The Company will instruct its transfer agent to credit each Purchaser the number of Shares set forth on **Exhibit A** (and, upon request, will deliver stock certificates to the Purchasers representing the Shares) and will deliver Warrants to purchase the Warrant Shares (defined below) against delivery of the aggregate Purchase Price on the Closing Date.

### ARTICLE 2

#### REPRESENTATIONS AND WARRANTIES OF THE COMPANY

Except as otherwise specifically contemplated by this Agreement, the Company represents and warrants to, and covenants and agrees with, each Purchaser as follows:

**2.1 Organization and Qualification.** The Company is duly incorporated, validly existing and in good standing under the laws of the State of Delaware, with full corporate power and authority to conduct its business as currently conducted and as disclosed in the SEC Documents. The Company is duly qualified to do business and is in good standing in every jurisdiction in which the nature of the business conducted by it or property owned by it makes such qualification necessary, except where the failure to be so qualified or in good standing, as the case may be, would not reasonably be expected to have a Material Adverse Effect.

**2.2 Authorization; Enforcement.** The Company has all requisite corporate power and authority to enter into and to perform its obligations under this Agreement and the Warrant, to consummate the transactions contemplated hereby and thereby and to issue the Securities and Warrant Shares in accordance with the terms hereof and thereof. The execution, delivery and performance of this Agreement and the Warrants by the Company and the consummation by it of the transactions contemplated hereby and thereby (including the issuance of the Securities and Warrant Shares) have been duly authorized by the Company’s Board of Directors and no further consent or authorization of the Company, its Board of Directors, or its stockholders is

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each of the Warrants will have been duly executed and delivered by the Company and will constitute a legal, valid and binding obligation of the Company enforceable against the Company in accordance with its terms, in each case, except as enforceability may be limited by applicable bankruptcy, insolvency, reorganization, or moratorium or similar laws affecting creditors' and contracting parties' rights generally and except as enforceability may be subject to general principles of equity and except as rights to indemnity and contribution may be limited by state or federal securities laws or public policy underlying such laws.

**2.3 Capitalization.** The SEC Documents accurately reflected the authorized and outstanding capital stock of the Company in all material respects as of June 30, 2005. Except as disclosed in or contemplated by the SEC Documents, the Company does not have outstanding any options to purchase, or any preemptive rights or other rights to subscribe for or to purchase, or any securities or obligations convertible or exchangeable or exercisable for, or any contracts or commitments to issue or sell, shares of its capital stock or any such options, rights, convertible, exchangeable or exercisable securities or obligations other than options granted under the Company's stock option plans and its employee stock purchase plan or disclosed in the SEC Documents. True, correct and complete copies of the Company's Restated Certificate of Incorporation (the "**Certificate of Incorporation**") and the Company's Bylaws (the "**Bylaws**") are each filed as exhibits to the SEC Documents. The capital stock of the Company, including the Common Stock, conforms to the description thereof contained in the SEC Documents.

**2.4 Issuance of Securities.** The Shares and all of the shares of Common Stock issuable upon exercise of the Warrants (the "**Warrant Shares**") have been duly authorized by the Company and, upon issuance in accordance with the terms of this Agreement (and in case of the Warrant Shares, the Warrants), will be validly issued, fully paid and non-assessable and will not be subject to preemptive rights, co-sale rights, rights of first refusal or other similar rights of stockholders of the Company. Except as disclosed in the SEC Documents, there are no stockholder agreements, voting agreements or other similar agreements with respect to the Common Stock to which the Company is a party.

**2.5 No Conflicts; Government Consents and Permits.**

(a) The execution, delivery and performance of this Agreement and the Warrants by the Company and the consummation by the Company of the transactions contemplated hereby and thereby (including the issuance of the Securities and the Warrant Shares) do not and will not (i) conflict with or result in a violation of any provision of the Certificate of Incorporation or Bylaws or require the approval of the Company's stockholders, or (ii) violate or conflict with, or result in a breach of any provision of, or constitute a default under, any agreement, indenture, or instrument to which the Company is a party, or (iii) result in a violation of any law, rule, regulation, order, judgment or decree (including United States federal and state securities laws and regulations and regulations of any self-regulatory organizations to which the Company is subject) applicable to the Company, except in the case of clause (ii) only, for such conflicts, breaches, defaults, and violations as would not reasonably be expected to have a Material Adverse Effect.

(b) The Company is not required to obtain any consent, authorization or order of, or make any filing or registration with, any court or governmental agency or any regulatory or

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self regulatory agency in order for the Company to execute, deliver or perform any of its obligations under this Agreement or the Warrants in accordance with the terms hereof or thereof, or to issue and sell the Securities in accordance with the terms hereof or to issue the Warrant Shares upon exercise of the Warrants other than such as have been made or obtained, and except for the registration of the Shares and Warrant Shares under the Securities Act pursuant to Section 6 hereof, any filings required to be made under federal or state securities laws (which filings have been or will be made as and when required), and any required filings or notifications regarding the issuance or listing of additional shares with Nasdaq (which filings and notifications have been or will be made as and when required).

(c) The Company has all franchises, permits, licenses, and any similar authority necessary for the conduct of its business as now being conducted, except for such franchises, permits, licenses or similar authorities, the lack of which would not reasonably be expected to have a Material Adverse Effect. The Company has not received any actual notice of any proceeding relating to revocation or modification of any such franchise, permit, license, or similar authority except where such revocation or modification would not reasonably be expected to have a Material Adverse Effect.

**2.6 SEC Documents, Financial Statements.** The Company has timely filed all reports, schedules, forms, statements and other documents required to be filed by it with the SEC since December 31, 2004, pursuant to the reporting requirements of the Exchange Act (all of the foregoing filed prior to the date hereof and all exhibits included or incorporated by reference therein and financial statements and schedules thereto and documents (other than exhibits) included or incorporated by reference therein, being hereinafter referred to herein as the "**SEC Documents**"). As of their respective dates, the SEC Documents complied in all material respects with the requirements of the Exchange Act or the Securities Act, as the case may be, and the rules and regulations of the SEC promulgated thereunder applicable to the SEC Documents, and none of the SEC Documents, at the time they were filed with the SEC, contained any untrue statement of a material fact or omitted to state a material fact required to be stated therein or necessary in order to make the statements therein, in light of the circumstances under which they were made, not misleading (except as set forth in amendments or supplements to such SEC Documents). As of their respective dates, the Financial Statements and the related notes complied as to form in all material respects with applicable accounting requirements and the published rules and regulations of the SEC with respect thereto. The Financial Statements and the related notes have been prepared in accordance with accounting principles generally accepted in the United States, consistently applied, during the periods involved (except (i) as may be otherwise indicated in the Financial Statements or the notes thereto, or (ii) in the case of unaudited interim statements, to the extent they may not include footnotes, may be condensed or summary statements or may conform to the SEC's rules and instructions for Reports on Form 10-Q) and fairly present in all material respects the consolidated financial position of the Company as of the dates thereof and the consolidated results of its operations and cash flows for the periods then ended (subject, in the case of unaudited statements, to normal and recurring year-end audit adjustments).

**2.7 Accounting Controls.** Except as disclosed in the SEC Documents, the Company maintains a system of accounting controls sufficient to provide reasonable assurances that (i) transactions are executed in accordance with management's general or specific authorization,

(ii) transactions are recorded as necessary to permit preparation of financial statements in conformity with generally accepted accounting principles as applied in the United States and to maintain accountability for assets, (iii) access to assets is permitted only in accordance with management's general or specific authorization, and (iv) the recorded accountability for assets is compared with existing assets at reasonable intervals and appropriate action is taken with respect to any differences.

**2.8 Absence of Litigation.** Except as set forth in the SEC Documents, as of the date hereof, there is no action, suit, proceeding or investigation before or by any court, public board, government agency, self-regulatory organization or body pending or, to the Company's knowledge, threatened against the Company that if determined adversely to the Company would reasonably be expected to have a Material Adverse Effect or would reasonably be expected to impair the ability of the Company to perform its obligations under this Agreement or the Warrants. Neither the Company, nor any of its directors or officers, is or has been the subject of any action involving a claim of violation of or liability under federal or state securities laws or a claim of breach of fiduciary duty relating to the Company. There has not been, and to the knowledge of the Company, there is not pending, any investigation by the SEC involving the Company or any current or former director or officer of the Company. The Company has not received any stop order or other order suspending the effectiveness of any registration statement filed by the Company under the Exchange Act or the Securities Act and, to the Company's knowledge, the SEC has not issued any such order.

**2.9 Intellectual Property Rights.** To the Company's knowledge, the Company owns or possesses licenses or sufficient rights to use all patents, patent applications, patent rights, inventions, know-how, trade secrets, trademarks, trademark applications, service marks, service names, trade names and copyrights necessary to enable them to conduct their business as conducted as of the date hereof (the "**Intellectual Property**"). To the Company's knowledge, the Company has not infringed the intellectual property rights of third parties which could reasonably be expected to result in a Material Adverse Effect. Except as disclosed in the SEC Documents, there are no material options, licenses or agreements relating to the Intellectual Property, nor is the Company bound by or a party to any material options, licenses or agreements relating to the patents, patent applications, patent rights, inventions, know-how, trade secrets, trademarks, trademark applications, service marks, service names, trade names or copyrights of any other person or entity. Except as disclosed in the SEC Documents, there is no material claim or action or proceeding pending or, to the Company's knowledge, threatened that challenges the right of the Company with respect to any Intellectual Property which could reasonably be expected to result in a Material Adverse Effect.

**2.10 Placement Agents.** The Company has taken no action that would give rise to any claim by any person for brokerage commissions, placement agent's fees or similar payments relating to this Agreement or the transactions contemplated hereby, except for dealings with the Placement Agents, whose commissions and fees will be paid by the Company.

**2.11 Investment Company.** The Company is not and, after giving effect to the offering and sale of the Securities and the receipt of the proceeds therefrom, will not be an "investment company" as such term is defined in the Investment Company Act of 1940, as amended (the "**Investment Company Act**").

**2.12 No Material Adverse Change.** Since December 31, 2004, except as described or referred to in the SEC Documents and except for cash expenditures in the ordinary course of business, there has not been any change in the assets, business, properties, financial condition or results of operations of the Company that would reasonably be expected to have a Material Adverse Effect. Since December 31, 2004, (i) there has not been any dividend or distribution of any kind declared, set aside for payment, paid or made by the Company on any class of capital stock, (ii) the Company has not sustained any material loss or interference with its business from fire, explosion, flood or other calamity, whether or not covered by insurance, or from any labor disturbance or dispute or any action, order or decree of any court or arbitrator or governmental or regulatory authority, (iii) the Company has not incurred any liabilities except in the ordinary course of business, (iv) the Company has not altered its method of accounting, and (v) the Company has not issued any equity securities to any officer, director, or Affiliate of the Company, except pursuant to the transaction contemplated by this Agreement or pursuant to existing Company stock option or purchase plans.

**2.13 Nasdaq National Market.** The Common Stock is listed on Nasdaq, and, to the Company's knowledge, there are no proceedings to revoke or suspend such listing or the listing of the Shares and the Warrant Shares. The Company is in compliance with the requirements of Nasdaq for continued listing of the Common Stock thereon and any other Nasdaq listing and maintenance requirements.

**2.14 Insurance.** The Company is insured by insurers of recognized financial responsibility against such losses and risks and in such amounts as the Company believes are prudent and customary for a company (i) in the businesses and location in which the Company, as the case may be, is engaged, (ii) with the resources of the Company, and (iii) at a similar stage of development as the Company. The Company has not received any written notice that it will not be able to renew its existing insurance coverage as and when such coverage expires. The Company believes it will be able to obtain similar coverage at reasonable cost from similar insurers as may be necessary for the Company to continue its business.

**2.15 Private Placement.** Neither the Company nor any affiliates, nor any person acting on its or their behalf, has, directly or indirectly, made any offers or sales of any security or solicited any offers to buy any security, that would require registration of the Securities under the Securities Act.

**2.16 No Integrated Offering.** Neither the Company nor any of its Affiliates, nor any Person acting on its or their behalf has, directly or indirectly, made any offers or sales of any Company security or solicited any offers to buy any security, under circumstances that would adversely affect reliance by the Company on Section 4(2) for the exemption from registration for the transactions contemplated hereby or would require registration of the Securities under the Securities Act.

**2.17 Private Placement.** Assuming the truth and accuracy of the Purchasers' representations and warranties contained in Article 3 hereof, the offer and sale of the Securities to the Purchasers as contemplated hereby is exempt from the registration requirements of the Securities Act.

**2.18 No Registration Rights.** No person has the right, which right has not been waived, to (i) prohibit the Company from filing the Registration Statement, or (ii) require the Company to register any securities for sale under the Securities Act by reason of the filing of the Registration Statement or (iii) register any securities (other than Securities and Warrant Shares) pursuant to the Registration Statement.

**2.19 Taxes.** The Company has filed (or has obtained an extension of time within which to file) all necessary federal, state and foreign income and franchise tax returns and has paid all taxes shown as due on such tax returns, except where the failure to so file or the failure to so pay would not reasonably be expected to have a Material Adverse Effect. The Company is not aware of any tax deficiency that has been or might be asserted against it that would have a Material Adverse Effect.

**2.20 Real and Personal Property.** The Company has good and marketable title to, or has valid rights to lease or otherwise use, all items of real and personal property that are material to its business free and clear of all liens, encumbrances, claims and defects and imperfections of title except those that (i) do not materially interfere with the use of such property or (ii) would not reasonably be expected to have a Material Adverse Effect.

**2.21 No Manipulation of Stock.** The Company has not taken, nor will it take, directly or indirectly, any action designed to stabilize or manipulate the price of the Common Stock or any security of the Company to facilitate the sale or resale of any of the Shares in violation of Regulation M under the Exchange Act.

**2.22 Compliance.** The Company is not (i) in default under or in violation of (and to the knowledge of the Company no event has occurred that has not been waived that, with notice or lapse of time or both, would result in a default by the Company), nor has the Company received notice of a claim that it is in default under or that it is in violation of, any Material Agreement, (ii) in violation of any order of any court, arbitrator or governmental body, or (iii) is or has been in violation of any statute, rule or regulation of any governmental authority or self regulatory authority, including without limitation all foreign, federal, state and local laws applicable to its business, except in each case as would not reasonably be expected to have a Material Adverse Effect.

**2.23 Sarbanes-Oxley; Disclosure Controls and Procedures.** The Company is in compliance in all material respects with all of the provisions of the Sarbanes-Oxley Act of 2002 that are applicable to it. Except as disclosed in the SEC Documents, the Company has established and maintains disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) that are effective in all material respects to ensure that material information relating to the Company is made known to its chief executive officer and chief financial officer by others within the Company. The Company's certifying officers have evaluated the effectiveness of the Company's controls and procedures as of the end of the period covered by the most recently filed quarterly or annual periodic report under the Exchange Act (such date, the "**Evaluation Date**"). The Company presented in its most recently filed quarterly or annual periodic report under the Exchange Act the conclusions of the certifying officers about the effectiveness of the disclosure controls and procedures based on their evaluations as of the Evaluation Date. Since the Evaluation Date, there have been no significant changes in the

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Company's internal controls (as such term is defined in Item 307(b) of Regulation S-K under the Exchange Act) or, to the Company's knowledge, in other factors that could significantly affect the Company's internal controls.

**2.24 Foreign Corrupt Practices.** Since December 31, 2004, neither the Company, nor to the Company's knowledge, any director, officer, agent, employee or other person acting on behalf of the Company has, in the course of its actions for, or on behalf of, the Company (i) used any corporate funds for any unlawful contribution, gift, entertainment or other unlawful expenses relating to political activity; (ii) made any direct or indirect unlawful payment to any foreign or domestic government official or employee from corporate funds; (iii) violated or is in violation of in any material respect any provision of the U.S. Foreign Corrupt Practices Act of 1977, as amended; or (iv) made any unlawful bribe, rebate, payoff, influence payment, kickback or other unlawful payment to any foreign or domestic government official or employee.

**2.25 Related Party Transactions.** Except with respect to the transactions contemplated hereby, all transactions that have occurred between or among the Company, on the one hand, and any of their respective officers or directors, or any affiliate or affiliates of any such officer or director, on the other hand, prior to the date hereof have been disclosed in the SEC Documents to the extent required to be disclosed by the Exchange Act and the rules and regulations promulgated thereunder.

### ARTICLE 3

#### PURCHASER'S REPRESENTATIONS AND WARRANTIES

Each Purchaser represents and warrants to, and covenants and agrees with, the Company, severally and not jointly, with respect to itself and its purchase hereunder, as follows:

**3.1 Investment Purpose.** Such Purchaser is purchasing the Securities for its own account and not with a present view toward the public sale or distribution thereof and has no intention of selling or distributing any of such Securities or any arrangement or understanding with any other persons regarding the sale or distribution of such Securities except in accordance with the provisions of Article 6 and except as would not result in a violation of the Securities Act. Such Purchaser will not, directly or indirectly, offer, sell, pledge, transfer or otherwise dispose of (or solicit any offers to buy, purchase or otherwise acquire or take a pledge of) any of the Securities except in accordance with the provisions of Article 6 or pursuant to and in accordance with the Securities Act.

**3.2 Accredited Investor.** Such Purchaser is an "accredited investor" as such term is defined in Regulation D promulgated under the Securities Act.

**3.3 Questionnaires.** The information submitted by Purchaser pursuant to the Stockholder Questionnaire attached to the signature page of this Agreement (the "**Stockholder Questionnaire**") was complete, accurate and correct when delivered and is complete, accurate and correct as of the date hereof.

**3.4 Reliance on Exemptions.** Such Purchaser understands that the Securities are being offered and sold to it in reliance upon specific exemptions from the registration

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requirements of United States federal and state securities laws and that the Company is relying upon the truth and accuracy of, and such Purchaser's compliance with, the representations, warranties, agreements, acknowledgments and understandings of such Purchaser set forth herein in order to determine the availability of such exemptions and the eligibility of such Purchaser to acquire the Securities.

**3.5 Information.** Such Purchaser has been furnished with all relevant materials relating to the business, finances and operations of the Company necessary to make an investment decision, and materials relating to the offer and sale of the Securities, that have been requested by such Purchaser, including, without limitation, the Company's SEC Documents, and such Purchaser has had the opportunity to review the SEC Documents. Such Purchaser has been afforded the opportunity to ask questions, and to receive answers from, officers and employees of the Company concerning the Company and the terms and conditions of this offering and to obtain additional information about the Company and the Securities. Notwithstanding anything set forth in this Section 3.5, Purchaser is entitled to rely on the representations and warranties made by the Company under Article 2.

**3.6 Acknowledgement of Risk.**

(a) Such Purchaser acknowledges and understands that its investment in the Securities involves a significant degree of risk, including, without limitation, (i) the Company remains a development stage business with limited operating history and requires substantial funds in addition to the proceeds from the sale of the Securities; (ii) an investment in the Company is speculative, and only purchasers who can afford the loss of their entire investment should consider investing in the Company and the Securities; (iii) such Purchaser may not be able to liquidate its investment; (iv) transferability of the Securities is extremely limited; (v) in the event of a disposition of the Securities, such Purchaser could sustain the loss of its entire investment; and (vi) the Company has not paid any dividends on its Common Stock since inception and does not anticipate the payment of dividends in the foreseeable future. Such risks, and others applicable to the Company, are more fully set forth in the SEC Documents;

(b) Such Purchaser is able to bear the economic risk of holding the Securities for an indefinite period, and has knowledge and experience in financial and business matters such that it is capable of evaluating the risks of the investment in the Securities; and

(c) Such Purchaser has, in connection with such Purchaser's decision to purchase Securities, not relied upon any representations or other information (whether oral or written) other than as set forth in the representations and warranties of the Company contained herein and in the SEC Documents, and such Purchaser has, with respect to all matters relating to this Agreement and the offer and sale of the Securities, relied solely upon the advice of such Purchaser's own counsel and has not relied upon or consulted any counsel to the Placement Agents or counsel to the Company and has not relied upon any Placement Agent.

**3.7 Governmental Review.** Such Purchaser understands that no United States federal or state agency or any other government or governmental agency has passed upon or made any recommendation or endorsement of the Securities or an investment therein.

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**3.8 Transfer or Resale.** Such Purchaser understands that:

(a) the Securities have not been and are not being registered under the Securities Act (other than as contemplated in Article 6) or any applicable state securities laws and, consequently, such Purchaser may have to bear the risk of owning the Securities for an indefinite period of time because the Securities may not be transferred unless (i) the resale of the Securities is registered pursuant to an effective registration statement under the Securities Act, as contemplated in Article 6; or (ii) such Purchaser has delivered to the Company an opinion of counsel (in form, substance and scope customary for opinions of counsel in comparable transactions) to the effect that the Securities to be sold or transferred may be sold or transferred pursuant to an exemption from or in a transaction not subject to such registration; or (iii) the Securities are sold or transferred pursuant to Rule 144;

(b) any sale of the Securities made in reliance on Rule 144 may be made only in accordance with the terms of Rule 144 and, if Rule 144 is not applicable, any resale of the Securities under circumstances in which the seller (or the person through whom the sale is made) may be deemed to be an underwriter (as that term is defined in the Securities Act) may require compliance with some other exemption under the Securities Act or the rules and regulations of the SEC thereunder; and

(c) except as set forth in Article 6, neither the Company nor any other person is under any obligation to register the resale of the Shares or the Warrant Shares under the Securities Act or any state securities laws or to comply with the terms and conditions of any exemption thereunder.

**3.9 Legends.**

(a) Such Purchaser understands the certificates representing the Securities and the Warrant Shares will bear a restrictive legend in substantially the following form (and a stop-transfer order may be placed against transfer of the certificates for such Securities and Warrant Shares):

THE SECURITIES REPRESENTED BY THIS CERTIFICATE HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED, OR THE SECURITIES LAWS OF ANY STATE OF THE UNITED STATES. THE SECURITIES MAY NOT BE SOLD, OFFERED FOR SALE, PLEDGED, HYPOTHECATED, TRANSFERRED OR ASSIGNED IN THE ABSENCE OF AN EFFECTIVE REGISTRATION STATEMENT FOR THE SECURITIES UNDER APPLICABLE SECURITIES LAWS, OR UNLESS OFFERED, SOLD, PLEDGED, HYPOTHECATED OR TRANSFERRED PURSUANT TO AN AVAILABLE EXEMPTION FROM OR IN A TRANSACTION NOT SUBJECT TO THE REGISTRATION REQUIREMENTS OF THOSE LAWS. THE COMPANY SHALL BE ENTITLED TO REQUIRE AN OPINION OF COUNSEL REASONABLY SATISFACTORY TO THE COMPANY THAT SUCH REGISTRATION IS NOT REQUIRED TO THE EXTENT THAT SUCH OPINION IS REQUIRED PURSUANT TO THAT CERTAIN SECURITIES PURCHASE AGREEMENT UNDER WHICH THE SECURITIES WERE ISSUED.

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(b) Such Purchaser may request that the Company remove, and the Company agrees to authorize the removal of any legend from the Securities and Warrant Shares, (i) following any sale of the Securities or Warrant Shares pursuant to an effective Registration Statement or Rule 144, or (ii) if

such Securities or Warrant Shares are eligible for sale under Rule 144(k). Following the time a legend is no longer required for the Securities or Warrant Shares hereunder, the Company will, as soon as practicable following the delivery by such Purchaser to the Company or the Company's transfer agent of a legended certificate representing such securities and notice to the Company requesting such removal, deliver or cause to be delivered to such Purchaser a certificate representing such securities that is free from all restrictive and other legends and is not subject to any stop transfer or other similar restrictions. When the Company is required to cause unlegended certificates to replace previously issued legended certificates, if unlegended certificates are not delivered to a Purchaser within three (3) Business Days of submission by that Purchaser of legended certificate(s) to the Company's transfer agent together with a representation letter in customary form, the Company shall be liable to the Investor for liquidated damages in an amount equal to 1.0% of the aggregate purchase price of the Securities evidenced by such certificate(s) for each thirty (30) day period (or portion thereof) beyond such three (3) Business Day that the unlegended certificates have not been so delivered.

**3.10 Authorization; Enforcement.** Such Purchaser has the requisite power and authority to enter into this Agreement and to consummate the transactions contemplated hereby. The Purchaser has taken all necessary action to authorize the execution, delivery and performance of this Agreement by such Purchaser. Upon the execution and delivery of this Agreement, this Agreement shall constitute a valid and binding obligation of such Purchaser enforceable in accordance with its terms, except as enforceability may be limited by applicable bankruptcy, insolvency, reorganization, moratorium or similar laws affecting creditors' and contracting parties' rights generally and except as enforceability may be subject to general principles of equity and except as rights to indemnity and contribution may be limited by state or federal securities laws or public policy underlying such laws.

**3.11 Residency.** Such Purchaser is a resident of the jurisdiction set forth immediately below such Purchaser's name on the signature pages hereto.

**3.12 No Trades.** Between the time such Purchaser learned about the Offering and the public announcement of the Offering, such Purchaser has not engaged in any purchase, sale or other transaction, including any short sales or similar transactions, with respect to the Common Stock, nor has such Purchaser, directly or indirectly, caused any Person to engage in any purchase, sale or other transaction, including any short sales, with respect to the Common Stock.

**3.13 Acknowledgements Regarding Placement Agent.** Such Purchaser acknowledges that the Placement Agents are acting as the exclusive placement agents for the Securities being offered hereby and will be compensated solely by the Company for acting in such capacity. Such Purchaser represents that (i) if such Purchaser is not a Company Representative, such Purchaser was contacted regarding the sale of the Securities by the Placement Agent (or an authorized agent or representative thereof) or, if such Purchaser is a Company Representative, such Purchaser was contacted regarding the sale of the Securities by

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the Company (or an authorized officer or employee thereof) and (ii) no Securities were offered or sold to it by means of any form of general solicitation or general advertising.

**3.14 Expenses.** Such Purchaser is liable for and will pay its own expenses incurred in connection with the negotiation, preparation, execution and delivery of this Agreement and the Warrants, including, without limitation, attorneys' and consultants' fees and expenses.

## ARTICLE 4

### COVENANTS

Except as specifically contemplated by this Agreement, the Company represents and warrants to, and covenants and agrees with, each Purchaser as follows:

**4.1 Reporting Status.** The Company's Common Stock is registered under Section 12 of the Exchange Act. Until the earlier of (i) the second anniversary of the Closing Date and (ii) the date all Shares and Warrant Shares may be sold under Rule 144(k), the Company will make and keep available adequate current public information (within the meaning of Rule 144(c)) concerning the Company.

**4.2 Expenses.** The Company is liable for and will pay its own expenses incurred in connection with the negotiation, preparation, execution and delivery of this Agreement and the Warrants, including, without limitation, attorneys' and consultants' fees and expenses.

**4.3 Financial Information.** The financial statements and related notes of the Company to be included in any documents filed with the SEC will be prepared in accordance with accounting principles generally accepted in the United States, consistently applied (except (i) as may be otherwise indicated in such financial statements or the notes thereto, or (ii) in the case of unaudited interim statements, to the extent they may not include footnotes, may be condensed or summary statements or may conform to the SEC's rules and instructions for Reports on Form 10-Q), and will fairly present in all material respects the consolidated financial position of the Company and consolidated results of its operations and cash flows as of, and for the periods covered by, such financial statements (subject, in the case of unaudited statements, to normal and recurring year-end audit adjustments).

**4.4 Securities Laws Disclosure; Publicity.** On or before 5:00 p.m., New York local time, on August 22, 2005 the Company shall issue a press release announcing the signing of this Agreement and describing the terms of the transactions contemplated by this Agreement. On or before August 26, 2005, the Company shall file a Current Report on Form 8-K with the SEC describing the terms of the transactions contemplated by this Agreement and including as an exhibit to such Current Report on Form 8-K this Agreement, in the form required by the Exchange Act. The Company shall not otherwise publicly disclose the name of any Purchaser, or include the name of any Purchaser in any filing with the Commission (other than the Registration Statement and in filings made in accordance with periodic filing requirements under the Exchange Act) or any regulatory agency, without the prior written consent of such Purchaser, except to the extent such disclosure is required by law or regulations.

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**4.5 Reservation of Common Stock.** The Company will reserve and keep available at all times during which the Warrants remain exercisable, free of preemptive rights, a sufficient number of shares of Common Stock for the purpose of enabling the Company to issue Warrant Shares pursuant to this



**4.6 Listing of Shares.** Promptly following the date hereof, the Company shall take all necessary action to cause the Shares and the Warrant Shares to be listed on the Nasdaq National Market as promptly as practicable after the Closing Date; *provided, however* that (i) the Company must file its Listing of Additional Shares notice with Nasdaq no later than three business days following the Closing Date and (ii) the Company will use its commercially reasonable efforts to have the Shares and Warrant Shares listed on the Nasdaq National Market within 30 days of such filing date. Further, if the Company applies to have its Common Stock or other securities traded on any other principal stock exchange or market, it shall include in such application the Shares and the Warrant Shares and will take such other action as is necessary to cause such Common Stock (including the Shares and the Warrant Shares) to be so listed. The Company will use commercially reasonable efforts to continue the listing and trading of its Common Stock (including the Shares and the Warrant Shares) on the Nasdaq Stock Market and, in accordance, therewith, will use commercially reasonable efforts to comply in all respects with the Company's reporting, filing and other obligations under the bylaws or rules of such market.

Except as specifically contemplated by this Agreement, each Purchaser represents and warrants to, and covenants and agrees with, the Company as follows:

**4.7 Sales by Purchasers.** Each Purchaser will sell any Securities and Warrant Shares held by it in compliance with applicable prospectus delivery requirements, if any, or otherwise in compliance with the requirements for an exemption from registration under the Securities Act and the rules and regulations promulgated thereunder. No Purchaser will make any sale, transfer or other disposition of the Securities in violation of federal or state securities laws.

## ARTICLE 5

### CONDITIONS TO CLOSING

**5.1 Conditions to Obligations of the Company.** The Company's obligation to complete the sale of the Securities and deliver stock certificate(s) and Warrants to each Purchaser is subject to the fulfillment or waiver as of the Closing Date of the following conditions:

- (a) **Receipt of Funds.** The Company shall have received immediately available funds in the full amount of the purchase price for the Securities being purchased hereunder as set forth opposite such Purchaser's name on **Exhibit A** hereto.
- (b) **Representations and Warranties.** The representations and warranties made by each Purchaser in Article 3 shall be true and correct in all material respect as of the Closing Date.
- (c) **Covenants.** All covenants, agreements and conditions contained in this Agreement to be performed by the Purchasers on or prior to the Closing Date shall have been performed or complied with in all material respects.

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- (d) **Blue Sky.** The Company shall have obtained all necessary blue sky law permits and qualifications, or secured exemptions therefrom, required by any state for the offer and sale of the Securities.
- (e) **Absence of Litigation.** No proceeding challenging this Agreement or the transactions contemplated hereby, or seeking to prohibit, alter, prevent or materially delay the Closing, shall have been instituted or be pending before any court, arbitrator, governmental body, agency or official.
- (f) **No Governmental Prohibition.** The sale of the Securities by the Company shall not be prohibited by any law or governmental order or regulation.

**5.2 Conditions to Purchasers' Obligations at the Closing.** Each Purchaser's obligation to complete the purchase of the Securities set forth opposite such Purchaser's name on **Exhibit A** hereto is subject to the fulfillment or waiver as of the Closing Date of the following conditions:

- (a) **Representations and Warranties.** The representations and warranties made by the Company in Article 2 shall be true and correct in all material respects as of the Closing Date.
- (b) **Covenants.** All covenants, agreements and conditions contained in this Agreement to be performed by the Company on or prior to the Closing Date shall have been performed or complied with in all material respects.
- (c) **Blue Sky.** The Company shall have obtained all necessary blue sky law permits and qualifications, or secured exemptions therefrom, required by any state or foreign or other jurisdiction for the offer and sale of the Securities.
- (d) **Legal Opinion.** The Company shall have delivered to such Purchaser an opinion, dated as of the Closing Date, from the Company's general counsel, rendering the opinions as set forth on **Exhibit C** attached hereto.
- (e) **Transfer Agent Instructions.** The Company shall have delivered to its transfer agent irrevocable instructions to issue to such Purchaser or in such nominee name(s) as designated by such Purchaser in writing such number of Shares set forth opposite such Purchaser's name on **Exhibit A** hereto or, if requested by the Purchaser, one or more certificates representing such shares, and a Warrant to purchase the number of Warrant Shares set forth opposite such Purchaser's name on **Exhibit A**.
- (f) **Absence of Litigation.** No proceeding challenging this Agreement or the transactions contemplated hereby, or seeking to prohibit, alter, prevent or materially delay the Closing, shall have been instituted or be pending before any court, arbitrator, governmental body, agency or official.
- (g) **No Governmental Prohibition.** The sale of the Securities by the Company and the purchase of Securities by such Purchaser shall not be prohibited by any law or governmental order or regulation.

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(h) No stop order or suspension of trading shall have been imposed by Nasdaq, the SEC or any other governmental or regulatory body with respect to public trading in the Common Stock.

## ARTICLE 6

### REGISTRATION RIGHTS

6.1 As soon as reasonably practicable, but in no event later than 15 days after the Closing Date (the “**Filing Date**”), the Company shall file a registration statement covering the resale of the Registrable Securities on a registration statement (the “**Registration Statement**”) with the SEC; *provided, however*, that the Purchaser has provided the Company with the information required to complete the Registration Statement. As promptly as possible after the filing of the Registration Statement, but in any event prior to the Effectiveness Date (defined below) the Company will use its commercially reasonable efforts to cause the Registration Statement to be declared effective by the SEC and will otherwise effect all such registrations, obtain all such qualifications and comply with all such laws, rules and regulations as may be necessary in order to permit the sale, transfer and other disposition of the Registrable Securities by the Holders thereof pursuant to the Registration Statement (including, without limitation, the execution of any required undertaking to file post-effective amendments, appropriate qualifications or exemptions under applicable blue sky or other state securities laws and appropriate compliance with applicable securities laws, requirements or regulations). As used herein, “**Effectiveness Date**” means the date which is (i) 60 days after the Closing Date if the Registration Statement is not reviewed by the SEC, or (ii) 90 days after the Closing Date, if the Registration Statement is reviewed by the SEC (including but not limited to any pending confidential treatment requests).

6.2 All Registration Expenses incurred in connection with any registration, qualification, exemption or compliance pursuant to Section 6.1 shall be borne by the Company. All Selling Expenses relating to the sale of Registrable Securities registered by or on behalf of any Holder shall be borne by such Holder.

6.3 The Company further agrees that, in the event that the Registration Statement (i) has not been filed with the SEC within 30 days after the Closing Date, (ii) has not been declared effective by the SEC by the Effectiveness Date or (iii) after the Registration Statement is declared effective by the SEC, the use of the Registration Statement or the related prospectus is suspended by the Company, or the Registration Statement ceases to remain continuously effective as to all Registrable Securities for which it is required to be effective, in each case other than within the time period(s) permitted by Section 6.7(b) (each such event referred to in clauses (i), (ii) and (iii), a “**Registration Default**”), then, for any thirty-day period (a “**Penalty Period**”) during which the Registration Default remains uncured, the Company shall pay to each Holder an amount in cash equal to 1% of such Holder’s aggregate deemed purchase price of his or her Registrable Securities for each whole Penalty Period during which the Registration Default remains uncured (for purposes of clarity, it is hereby understood and agreed that, solely for the purpose of this Section 6.3, the deemed purchase price for each Share is \$4.225 and the purchase price of each Warrant Share shall be deemed to be equal to \$0.025, *provided* that the dollar amounts set forth in this parenthetical clause shall be appropriately adjusted in the event of any

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adjustment, pursuant to the terms of the Warrants, in the exercise price of the Warrants or the number of shares issuable upon exercise of the Warrants); *provided, however*, that if a Holder fails to provide the Company with any information that is required to be provided in the Registration Statement with respect to such Holder as set forth herein, then solely with respect to such Holder the commencement of the Penalty Period described above shall be extended until two Business Days following the date of receipt by the Company of such required information; *and provided, further*, that in no event shall the Company be required hereunder to pay to any Holder pursuant to this Agreement an aggregate amount that exceeds 15% of the aggregate deemed purchase price for such Holder’s Securities; *and provided further* that the amount payable to any Holder hereunder for any partial Penalty Period will not be pro-rated for the number of actual days during such Penalty Period during which a Registration Default remains uncured. The Company shall deliver said cash payment to each Holder entitled thereto by the fifth Business Day after the end of such Penalty Period. If the Company fails to pay said cash payment to a Holder entitled thereto by the applicable date specified in the immediately preceding sentence, the Company will pay interest thereon at a rate of 12% per annum (or such lesser maximum amount that is permitted to be paid by applicable law) to such Holder, accruing daily from the date such liquidated damages are due until such amounts, plus all such interest thereon, are paid in full. Notwithstanding the foregoing, Holder shall not be entitled to any payments pursuant to this Section 6.3 with respect to the Registrable Securities of such Holder that such Holder has the right to resell on the open market, at any time during the Penalty Period, pursuant to an exemption from registration under the Securities Act.

6.4 In the case of the registration, qualification, exemption or compliance effected by the Company pursuant to this Agreement, the Company shall, upon reasonable request, inform each Holder as to the status of such registration, qualification, exemption and compliance. At its expense the Company shall:

(a) except for such times as the Company is permitted hereunder to suspend the use of the prospectus forming part of the Registration Statement, use all commercially reasonable efforts to keep such registration, and any qualification, exemption or compliance under state securities laws which the Company determines to obtain or which the Company obtains at the request of a Holder pursuant to Section 6.4(g), continuously effective with respect to a Holder, and to keep such Registration Statement and the related prospectus free of any material misstatements or omissions, until the earlier of the following: (i) the second anniversary of the Closing Date, (ii) the date all Shares and Warrant Shares held by such Holder may be sold under Rule 144 during any 90 day period, and (iii) the date all the Registrable Securities issued or issuable pursuant to this Agreement and the Warrants have been sold. The period of time during which the Company is required hereunder to keep the Registration Statement effective is referred to herein as the “**Registration Period**.”

(b) advise the Holders:

(i) within three Business Days when the Registration Statement or any post-effective amendment thereto has become effective;

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(ii) as promptly as practicable of any request by the SEC for amendments or supplements to the Registration Statement or the prospectus included therein or for additional information;

(iii) as promptly as practicable of the issuance by the SEC of any stop order suspending the effectiveness of the Registration Statement or the initiation of any proceedings for such purpose;

(iv) as promptly as practicable of the receipt by the Company of any notification with respect to the suspension of the qualification of the Registrable Securities included therein for sale in any jurisdiction or the initiation or threatening of any proceeding for such purpose; and

(v) as promptly as practicable of the occurrence of any event or the existence of any condition that requires the making of any changes in the Registration Statement or the prospectus so that, as of such date, the statements therein are not misleading and do not omit to state a material fact required to be stated therein or necessary to make the statements therein (in the case of the prospectus, in the light of the circumstances under which they were made) not misleading;

(c) use its commercially reasonable efforts to obtain the withdrawal of any order suspending the effectiveness of any Registration Statement as soon as reasonably practicable;

(d) if a Holder so requests in writing, promptly furnish to each such Holder, without charge, at least one copy of such Registration Statement and any post-effective amendment thereto, including financial statements and schedules, and, if explicitly requested, all exhibits in the form filed with the SEC;

(e) during the Registration Period, if a Holder so requests in writing, promptly deliver to each such Holder, without charge, a reasonable number of copies of the prospectus included in such Registration Statement and any amendment or supplement thereto; and the Company consents to the use, consistent with the provisions hereof, of the prospectus or any amendment or supplement thereto by each of the Holders in connection with the offering and sale of the Registrable Securities covered by the prospectus or any amendment or supplement thereto;

(f) during the Registration Period, if a Holder so requests in writing, deliver to each Holder, without charge, (i) one copy of the following documents, other than those documents available via EDGAR (and excluding, in each case, exhibits thereto): (A) its annual report to its stockholders, if any (which annual report shall contain financial statements audited in accordance with generally accepted accounting principles in the United States of America by a firm of certified public accountants of recognized standing), (B) if not included in substance in its annual report to stockholders, its annual report on Form 10-K (or similar form), (C) its definitive proxy statement with respect to its annual meeting of stockholders, (D) each of its quarterly reports to its stockholders, and, if not included in substance in its quarterly reports to stockholders, its quarterly report on Form 10-Q (or similar form), and (E) a copy of the

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Registration Statement; and (ii) if explicitly requested, any exhibits filed with respect to the foregoing (excluding exhibits, unless requested);

(g) promptly take such actions as may be necessary to register or qualify or obtain an exemption for offer and sale under the securities or blue sky laws of such United States jurisdictions as any Holders reasonably request in writing, provided that the Company shall not for any such purpose be required to qualify generally to transact business as a foreign corporation in any jurisdiction where it is not so qualified or to consent to general service of process in any such jurisdiction, and do any and all other acts or things reasonably necessary or advisable to enable the offer and sale in such jurisdictions of the Registrable Securities covered by such Registration Statement;

(h) upon the occurrence of any event contemplated by Section 6.4(b)(v) above, except for such times as the Company is permitted hereunder to suspend the use of the prospectus forming part of the Registration Statement and has suspended such use, the Company shall use all commercially reasonable efforts to as soon as reasonably practicable prepare a post-effective amendment to the Registration Statement or a supplement to the related prospectus, or file any other required document so that, as thereafter delivered to purchasers of the Registrable Securities, the prospectus will not include any untrue statement of a material fact or omit to state any material fact required to be stated therein or necessary to make the statements therein, in the light of the circumstances under which they were made, not misleading;

(i) use all commercially reasonable efforts to cause all Registrable Securities to be listed on each securities exchange or market, if any, on which equity securities issued by the Company have been listed;

(j) use all commercially reasonable efforts to take all other steps necessary to effect the registration of the Registrable Securities contemplated hereby and to enable the Holders to sell Registrable Securities under Rule 144;

**6.5** The Company shall not be required to make any payment to any Holder otherwise required by Section 6.3 hereof allocable to any day on which a Registration Default exists or existed solely as a result of (i) any request by such Holder to incorporate any comment in any Registration Statement or amendment or supplement thereto or (ii) any unreasonable action by such Holder to restrain, enjoin or otherwise delay any registration pursuant to Section 6.1 hereof.

**6.6 (a)** To the extent permitted by law, the Company shall indemnify each Holder and each person controlling such Holder within the meaning of Section 15 of the Securities Act or Section 20 of the Exchange Act, against all claims, losses, damages and liabilities (or action in respect thereof), including any of the foregoing incurred in settlement of any litigation, commenced or threatened (subject to Section 6.6(c) below), to the extent (i) arising out of or based on any untrue statement of a material fact contained in the Registration Statement, any prospectus, any amendment or supplement to any such Registration Statement or prospectus, or any other document incident to any such registration, qualification or compliance or (ii) arising out of or based on any omission to state therein a material fact required to be stated therein or necessary to make the statements therein not misleading, in light of the circumstances in which

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they were made, or (iii) based on any violation by the Company of any securities laws, rule or regulation promulgated by the SEC applicable to the Company and relating to any action or inaction required of the Company in connection with any such registration, qualification or compliance, and will reimburse each Holder and each person controlling such Holder, for out-of-pocket legal and other out-of-pocket expenses reasonably incurred in connection with investigating or defending any such claim, loss, damage, liability or action as incurred, or (iv) arising out of or based on a material breach by the Company of a representation and warranty or covenants made by the Company under this Agreement; *provided* that the Company will not be liable in any such case to the extent that any untrue statement or omission or allegation thereof is made in reliance upon and in conformity with written information furnished to the Company by or on behalf of such Holder for use in preparation of such Registration Statement, prospectus, amendment or supplement; *provided further* that (i) that the Company will not be liable in any such case where the claim, loss, damage or liability arises out of or is related to the failure of such Holder to comply with the covenants and agreements contained in this Agreement respecting sales of Registrable Securities, and (ii) the foregoing indemnity agreement is subject to the condition that, insofar as it relates to any such untrue statement or alleged untrue statement or omission or alleged omission made in the preliminary prospectus but eliminated or remedied in the prospectus on file with the SEC at the time the Registration Statement becomes effective or in the prospectus filed with the SEC pursuant to Rule 424(b) (the “**Final Prospectus**”), such indemnity shall not inure to the benefit of any such Holder or any such controlling person, if a copy of the Final Prospectus furnished by the Company to Holder for delivery was not furnished to the person or entity asserting the loss, liability, claim or damage at or prior to the time such furnishing is required by the Securities Act and the Final Prospectus would have cured the defect giving rise to such loss, liability, claim or damage.

(b) Each Holder will severally, and not jointly, indemnify the Company, each of its directors, each of its officers, and each person who controls the Company within the meaning of Section 15 of the Securities Act or Section 20 of the Exchange Act, against all claims, losses, damages and liabilities (or actions in respect thereof), including any of the foregoing incurred in settlement of any litigation, commenced or threatened (subject to Section 6.6(c) below), arising out of or based on any untrue statement of a material fact contained in the Registration Statement, any prospectus, or any amendment or supplement to any such Registration Statement or prospectus, or arising out of or based on any omission to state therein a material fact required to be stated therein or necessary to make the statements therein not misleading, in light of the circumstances in which they were made, and will reimburse the Company, such directors and officers, and each person controlling the Company for out-of-pocket legal and any other out-of-pocket expenses reasonably incurred in connection with investigating or defending any such claim, loss, damage, liability or action as incurred, in each case to the extent, but only to the extent, that such untrue statement or omission or allegation thereof is made in reliance upon and in conformity with written information furnished to the Company by or on behalf of the Holder for use in preparation of the Registration Statement or such prospectus, amendment or supplement. Notwithstanding the foregoing, a Holder’s aggregate liability pursuant to this subsection (b) and subsection (d) shall be limited to the net amount received by the Holder from the sale of the Registrable Securities giving rise to such claims, losses, damages and liabilities (or actions in respect thereof).

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(c) Each party entitled to indemnification under this Section 6.6 (the “**Indemnified Party**”) shall give notice to the party required to provide indemnification (the “**Indemnifying Party**”) promptly after such Indemnified Party has actual knowledge of any claim as to which indemnity may be sought, and shall permit the Indemnifying Party (at its expense) to assume the defense of any such claim or any litigation resulting therefrom, provided that counsel for the Indemnifying Party, who shall conduct the defense of such claim or litigation, shall be approved by the Indemnified Party (whose approval shall not unreasonably be withheld), and the Indemnified Party may participate in such defense at such Indemnified Party’s expense, and provided further that the failure of any Indemnified Party to give notice as provided herein shall not relieve the Indemnifying Party of its obligations under this Article 6, unless such failure is materially prejudicial to the Indemnifying Party in defending such claim or litigation and in any event shall not relieve the Indemnifying Party from any liability which it may have otherwise then on account of this Article 6. Notwithstanding the foregoing, the Indemnified Party shall have the right to assume the defense at the Indemnifying Party’s expense of any such claim or any litigation resulting therefrom if (i) the Indemnifying Party and the Indemnified Party shall have mutually agreed to the retention of such counsel by the Indemnified Party or (ii) the named parties to any such proceeding (including any impleaded parties) include both the Indemnifying Party and the Indemnified Party and the Indemnified Party shall have reasonably concluded that representation of both the Indemnifying Party and the Indemnified Party by the same counsel would be inappropriate due to actual or potential conflict of interest between them. It is understood that the Indemnifying Party shall not, in respect of the legal expenses of any Indemnified Party in connection with any proceeding or related proceedings in the same jurisdiction, be liable for the fees and expenses of more than one separate firm (in addition to any local counsel) for all Indemnified Parties and that all such fees and expenses shall be reimbursed as they are incurred. Such firm shall be designated by the Company, in the case of the Indemnified Parties pursuant to Section 6.6(a), and by a majority in interest of the Indemnified Parties, in the case of indemnity pursuant to Section 6.6(b) hereof. An Indemnifying Party shall not be liable for any settlement of an action or claim effected without its written consent (which consent will not be unreasonably withheld). No Indemnifying Party, in its defense of any such claim or litigation, shall, except with the consent of each Indemnified Party, consent to entry of any judgment or enter into any settlement which does not include as an unconditional term thereof the giving by the claimant or plaintiff to each Indemnified Party of a release from all liability in respect to such claim or litigation.

(d) If the indemnification provided for in this Section 6.6 is held by a court of competent jurisdiction to be unavailable to an Indemnified Party or is insufficient with respect to any loss, liability, claim, damage or expense referred to therein, then the Indemnifying Party, in lieu of indemnifying such Indemnified Party thereunder, shall contribute to the amount paid or payable by such Indemnified Party as a result of such loss, liability, claim, damage or expense in such proportion as is appropriate to reflect the relative fault of the Indemnifying Party on the one hand and of the Indemnified Party on the other in connection with the statements or omissions or other matter that resulted in such loss, liability, claim, damage or expense as well as any other relevant equitable considerations. The relative fault of the Indemnifying Party and of the Indemnified Party shall be determined by reference to, among other things, whether the untrue or alleged untrue statement of a material fact or the omission or alleged omission to state a material fact relates to information supplied by the Indemnifying Party or by the Indemnified Party and

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the parties’ relative intent, knowledge, access to information and opportunity to correct or prevent such statement or omission.

6.7 (a) Each Holder agrees that, upon receipt of any notice from the Company of the happening of any event requiring the preparation of a supplement or amendment to a prospectus relating to Registrable Securities so that, as thereafter delivered to the Holders, such prospectus shall not contain an untrue statement of a material fact or omit to state any material fact required to be stated therein or necessary to make the statements therein not misleading, each Holder will forthwith discontinue disposition of Registrable Securities pursuant to the Registration Statement and prospectus contemplated by Section 6.1 until its receipt of copies of the supplemented or amended prospectus from the Company or notice from the Company that the use of the existing

prospectus may be resumed and, if so directed by the Company, each Holder shall deliver to the Company all copies, other than permanent file copies then in such Holder's possession, of the prospectus covering such Registrable Securities current at the time of receipt of such notice.

(b) Each Holder shall suspend, upon written request of the Company, any disposition of Registrable Securities pursuant to the Registration Statement and prospectus contemplated by Section 6.1 during no more than two periods of no more than 30 calendar days each during any 12-month period to the extent that the Board of Directors of the Company determines in good faith based on the advice of counsel that the sale of Registrable Securities under the Registration Statement would be reasonably likely to cause a violation of the Securities Act or Exchange Act.

(c) As a condition to the inclusion of its Registrable Securities, each Holder shall furnish to the Company such information regarding such Holder and the distribution proposed by such Holder as the Company may reasonably request in writing, including completing a stockholder questionnaire in the form attached to the signature page of this Agreement, or as shall be required in connection with any registration referred to in this Article 6.

(d) Each Holder, severally and not jointly, hereby covenants with the Company that such Holder will not make any sale of the Registrable Securities without effectively causing the prospectus delivery requirements under the Securities Act to be satisfied unless such sale is exempt from registration.

(e) Each Holder acknowledges and agrees that the Registrable Securities sold pursuant to the Registration Statement are not transferable on the books of the Company unless the stock certificate submitted to the transfer agent evidencing such Registrable Securities is accompanied by a certificate reasonably satisfactory to the Company to the effect that (i) the Registrable Securities have been sold in accordance with such Registration Statement and (ii) the requirement of delivering a current prospectus has been satisfied.

(f) Each Holder, severally and not jointly, agrees not to take any action with respect to any distribution deemed to be made pursuant to such Registration Statement which would constitute a violation of Regulation M under the Exchange Act or any other applicable rule, regulation or law.

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(g) At the end of the Registration Period the Holders shall discontinue sales of shares pursuant to such Registration Statement upon receipt of notice from the Company of its intention to remove from registration the shares covered by such Registration Statement which remain unsold, and such Holders shall notify the Company of the number of shares registered which remain unsold as soon as practical upon receipt of such notice from the Company.

**6.8** With a view to making available to the Holders the benefits of certain rules and regulations of the SEC which at any time permit the sale of the Registrable Securities to the public without registration, so long as the Holders still own Registrable Securities, the Company shall use its reasonable best efforts to:

(a) make and keep public information available, as those terms are understood and defined in Rule 144 under the Securities Act, at all times;

(b) file with the SEC in a timely manner all reports and other documents required of the Company under the Exchange Act; and

(c) so long as a Holder owns any Registrable Securities, furnish to such Holder, upon any reasonable request, a written statement by the Company as to its compliance with Rule 144 under the Securities Act, and of the Exchange Act, a copy of the most recent annual or quarterly report of the Company, and such other reports and documents of the Company as such Holder may reasonably request in availing itself of any rule or regulation of the SEC allowing a Holder to sell any such securities without registration.

**6.9** The rights to cause the Company to register Registrable Securities granted to the Holders by the Company under Section 6.1 are deemed to be transferred to a Holder in connection with a transfer by such Holder of all or a portion of its Registrable Securities, *provided, however*, that (i) such Holder complies with all laws applicable thereto and provides written notice of assignment to the Company promptly after such assignment is effected and (ii) such transferee agrees to comply with the terms and provisions of this Agreement and has provided the Company with a completed questionnaire in the form of the Selling Stockholder Questionnaire attached to the signature page of this Agreement. Except as specifically permitted by this Section 6.9, the rights of a Holder with respect to Registrable Securities as set out herein shall not be transferable to any other Person, and any attempted transfer in violation of this Section 6.9 shall be null and void *ab initio*.

**6.10** The rights of any Holder under any provision of this Article 6 may be waived (either generally or in a particular instance, either retroactively or prospectively and either for a specified period of time or indefinitely) or amended by an instrument in writing signed by such Holder.

**6.11** In addition to the rights set forth above, each Holder will have the demand registration rights set forth on **Exhibit D** attached hereto.

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## ARTICLE 7

### DEFINITIONS

**7.1** *"Affiliate"* means, with respect to any Person, any other Person controlling, controlled by or under direct or indirect common control with such Person (for the purposes of this definition *"control,"* when used with respect to any specified Person, shall mean the power to direct the management and policies of such Person, directly or indirectly, whether through ownership of voting securities, by contract or otherwise; and the terms *"controlling"* and *"controlled"* shall have meanings correlative to the foregoing).

**7.2** *"Business Day"* means a day Monday through Friday on which banks are generally open for business in New York City.

- 7.3 “**Bylaws**” has the meaning set forth in Section 2.3.
- 7.4 “**Certificate of Incorporation**” has the meaning set forth in Section 2.3.
- 7.5 “**Closing**” has the meaning set forth in Section 1.3.
- 7.6 “**Closing Date**” has the meaning set forth in Section 1.3.
- 7.7 “**Common Stock**” means the common stock, par value \$0.001 per share, of the Company.
- 7.8 “**Company**” means Isis Pharmaceuticals, Inc., a Delaware corporation.
- 7.9 “**Demand Registrable Securities**” has the meaning set forth on Exhibit D.
- 7.10 “**Demand Registration Statement**” has the meaning set forth on Exhibit D.
- 7.11 “**Exchange Act**” means the Securities Exchange Act of 1934, as amended.
- 7.12 “**Filing Date**” has the meaning set forth in Section 6.1.
- 7.13 “**Final Prospectus**” has the meaning set forth in Section 6.6(a).
- 7.14 “**Financial Statements**” means the financial statements of the Company included in the SEC Documents.
- 7.15 “**Holder**” means any Person holding Registrable Securities or any person to whom the rights under Article 6 have been transferred in accordance with Section 6.9 hereof.
- 7.16 “**Indemnified Party**” has the meaning set forth in Section 6.6(c).
- 7.17 “**Indemnifying Party**” has the meaning set forth in Section 6.6(c).
- 7.18 “**Intellectual Property**” has the meaning set forth in Section 2.9.

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7.19 “**Material Adverse Effect**” means a material adverse effect on (a) the business, assets, financial condition, or results of operations or prospects (as described in the SEC Documents as of the date of this Agreement) of the Company, taken as a whole, or (b) the ability of the Company to perform its obligations pursuant to the transactions contemplated by this Agreement.

7.20 “**Material Agreement**” means any contract, commitment or instrument to which the Company is a party or the property or assets of the Company are bound that is listed as an exhibit to a periodic or current report filed by the Company with the SEC after December 31, 2004.

7.21 “**Nasdaq**” means The Nasdaq National Market.

7.22 “**Offering**” means the private placement of the Company’s Securities contemplated by this Agreement.

7.23 “**Penalty Period**” has the meaning set forth in Section 6.3.

7.24 “**Person**” or “**person**” means any person, individual, corporation, limited liability company, partnership, trust or other nongovernmental entity or any governmental agency, court, authority or other body (whether foreign, federal, state, local or otherwise).

7.25 “**Placement Agents**” means, collectively, Needham & Company, LLC and Fortis Securities LLC.

7.26 “**Purchasers**” mean the Purchasers whose names are set forth on the signature pages of this Agreement, and their permitted transferees.

7.27 “**Purchase Price**” has the meaning set forth in Section 1.1.

7.28 “**Registrable Securities**” means (i) the Shares and (ii) the Warrant Shares; *provided, however*, that securities shall only be treated as Registrable Securities if and only for so long as they (A) have not been disposed of pursuant to a registration statement that is effective under the Securities Act, (B) have not been sold in a transaction exempt from the registration and prospectus delivery requirements of the Securities Act so that all transfer restrictions and restrictive legends with respect thereto are removed upon the consummation of such sale, (C) are held by a Purchaser or any permitted transferee for less than two years following the issuance of such shares; and (D) are not eligible to be sold pursuant to Rule 144(k) promulgated under the Securities Act.

7.29 “**Registration Default**” has the meaning set forth in Section 6.3.

7.30 “**Registration Expenses**” means all expenses incurred by the Company in complying with Section 6.1 hereof, including, without limitation, all registration, qualification and filing fees, printing expenses, escrow fees, fees and expenses of counsel and auditors for the Company, blue sky fees and expenses and the expense of any special audits incident to or required by any such registration (but excluding the fees of legal counsel for any Holder).

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- 7.31 “**Registration Statement**” has the meaning set forth in Section 6.1.
- 7.32 “**Registration Period**” has the meaning set forth in Section 6.4(a).
- 7.33 “**Rule 144**” means Rule 144 promulgated under the Securities Act, or any successor rule.
- 7.34 “**SEC**” means the United States Securities and Exchange Commission.
- 7.35 “**SEC Documents**” has the meaning set forth in Section 2.6.
- 7.36 “**Securities**” has the meaning set forth in Section 1.1.
- 7.37 “**Securities Act**” means the Securities Act of 1933, as amended, and the rules and regulations thereunder, or any similar successor statute.
- 7.38 “**Selling Expenses**” means all selling commissions applicable to the sale of Registrable Securities by any Holder and all related fees and expenses of legal counsel for any Holder.
- 7.39 “**Shares**” has the meaning set forth in Section 1.1.
- 7.40 “**Warrant Shares**” has the meaning set forth in Section 2.4.
- 7.41 “**Warrants**” has the meaning set forth in Section 1.1.

## ARTICLE 8

### GOVERNING LAW; MISCELLANEOUS

**8.1 Governing Law; Jurisdiction.** This Agreement will be governed by and interpreted in accordance with the laws of the State of New York without regard to the principles of conflict of laws. Each of the parties hereto irrevocably submits and consents to the exclusive jurisdiction of the courts of the State of New York located in New York County and the United States District Court for the Southern District of New York for the purpose of any suit, action, proceeding or judgment relating to or arising out of this Agreement and the transactions contemplated hereby. Each party hereto irrevocably waives any objection to the laying of venue of any such suit, action or proceeding brought in such courts and irrevocably waives any claim that any such suit, action or proceeding brought in any such court has been brought in an inconvenient forum. **EACH OF THE PARTIES HERETO WAIVES ANY RIGHT TO REQUEST A TRIAL BY JURY IN ANY LITIGATION WITH RESPECT TO THIS AGREEMENT AND REPRESENTS THAT COUNSEL HAS BEEN CONSULTED SPECIFICALLY AS TO THIS WAIVER.**

**8.2 Counterparts; Signatures by Facsimile.** This Agreement may be executed in two or more counterparts, all of which are considered one and the same agreement and will become effective when counterparts have been signed by each party and delivered to the other parties. This Agreement, once executed by a party, may be delivered to the other parties hereto

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by facsimile transmission of a copy of this Agreement bearing the signature of the party so delivering this Agreement.

**8.3 Headings.** The headings of this Agreement are for convenience of reference only, are not part of this Agreement and do not affect its interpretation.

**8.4 Severability.** If any provision of this Agreement is invalid or unenforceable under any applicable statute or rule of law, then such provision will be deemed modified in order to conform with such statute or rule of law. Any provision hereof that may prove invalid or unenforceable under any law will not affect the validity or enforceability of any other provision hereof.

**8.5 Entire Agreement; Amendments.** This Agreement (including all schedules and exhibits hereto) and the certificates evidencing the Warrants constitute the entire agreement among the parties hereto with respect to the subject matter hereof and thereof. There are no restrictions, promises, warranties or undertakings, other than those set forth or referred to herein or therein. This Agreement supersedes all prior agreements and understandings among the parties hereto with respect to the subject matter hereof. No provision of this Agreement may be waived or amended other than by an instrument in writing signed by the party to be charged with such waiver or amendment.

**8.6 Notices.** All notices required or permitted hereunder shall be in writing and shall be deemed effectively given: (a) upon personal delivery to the party to be notified, (b) when sent by confirmed facsimile if sent during normal business hours of the recipient, if not, then on the next business day, (c) five days after having been sent by registered or certified mail, return receipt requested, postage prepaid, or (d) one business day after deposit with a nationally recognized overnight courier, specifying next day delivery, with written verification of receipt. The addresses for such communications are:

If to the Company:	Isis Pharmaceuticals, Inc. 1896 Rutherford Rd. Carlsbad, CA 92008-7208 Attn: B. Lynne Parshall
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With a copy to:	Isis Pharmaceuticals, Inc. 1896 Rutherford Rd. Carlsbad, CA 92008-7208 Attn: General Counsel
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If to a Purchaser: To the address set forth immediately below such Purchaser’s name on the signature pages hereto. Each party will provide ten days’ advance written notice to the other parties of any change in its address.

**8.7 Successors and Assigns.** This Agreement is binding upon and inures to the benefit of the parties and their successors and assigns. The Company will not assign this Agreement or any rights or obligations hereunder without the prior written consent of the Purchasers, and no Purchaser may assign this Agreement or any rights or obligations hereunder

without the prior written consent of the Company, except as permitted in accordance with Section 6.9 hereof.

**8.8 Third Party Beneficiaries.** This Agreement is intended for the benefit of the parties hereto, Holders, their respective permitted successors and assigns and the Placement Agents, and is not for the benefit of, nor may any provision hereof be enforced by, any other person.

**8.9 Further Assurances.** Each party will do and perform, or cause to be done and performed, all such further acts and things, and will execute and deliver all other agreements, certificates, instruments and documents, as another party may reasonably request in order to carry out the intent and accomplish the purposes of this Agreement and the consummation of the transactions contemplated hereby.

**8.10 No Strict Construction.** The language used in this Agreement is deemed to be the language chosen by the parties to express their mutual intent, and no rules of strict construction will be applied against any party.

**8.11 Equitable Relief.** The Company recognizes that, if it fails to perform or discharge any of its obligations under this Agreement, any remedy at law may prove to be inadequate relief to the Purchasers or Holders. The Company therefore agrees that the Purchasers or Holders are entitled to seek temporary and permanent injunctive relief in any such case. Each Purchaser also recognizes that, if it fails to perform or discharge any of its obligations under this Agreement, any remedy at law may prove to be inadequate relief to the Company. Each Purchaser therefore agrees that the Company is entitled to seek temporary and permanent injunctive relief in any such case.

**8.12 Survival of Representations and Warranties.** Notwithstanding any investigation made by any party to this Agreement, all representations and warranties made by the Company and the Purchasers herein shall survive for a period of one year following the date hereof.

**8.13 Independent Nature of Purchasers' Obligations and Rights.** Anything herein to the contrary notwithstanding, the representations, warranties, covenants and agreements of each Purchaser under this Agreement are several and not joint with the representations, warranties, covenants and agreements of any other Purchaser, and no Purchaser shall be responsible in any way for the performance of the obligations of any other Purchaser under this Agreement. Nothing contained herein and no action taken by any Purchaser pursuant thereto, shall be deemed to constitute the Purchasers as a partnership, an association, a joint venture or any other kind of entity, or create a presumption that the Purchasers are in any way acting in concert or as a group, or are deemed Affiliates with respect to such obligations or the transactions contemplated by this Agreement. Each Purchaser shall be entitled to independently protect and enforce its rights, including without limitation the rights arising out of this Agreement, and it shall not be necessary for any other Purchaser to be joined as an additional party in any proceeding for such purpose.

[Signature Page Follows]

**IN WITNESS WHEREOF**, the undersigned Purchasers and the Company have caused this Agreement to be duly executed as of the date first above written.

**ISIS PHARMACEUTICALS, INC.**

By: /s/ B. Lynne Parshall

Name: B. Lynne Parshall

Title: Executive Vice President and CFO

<u>Purchaser</u>	<u>Signature</u>
Federated Kaufmann Fund, a portfolio of Federated Equity Funds	<u>/s/ Hans P. Utsch</u> By: Hans P. Utsch, VP
Farallon Capital Partners, L.P.	<u>/s/ William F. Duhamel</u> By: William F. Duhamel, Managing Member
Farallon Capital Institutional Partners, L.P.	<u>/s/ William F. Duhamel</u> By: William F. Duhamel, Managing Member
Farallon Capital Institutional Partners II, L.P.	<u>/s/ William F. Duhamel</u> By: William F. Duhamel, Managing Member
Farallon Capital Institutional Partners III, L.P.	<u>/s/ William F. Duhamel</u> By: William F. Duhamel, Managing Member
Farallon Special Situation Partners II, L.P.	<u>/s/ William F. Duhamel</u> By: William F. Duhamel, Managing Member



Caduceus Capital Master Fund Limited

/s/ Samuel D. Isaly  
By: Samuel D. Isaly, President

Caduceus Capital II, LP

/s/ Samuel D. Isaly  
By: Samuel D. Isaly, Managing Member of General Partner

UBS Eucalyptus Fund LLC

/s/ Samuel D. Isaly  
By: Samuel D. Isaly, Managing  
Member of JV Partner

SECURITIES PURCHASE AGREEMENT  
SIGNATURE PAGE

PW Eucalyptus Fund Ltd

/s/ Samuel D. Isaly  
By: Samuel D. Isaly, Managing Member of JV Partner

HFR SHC Aggressive Master Fund

/s/ Samuel D. Isaly  
By: Samuel D. Isaly, Managing Partner of Advisor

Perceptive Life Sciences Master Fund, LTD.

/s/ Andrew G. Sankin  
By: Andrew G. Sankin, COO

SPECIAL SITUATIONS PRIVATE EQUITY FUND, L.P.

/s/ Austin Marxe  
By: Austin Marxe

SPECIAL SITUATIONS LIFE SCIENCES FUND, L.P.

/s/ Austin Marxe  
By: Austin Marxe

SPECIAL SITUATIONS FUND III, L.P.

/s/ Austin Marxe  
By: Austin Marxe

WHI Growth Fund, L.P.

/s/ Michael S. Resnick  
By: Michael S. Resnick, EVP

WPG-Farber Fund, L.P.

/s/ Steve Delco  
By: Steve Delco, VP

WPG-Farber QP Fund, L.P.

/s/ Steve Delco  
By: Steve Delco, VP

WPG-Farber Institutional Fund, L.P.

/s/ Steve Delco  
By: Steve Delco, VP

WPG-Farber Overseas, L.P.

/s/ Steve Delco  
By: Steve Delco, VP

Kamunting Street Master Fund, Ltd.

/s/ George Marionopolous  
By: George Marionopolous, Director

D3 LifeScience Ltd.

/s/ Nathan Fischel  
By: Nathan Fischel, MD, CFA, Managing Member

Buena Vista Investment Management

/s/ John Moffat  
By: John Moffat, Partner

**PURCHASER\***

\_\_\_\_\_  
(investor name)

By:

\_\_\_\_\_  
(signature)

\_\_\_\_\_  
(print name and title)

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

\_\_\_\_\_

Facsimile: \_\_\_\_\_

Custodian: \_\_\_\_\_

Custodian's address for  
delivery of Securities:

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\_\_\_\_\_  
\_\_\_\_\_

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**\*NOTE: PURCHASER MUST COMPLETE THE SELLING STOCKHOLDER QUESTIONNAIRE AS PART OF EXECUTING THIS STOCK PURCHASE AGREEMENT.** By signing above, the Purchaser acknowledges and agrees that the information contained in the Questionnaire below is complete and accurate and consents to the disclosure of the information contained herein in its answers to Items 1 through 6 below and the inclusion of such information in the Registration Statement and the related prospectus. The undersigned understands that such information will be relied upon by the Company in connection with the preparation or amendment of the Registration Statement and the related prospectus.

### SELLING STOCKHOLDER QUESTIONNAIRE

1. (a) Full Legal Name of Selling Securityholder:

(b) Full Legal Name of Registered Holder (if not the same as (a) above) through which Registrable Securities Listed in Item 3 below are held:

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(c) Full Legal Name of DTC participant (if applicable and if not the same as (b) above) through which Registrable Securities listed in Item 3 below are held:

(d) Status (yes/no) of Selling Securityholder as a registered broker-dealer or an affiliate of a registered broker-dealer (please describe to the extent applicable):

2. Address for Notices to Selling Securityholder:

Telephone:

Fax:

Contact Person:

3. Beneficial Ownership of Registrable Securities:

(a) Type and Principal Amount of Registrable Securities beneficially owned:

(b) CUSIP No(s). of such Registrable Securities beneficially owned:

4. Beneficial Ownership of Other Securities of the Company owned by the Selling Securityholder.

*Except as set forth below in this Item 4, the undersigned is not the beneficial or registered owner of any securities of the Company other than the Registrable Securities listed above in Item 3.*

(a) Type and Amount of Other Securities beneficially owned by the Selling Securityholder:

(b) CUSIP No(s). of such Other Securities beneficially owned:

5. Relationships with the Company:

*Except as set forth below, neither the undersigned nor any of its affiliates, officers, directors or principal equity holders (owners of 5% or more of the equity securities of the undersigned) has held any position or office or has had any other material relationship with the Company (or its predecessors or affiliates) during the past three years.*

State any exceptions here:

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6. Plan of Distribution:

*Except as set forth below, the undersigned (including its donees or pledgees) intends to distribute the Registrable Securities listed above in Item 3 pursuant to the Shelf Registration Statement only as follows (if at all):*

The Shares being registered are currently owned or, with respect to certain Selling Stockholders, may be acquired by the Selling Stockholder upon exercise of warrants to purchase our common stock. The selling stockholders, which as used herein includes donees, pledgees, transferees or other successors-in-interest selling shares of common stock or interests in shares of common stock received after the date of this prospectus from a selling stockholder as a gift, pledge, partnership distribution or other transfer, or acquires common stock upon exercise of warrants received from a Selling Stockholder may, from time to time, sell, transfer or otherwise dispose of any or all of their shares of common stock or interests in shares of common stock on any stock exchange, market or trading facility on which the shares are traded or in private transactions. These dispositions may be at fixed prices, at prevailing market prices at the time of sale, at prices related to the prevailing market price, at varying prices determined at the time of sale, or at negotiated prices.

The selling stockholders may use any one or more of the following methods when disposing of shares or interests therein:

- ordinary brokerage transactions and transactions in which the broker-dealer solicits purchasers;
- block trades in which the broker-dealer will attempt to sell the shares as agent, but may position and resell a portion of the block as principal to facilitate the transaction;
- purchases by a broker-dealer as principal and resale by the broker-dealer for its account;
- an exchange distribution in accordance with the rules of the applicable exchange;
- privately negotiated transactions;
- short sales effected after the date the registration statement of which this Prospectus is a part is declared effective by the SEC;
- through the writing or settlement of options or other hedging transactions, whether through an options exchange or otherwise;
- broker-dealers may agree with the selling stockholders to sell a specified number of such shares at a stipulated price per share; and
- a combination of any such methods of sale.

The selling stockholders may, from time to time, pledge or grant a security interest in some or all of the shares of common stock owned by them and, if they default in the performance of their secured obligations, the pledgees or secured parties may offer and sell the shares of common stock, from time to time, under this prospectus, or under an amendment to this prospectus under Rule 424(b)(3) or other applicable provision of the Securities Act amending the list of selling stockholders to include the pledgee, transferee or other successors in interest as selling stockholders under this prospectus. The selling stockholders also may transfer the shares of common stock in other circumstances, in which case the transferees, pledgees or other successors in interest will be the selling beneficial owners for purposes of this prospectus.

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In connection with the sale of our common stock or interests therein, the selling stockholders may enter into hedging transactions with broker-dealers or other financial institutions, which may in turn engage in short sales of the common stock in the course of hedging the positions they assume. The selling stockholders may also sell shares of our common stock short and deliver these securities to close out their short positions, or loan or pledge the common stock to broker-dealers that in turn may sell these securities. The selling stockholders may also enter into option or other transactions with broker-dealers or other financial institutions or the creation of one or more derivative securities which require the delivery to such broker-dealer or other financial institution of shares offered by this prospectus, which shares such broker-dealer or other financial institution may resell pursuant to this prospectus (as supplemented or amended to reflect such transaction).

The aggregate proceeds to the selling stockholders from the sale of the common stock offered by them will be the purchase price of the common stock less discounts or commissions, if any. Each of the selling stockholders reserves the right to accept and, together with their agents from time to time, to reject, in whole or in part, any proposed purchase of common stock to be made directly or through agents. We will not receive any of the proceeds from this offering. Upon any exercise of the warrants by payment of cash, however, we will receive the exercise price of the warrants.

The selling stockholders also may resell all or a portion of the shares in open market transactions in reliance upon Rule 144 under the Securities Act of 1933, provided that they meet the criteria and conform to the requirements of that rule.

The selling stockholders and any underwriters, broker-dealers or agents that participate in the sale of the common stock or interests therein may be “underwriters” within the meaning of Section 2(11) of the Securities Act. Any discounts, commissions, concessions or profit they earn on any resale of the shares may be underwriting discounts and commissions under the Securities Act. Selling stockholders who are “underwriters” within the meaning of Section 2(11) of the Securities Act will be subject to the prospectus delivery requirements of the Securities Act.

To the extent required, the shares of our common stock to be sold, the names of the selling stockholders, the respective purchase prices and public offering prices, the names of any agents, dealer or underwriter, any applicable commissions or discounts with respect to a particular offer will be set forth in an accompanying prospectus supplement or, if appropriate, a post-effective amendment to the registration statement that includes this prospectus.

In order to comply with the securities laws of some states, if applicable, the common stock may be sold in these jurisdictions only through registered or licensed brokers or dealers. In addition, in some states the common stock may not be sold unless it has been registered or qualified for sale or an exemption from registration or qualification requirements is available and is complied with.

We have advised the selling stockholders that the anti-manipulation rules of Regulation M under the Exchange Act may apply to sales of shares in the market and to the activities of the selling stockholders and their affiliates. In addition, we will make copies of this prospectus (as it

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may be supplemented or amended from time to time) available to the selling stockholders for the purpose of satisfying the prospectus delivery requirements of the Securities Act. The selling stockholders may indemnify any broker-dealer that participates in transactions involving the sale of the shares against certain liabilities, including liabilities arising under the Securities Act.

We have agreed to indemnify the selling stockholders against liabilities, including liabilities under the Securities Act and state securities laws, relating to the registration of the shares offered by this prospectus.

We have agreed with the selling stockholders to keep the registration statement of which this prospectus constitutes a part effective until the earlier of (1) the two year anniversary of the closing of the private placement, (2) such time as all of the shares covered by this prospectus have been disposed or (3) the date on which the shares may be sold pursuant to Rule 144 of the Securities Act during any 90 day period.

State any exceptions here:

*Note:* In no event will such method(s) of distribution take the form of an underwritten offering of the Registrable Securities without the prior agreement of the Company.

## EXHIBIT A

### SCHEDULE OF PURCHASERS

Purchaser	Shares	Warrants	Aggregate Purchase Price
Federated Kaufmann Fund, a portfolio of Federated Equity Funds	4,705,882	1,176,470	\$ 19,999,998.50
Farallon Capital Partners, L.P.	934,118	233,529	\$ 3,970,001.50
Farallon Capital Institutional Partners, L.P.	904,927	226,231	\$ 3,845,939.75
Farallon Capital Institutional Partners II, L.P.	204,338	51,085	\$ 868,436.50
Farallon Capital Institutional Partners III, L.P.	204,338	51,085	\$ 868,436.50
Farallon Special Situation Partners II, L.P.	671,397	167,849	\$ 2,853,437.25
Caduceus Capital Master Fund Limited	460,000	115,000	\$ 1,955,000.00
Caduceus Capital II, LP	232,000	58,000	\$ 986,000.00
UBS Eucalyptus Fund LLC	380,000	95,000	\$ 1,615,000.00
PW Eucalyptus Fund Ltd	38,000	9,500	\$ 161,500.00
HFR SHC Aggressive Master Fund	90,000	22,500	\$ 382,500.00
Perceptive Life Sciences Master Fund, LTD.	1,000,000	250,000	\$ 4,250,000.00
SPECIAL SITUATIONS PRIVATE EQUITY FUND, L.P.	380,000	95,000	\$ 1,615,000.00
SPECIAL SITUATIONS LIFE SCIENCES FUND, L.P.	120,000	30,000	\$ 510,000.00
SPECIAL SITUATIONS FUND III, L.P.	500,000	125,000	\$ 2,125,000.00
WHI Growth Fund, L.P.	750,000	187,500	\$ 3,187,500.00
WPG-Farber Fund, L.P.	84,000	21,000	\$ 357,000.00
WPG-Farber QP Fund, L.P.	32,550	8,137	\$ 138,337.50
WPG-Farber Institutional Fund, L.P.	28,050	7,012	\$ 119,212.50
WPG-Farber Overseas, L.P.	5,400	1,350	\$ 22,950.00
Kamunting Street Master Fund, Ltd.	150,000	37,500	\$ 637,500.00
D3 LifeScience Ltd.	100,000	25,000	\$ 425,000.00
Buena Vista Investment Management	25,000	6,250	\$ 106,250.00
<b>Total</b>	<b>12,000,000</b>	<b>2,999,998</b>	<b>\$ 51,000,000.00</b>

## EXHIBIT B

### FORM OF WARRANT

SEE EXHIBIT 99.2 TO THIS FORM 8-K

## EXHIBIT C

### LEGAL OPINONS

- The Company has been duly incorporated and is a validly existing corporation in good standing under the laws of the State of Delaware. The Company has the requisite corporate power to own its property and assets and to conduct its business as it is currently being conducted. The Company has the corporate power to execute, deliver and perform its obligations under the Financing Agreements.
- The Company is duly qualified to do business as a foreign corporation and is in good standing under the laws of the state of Delaware and California.
- Each of the Financing Agreements has been duly and validly authorized, executed and delivered by the Company and each such agreement constitutes a valid and binding agreement of the Company.
- The Shares have been duly authorized, and upon issuance and delivery against payment therefor in accordance with the terms of the Purchase Agreement, the Shares will be validly issued, outstanding, fully paid and nonassessable.
- The Warrant Shares have been duly authorized, and upon issuance and delivery against payment therefor in accordance with the terms of the Purchase Agreement, and if issued on the date hereof, the Warrant Shares would be validly issued, outstanding, fully paid and nonassessable.

6. Immediately prior to the issuance of the Shares, the authorized capital stock of the Company consists of 100,000,000 shares of Common Stock, \$0.001 par value, of which \_\_\_\_\_ shares are issued and outstanding.

7. No approval, authorization, consent or order of or filing with any national, state or local governmental or regulatory commission, board, body, authority or agency is required to be obtained or made by the Company in connection with the execution and delivery of the Stock Purchase Agreement, the Warrants and the issuance and sale of the Shares and, if issued on the date hereof, the Warrant Shares, except for such as (A) may be required under state securities laws and except for the filing of a Form D with the Securities and Exchange Commission pursuant to Regulation D under the Act, (B) are required in connection with the filing of the shelf registration statement(s) as contemplated by the Stock Purchase Agreement and (C) have been obtained or made prior to the date hereof.

8. The execution and delivery of the Stock Purchase Agreement, and the Warrants by the Company and the issuance of the Shares and, if issued on the date hereof, the issuance of the Warrant Shares, will not violate or contravene or be in conflict with (A) any provision of the Certificate of Incorporation, as amended, or Bylaws of the Company, (B) any Material Agreement, (C) any law, regulation or rule applicable to the Company (other than state or foreign securities laws, as to which we express no opinion) or (D) any decree, judgment or order known by us to be applicable to the Company or any of the Subsidiaries other than, in the case of

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clause (B), such Default Events as would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect.

9. Assuming (A) the veracity of the representations and warranties of the Company set forth in Section 2 of the Stock Purchase Agreement and of the Purchasers set forth in Section 3 of the Stock Purchase Agreement and (B) compliance by the Company and the Purchasers with the covenants and agreements set forth in Section 4 of the Stock Purchase Agreement, it is not necessary in connection with (X) the offer, sale and delivery of the Shares and Warrants pursuant to the Stock Purchase Agreement to register the Shares or the Warrants under the Act, it being understood that no opinion is expressed as to any subsequent resale of any Share, Warrants or Warrant Shares.

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## EXHIBIT D

### DEMAND REGISTRATION RIGHT

If a Holder holding Demand Registrable Securities requests in writing that the Company effect a registration under the Securities Act to register for resale all or part of such Holder's Demand Registrable Securities, the Company will use commercially reasonable efforts to (A) cause the shares of Demand Registrable Securities specified in such request to be so registered as promptly as practicable, so as to permit the sale of such shares by such requesting Holder in the manner specified in such request (provided such manner is consistent with the plan of distribution set forth in the Stockholder Questionnaire), (B) prepare and file on a registration statement (the "**Demand Registration Statement**") under the Securities Act to effect such registration and effect all such qualifications and compliances as may be so reasonably requested and as are necessary to permit or facilitate the sale and distribution of all or such portion of the Holder's Demand Registrable Securities and (C) keep such registration, and any qualification, exemption or compliance under state securities laws which the Company determines to obtain or which the Company obtains at the request of a Holder pursuant to Section 6.4(g) of the Agreement, continuously effective with respect to a Holder, and to keep such Registration Statement and the related prospectus free of any material misstatements or omissions; *provided, however*, that the Company shall not be obligated to file or effect any such registration, qualification or compliance pursuant to this Exhibit D if the Company shall furnish to the Holder a certificate signed by the President of the Company stating that in the good faith judgment of the Board of Directors of the Company, it would be seriously detrimental to the Company and its shareholders for such registration statement to be filed or effected at such time, in which event the Company shall have the right to defer the filing or effectiveness of the registration statement for a period of not more than 90 days after providing notice under this Exhibit D; *provided, further*, that the Company shall not utilize this right more than twice in any calendar year (so long as there is at least a 45 day period between such restrictions). Notwithstanding the foregoing, for each Holder the Company will only be required to effect a registration under this Exhibit D once in any 12-month period. The Company shall maintain the effectiveness of such Demand Registration Statement until the Demand Registrable Securities held by the Holder have been sold or the securities registered thereunder are no longer Demand Registrable Securities. The provisions of Section 6.4(b) through 6.4(j), 6.6, Section 6.7 and 6.10 are incorporated herein by reference as if the Demand Registrable Securities are Registrable Securities and the Demand Registration Statement is a Registration Statement. Each Holder listed as a selling stockholder on any Demand Registration Statement will reimburse the Company (on a pro rata basis based on the number of Demand Registrable Securities listed in such Demand Registration Statement) for the Company's out-of-pocket expenses in connection with preparing, filing and maintaining such Demand Registration Statement, and the related prospectus. Notwithstanding the foregoing, the Company will have no obligation to effect a registration under this Exhibit D for a Holder if including such Holder on the Demand Registration Statement would prevent the Company from using Form S-3 (or any successor form) in connection with such Demand Registration Statement.

**Demand Registrable Securities** means shares of Common Stock (i) which are not Shares or Warrant Shares, (ii) which are otherwise freely-tradeable without registration or qualification of them under the Securities Act or any similar state law then in force, (iii) but upon acquisition by

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such Holder, the Holder may be deemed to be an "affiliate" (as defined under Rule 144 promulgated under the Securities Act) of the Company (whether on its individual basis or pursuant to being part of a control group, for example, if one or more Holders are managed by the same manager or one or more Holders have the same general partner) and as such, such shares of Common Stock are subject to the volume limitations of Rule 144 promulgated under the Securities Act.

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THIS WARRANT AND THE UNDERLYING SECURITIES HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED OR THE SECURITIES LAWS OF ANY STATE OF THE UNITED STATES. THE SECURITIES MAY NOT BE SOLD, OFFERED FOR SALE, PLEDGED, HYPOTHECATED, TRANSFERRED OR ASSIGNED IN THE ABSENCE OF AN EFFECTIVE REGISTRATION STATEMENT FOR THE SECURITIES UNDER APPLICABLE SECURITIES LAWS OR UNLESS OFFERED, SOLD, PLEDGED, HYPOTHECATED OR TRANSFERRED PURSUANT TO AN AVAILABLE EXEMPTION FROM OR IN A TRANSACTION NOT SUBJECT TO THE REGISTRATION REQUIREMENTS OF THOSE LAWS. THE COMPANY SHALL BE ENTITLED TO REQUIRE AN OPINION OF COUNSEL REASONABLY SATISFACTORY TO THE COMPANY THAT SUCH REGISTRATION IS NOT REQUIRED TO THE EXTENT THAT AN OPINION IS REQUIRED PURSUANT TO THAT CERTAIN SECURITIES PURCHASE AGREEMENT UNDER WHICH THE SECURITIES WERE ISSUED.

ISIS PHARMACEUTICALS, INC.

WARRANT TO PURCHASE COMMON STOCK

No. CW-

August 23, 2005

Void After August 23, 2010

THIS CERTIFIES THAT, for value received, \_\_\_\_\_, with its principal office at \_\_\_\_\_, or its assigns (the "**Holder**"), is entitled to subscribe for and purchase at the Exercise Price (defined below) from Isis Pharmaceuticals, Inc., a Delaware corporation, with its principal office at 1896 Rutherford Road, Carlsbad, CA 92008-7208 (the "**Company**") up to \_\_\_\_\_ shares of the Common Stock of the Company (the "**Common Stock**"), subject to adjustment as provided herein. This Warrant is one of a series of Warrants being issued pursuant to the terms of the Securities Purchase Agreement, dated August 19, 2005, by and among the Company and the original Holder of this Warrant and the other parties named therein (the "**Purchase Agreement**"). Capitalized terms not otherwise defined herein shall have the respective meanings ascribed to such terms in the Purchase Agreement.

1. **DEFINITIONS.** As used herein, the following terms shall have the following respective meanings:

- (a) "**Exercise Period**" shall mean the period commencing 180 days after the date hereof and ending August 23, 2010, unless sooner terminated as provided below or redeemed by the Company pursuant to Section 7 below.
- (b) "**Exercise Price**" shall mean \$5.2395 per share, subject to adjustment pursuant to Section 6 below.
- (c) "**Exercise Shares**" shall mean the shares of the Company's Common Stock issuable upon exercise of this Warrant, subject to adjustment pursuant to the terms herein, including but not limited to adjustment pursuant to Section 6 below.

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2. **EXERCISE OF WARRANT.**

2.1 **Method of Exercise.** The rights represented by this Warrant may be exercised in whole or in part at any time during the Exercise Period, by delivery of the following to the Company at its address set forth above (or at such other address as it may designate by notice in writing to the Holder):

- (a) An executed Notice of Exercise in the form attached hereto;
- (b) Payment of the Exercise Price of the Exercise Shares purchased thereby (i) in cash or by check or wire transfer of immediately available funds, (ii) pursuant to a Cashless Exercise, as described below, or (iii) by a combination of (i) and (ii); and
- (c) This Warrant.

Upon the exercise of the rights represented by this Warrant, shares of Common Stock shall be issued for the Exercise Shares so purchased, and shall be registered in the name of the Holder or persons affiliated with the Holder, if the Holder so designates, within a reasonable amount of time following receipt by the Company of all of the items designated in clauses (a), (b) and (c) above and shall be issued in certificate form and delivered to the Holder, if so requested.

The person in whose name any Exercise Shares are to be issued upon exercise of this Warrant shall be deemed to have become the holder of record of such shares on the date on which this Warrant was surrendered and payment of the Exercise Price was made, irrespective of the date of issuance of the shares of Common Stock, except that, if the date of such surrender and payment is a date when the stock transfer books of the Company are closed, such person shall be deemed to have become the holder of such shares at the close of business on the next succeeding date on which the stock transfer books are open.

2.2 **Cashless Exercise.** Notwithstanding any provisions herein to the contrary, if, at any time during the Exercise Period, the Current Market Price (as defined below) of one share of Common Stock is greater than the Exercise Price (at the date of calculation as set forth below), in lieu of exercising this Warrant by payment of cash, the Holder may exercise this Warrant in whole or part by a cashless exercise by surrender of this Warrant at the principal office of the Company together with the properly endorsed Notice of Exercise and the Company shall issue to the Holder a number of shares of Common Stock computed using the following formula:

$$X = \frac{Y(B-A)}{B}$$

Where: X = the number of shares of Common Stock to be issued to the Holder.

Y = the number of shares of Common Stock purchasable upon exercise of all of the Warrant or, if only a portion of the Warrant is being exercised, the portion of the Warrant being exercised (in each case subject to adjustment)

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pursuant to the terms herein, including but not limited to adjustment pursuant to Section 6 below).

A = the Exercise Price.

B = the Current Market Price of one share of Common Stock.

“**Current Market Price**” means on any particular date:

(a) if the Common Stock is traded on the Nasdaq SmallCap Market or the Nasdaq National Market, the average of the closing prices of the Common Stock of the Company on such market over the five (5) trading days ending immediately prior to the applicable date of valuation (in the case of a cashless exercise, the date of valuation will be the exercise date);

(b) if the Common Stock is traded on any registered national stock exchange but is not traded on the Nasdaq SmallCap Market or the Nasdaq National Market, the average of the closing prices of the Common Stock of the Company on such exchange over the five (5) trading days ending immediately prior to the applicable date of valuation (in the case of a cashless exercise, the date of valuation will be the exercise date).

(c) if the Common Stock is traded over-the-counter, but not on the Nasdaq SmallCap Market, the Nasdaq National Market or a registered national stock exchange, the average of the closing bid prices over the 30-day period ending immediately prior to the applicable date of valuation (in the case of a cashless exercise, the date of valuation will be the exercise date); and

(d) if there is no active public market for the Common Stock, the value thereof, as determined in good faith by the Board of Directors of the Company upon due consideration of the proposed determination thereof by the Holder.

**2.3 Partial Exercise.** If this Warrant is exercised in part only, the Company shall, upon surrender of this Warrant, execute and deliver, within 10 days of the date of exercise, a new Warrant evidencing the rights of the Holder, or such other person as shall be designated in the Notice of Exercise, to purchase the balance of the Exercise Shares purchasable hereunder. In no event shall this Warrant be exercised for a fractional Exercise Share, and the Company shall not distribute a Warrant exercisable for a fractional Exercise Share. Fractional Exercise Shares shall be treated as provided in Section 5 hereof.

### 3. COVENANTS OF THE COMPANY.

**3.1 Covenants as to Exercise Shares.** The Company covenants and agrees that all Exercise Shares that may be issued upon the exercise of the rights represented by this Warrant will, upon issuance, be duly authorized and validly issued and outstanding, fully paid and nonassessable, and free from all taxes, liens and charges with respect to the issuance thereof. The Company further covenants and agrees that the Company will at all times during the Exercise Period, have authorized and reserved, free from preemptive rights, a sufficient number of shares of its Common Stock to provide for the exercise of the rights represented by this

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Warrant. If at any time during the Exercise Period the number of authorized but unissued shares of Common Stock shall not be sufficient to permit exercise of this Warrant, the Company will take such corporate action as may, in the opinion of counsel, be necessary to increase its authorized but unissued shares of Common Stock (or other securities as provided herein) to such number of shares as shall be sufficient for such purposes.

**3.2 No Impairment.** Except and to the extent as waived or consented to by the Holder in accordance with Section 10 hereof, the Company will not, by amendment of its Certificate of Incorporation (as such may be amended from time to time), or through any means, avoid or seek to avoid the observance or performance of any of the terms to be observed or performed hereunder by the Company, but will at all times in good faith carry out of all the provisions of this Warrant and take all such action as may be necessary or appropriate in order to protect the exercise rights of the Holder against such impairment.

**3.3 Notices of Record Date.** In the event of any taking by the Company of a record of the holders of any class of securities for the purpose of determining the holders thereof who are entitled to receive any dividend (other than a cash dividend which is the same as cash dividends paid in previous quarters) or other distribution, the Company shall mail to the Holder, at least ten days prior to the date specified therein, a notice specifying the date on which any such record is to be taken for the purpose of such dividend or distribution.

### 4. REPRESENTATIONS OF HOLDER.

**4.1 Acquisition of Warrant for Personal Account.** The Holder represents and warrants that it is acquiring the Warrant and the Exercise Shares solely for its account for investment and not with a present view toward the public sale or public distribution of said Warrant or Exercise Shares or any part thereof and has no intention of selling or distributing said Warrant or Exercise Shares or any arrangement or understanding with any other persons regarding the sale or distribution of said Warrant or the Exercise Shares, except as would not result in a violation of the Securities Act. The Holder will not, directly or indirectly, offer, sell, pledge, transfer or otherwise dispose of (or solicit any offers to buy, purchase or otherwise acquire or take a pledge of) the Warrant except in accordance with Section 3.8 of the Purchase Agreement and will not, directly or indirectly, offer, sell, pledge, transfer or otherwise dispose of (or solicit any offers to buy, purchase or otherwise acquire or take a pledge of) the Exercise Shares except in accordance with the provisions of Article 6 or Section 3.8 of the Purchase Agreement or pursuant to and in accordance with the Securities Act.

#### 4.2 Securities Are Not Registered.

(a) The Holder understands that the offer and sale of neither the Warrant nor the Exercise Shares has been registered under the Securities Act.

(b) The Holder recognizes that the Warrant and the Exercise Shares must be held indefinitely unless they are subsequently registered under the Securities Act or an exemption from such registration is available. The Holder recognizes that the Company has no obligation to register the Warrant or, except as provided in the Purchase Agreement, the Exercise Shares, or to comply with any exemption from such registration.

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(c) The Holder is aware that neither the Warrant nor the Exercise Shares may be sold pursuant to Rule 144 adopted under the Securities Act unless certain conditions are met, including, among other things, the availability of certain current public information about the Company and the expiration of the required holding period under Rule 144.

#### 4.3 Disposition of Warrant and Exercise Shares.

(a) The Holder further agrees not to make any disposition of all or any part of the Warrant or Exercise Shares in any event unless and until one of the following occurs:

(i) The Company shall have received a letter secured by the Holder from the SEC stating that no action will be recommended to the Commission with respect to the proposed disposition;

(ii) There is then in effect a registration statement under the Securities Act covering such Warrant or Exercise Shares and such disposition is made in accordance with said registration statement; or

(iii) The Holder shall have furnished the Company with an opinion of counsel, reasonably satisfactory to the Company, for the Holder to the effect that such disposition will not require registration of such Warrant or Exercise Shares under the Securities Act or any applicable state securities laws; *provided*, that so long as the Holder provides the Company with a representation letter in customary form with respect to such Rule 144 disposition, no opinion shall be required for any disposition made or to be made in accordance with the provisions of Rule 144.

(b) The Holder understands and agrees that all certificates evidencing the Exercise Shares to be issued to the Holder may bear a legend in substantially the following form (provided that no such legend will be borne by Exercise Shares issued following the disposition of such shares pursuant to a registration statement which is effective under the Securities Act and provided, further, that the Company will remove such legend at the request of the Holder (i) following any sale of the Exercise Shares pursuant to an effective registration statement or Rule 144, or (ii) if such Exercise Shares are eligible for sale under Rule 144(k)):

**THE SECURITIES REPRESENTED BY THIS CERTIFICATE HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED, OR THE SECURITIES LAWS OF ANY STATE OF THE UNITED STATES. THE SECURITIES MAY NOT BE SOLD, OFFERED FOR SALE, PLEDGED, HYPOTHECATED, TRANSFERRED OR ASSIGNED IN THE ABSENCE OF AN EFFECTIVE REGISTRATION STATEMENT FOR THE SECURITIES UNDER APPLICABLE SECURITIES LAWS, OR UNLESS OFFERED, SOLD, PLEDGED, HYPOTHECATED OR TRANSFERRED PURSUANT TO AN AVAILABLE EXEMPTION FROM OR IN A TRANSACTION NOT SUBJECT TO THE REGISTRATION REQUIREMENTS OF THOSE LAWS. THE COMPANY SHALL BE ENTITLED TO REQUIRE AN OPINION OF COUNSEL**

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**REASONABLY SATISFACTORY TO THE COMPANY THAT SUCH REGISTRATION IS NOT REQUIRED TO THE EXTENT THAT AN OPINION IS REQUIRED PURSUANT TO THE AGREEMENT UNDER WHICH THE SECURITIES WERE ISSUED.**

5. **FRACTIONAL SHARES.** No fractional shares shall be issued upon the exercise of this Warrant as a consequence of any adjustment pursuant hereto. All Exercise Shares (including fractions) issuable upon exercise of this Warrant may be aggregated for purposes of determining whether the exercise would result in the issuance of any fractional share. If, after aggregation, the exercise would result in the issuance of a fractional share, the Company shall, in lieu of issuance of any fractional share, pay the Holder otherwise entitled to such fraction a sum in cash equal to the product resulting from multiplying the then Current Market Price (as of the applicable exercise date) of an Exercise Share by such fraction.

#### 6. CERTAIN EVENTS.

6.1 **Distribution of Assets.** In case the Company shall declare or make any distribution of its assets (or rights to acquire its assets) to holders of Common Stock as a partial liquidating dividend, by way of return of capital or otherwise (including any dividend or distribution to the Company's stockholders of cash or shares (or rights to acquire shares) of capital stock of a subsidiary) (a "**Distribution**"), at any time after the initial issuance of this Warrant, then the Holder shall be entitled upon exercise of this Warrant for the purchase of any or all of the shares of Common Stock subject hereto, to receive the amount of such assets (or rights) which would have been payable to the Holder had such Holder been the holder of such shares of Common Stock on the record date for the determination of stockholders entitled to such Distribution.

6.2 **Dividends, Subdivisions, Combinations and Reclassifications.** The number and kind of securities purchasable upon the exercise of this Warrant and the Exercise Price shall be subject to adjustment from time to time upon the happening of any of the following. In case the Company shall (i) pay a dividend in shares of Common Stock or make a distribution in shares of Common Stock to holders of its outstanding Common Stock, (ii) subdivide its outstanding shares of Common Stock into a greater number of shares, (iii) combine its outstanding shares of Common Stock into a smaller number of shares of Common Stock, or (iv) issue any shares of its capital stock in a reclassification of the Common Stock, then the number of Warrant Shares purchasable upon exercise of this Warrant immediately prior thereto shall be adjusted so that the Holder shall be entitled to receive the kind and number of Warrant Shares or other securities of the Company which it would have owned or have been entitled to receive had such Warrant been exercised in advance thereof. Upon each such adjustment of the kind and number of Warrant Shares or other securities of the Company which are purchasable hereunder, the



Holder shall thereafter be entitled to purchase the number of Warrant Shares or other securities resulting from such adjustment at an Exercise Price per Warrant Share or other security obtained by multiplying the Exercise Price in effect immediately prior to such adjustment by the number of Warrant Shares purchasable pursuant hereto immediately prior to such adjustment and dividing by the number of Warrant Shares or other securities of the Company resulting from such adjustment. An adjustment made pursuant to this paragraph shall

become effective immediately after the effective date of such event retroactive to the record date, if any, for such event.

**6.3 Reorganization, Reclassification, Merger, Consolidation or Disposition of Assets.** In case the Company shall reorganize its capital, reclassify its capital stock, consolidate or merge with or into another corporation (where the Company is not the surviving corporation or where there is a change in or distribution with respect to the Common Stock of the Company), or sell, transfer or otherwise dispose of all or substantially all its property, assets or business to another corporation and, pursuant to the terms of such reorganization, reclassification, merger, consolidation or disposition of assets, shares of common stock of the successor or acquiring corporation, or any cash, shares of stock or other securities or property of any nature whatsoever (including warrants or other subscription or purchase rights) in addition to or in lieu of common stock of the successor or acquiring corporation (“**Other Property**”), are to be received by or distributed to the holders of Common Stock of the Company, then the Holder shall have the right thereafter to receive upon exercise of this Warrant, the number of shares of Common Stock of the successor or acquiring corporation or of the Company, if it is the surviving corporation, and Other Property receivable upon or as a result of such reorganization, reclassification, merger, consolidation or disposition of assets by a Holder of the number of shares of Common Stock for which this Warrant is exercisable immediately prior to such event. In case of any such reorganization, reclassification, merger, consolidation or disposition of assets, the successor or acquiring corporation (if other than the Company) shall expressly assume the due and punctual observance and performance of each and every covenant and condition of this Warrant to be performed and observed by the Company and all the obligations and liabilities hereunder, subject to such modifications as may be deemed appropriate (as determined in good faith by resolution of the Board of Directors of the Company) in order to provide for adjustments of Warrant Shares for which this Warrant is exercisable which shall be as nearly equivalent as practicable to the adjustments provided for in this Section 6.3. For purposes of this Section 6.3, “common stock of the successor or acquiring corporation” shall include stock of such corporation of any class which is not preferred as to dividends or assets over any other class of stock of such corporation and which is not subject to redemption and shall also include any evidences of indebtedness, shares of stock or other securities which are convertible into or exchangeable for any such stock, either immediately or upon the arrival of a specified date or the happening of a specified event and any warrants or other rights to subscribe for or purchase any such stock. The foregoing provisions of this Section 6.3 shall similarly apply to successive reorganizations, reclassifications, mergers, consolidations or disposition of assets.

**6.4 Adjustment of Exercise Price.** The form of this Warrant need not be changed because of any adjustment in the number, class, and kind of shares or Other Property subject to this Warrant. The Company shall promptly provide a certificate from its principal accounting officer notifying the Holder in writing of any adjustment in the Exercise Price and/or the total number, class, and kind of shares or Other Property issuable upon exercise of this Warrant, which certificate shall specify the Exercise Price and number, class and kind of shares or Other Property under this Warrant after giving effect to such adjustment and shall set forth a brief statement of the facts requiring such adjustment and setting forth the computation by which such adjustment was made.

**7. CALL PROVISION.** Notwithstanding any other provision contained in this Warrant to the contrary, if at any time following August 23, 2008, the closing bid price per share of Common Stock as traded on the Nasdaq (or such other exchange or stock market on which the Common Stock may then be listed or quoted) equals or exceeds \$14.408 (appropriately adjusted for any stock split, reverse stock split, stock dividend or other reclassification or combination of the Common Stock occurring after the date hereof) for twenty (20) consecutive trading days commencing after the Registration Statement (as defined in the Purchase Agreement) has been declared effective, the Company, upon thirty (30) days prior written notice (the “Notice Period”) (and the written notice will specify the date of the end of the Notice Period) given to the Warrantholder within one business day immediately following the end of such twenty (20) trading day period, may call this Warrant, in whole but not in part, at a redemption price equal to \$0.01 per share of Common Stock then purchasable pursuant to this Warrant; provided that (i) the Company simultaneously calls all Warrants issued pursuant to the Purchase Agreement on the same terms, (ii) all of the Exercise Shares either (A) are registered pursuant to an effective Registration Statement which is not suspended and for which no stop order is in effect, and pursuant to which the Warrantholder is able to sell such Exercise Shares at all times during the Notice Period or (B) no longer constitute Registrable Securities (as defined in the Purchase Agreement) and (iii) this Warrant is fully exercisable for the full amount of Exercise Shares covered hereby. Notwithstanding any such notice by the Company, the Warrantholder shall have the right to exercise this Warrant prior to the end of the Notice Period.

**8. NO STOCKHOLDER RIGHTS.** This Warrant in and of itself shall not entitle the Holder to any voting rights or other rights as a stockholder of the Company.

**9. TRANSFER OF WARRANT.** Subject to applicable laws and compliance with Section 4.3 hereof, this Warrant and all rights hereunder are transferable, by the Holder in person or by duly authorized attorney, upon delivery of this Warrant and the form of assignment attached hereto to any transferee designated by Holder. The transferee will sign an investment letter in form and substance reasonably satisfactory to the Company.

**10. LOST, STOLEN, MUTILATED OR DESTROYED WARRANT.** If this Warrant is lost, stolen, mutilated or destroyed, the Company may, on such terms as to indemnity or otherwise as it may reasonably impose (which shall, in the case of a mutilated Warrant, include the surrender thereof), issue a new Warrant of like denomination and tenor as the Warrant so lost, stolen, mutilated or destroyed. Any such new Warrant shall constitute an original contractual obligation of the Company, whether or not the allegedly lost, stolen, mutilated or destroyed Warrant shall be at any time enforceable by anyone.

**11. MODIFICATIONS AND WAIVER.** This Warrant and any provision hereof may be changed, waived, discharged or terminated only by an instrument in writing signed by the Company and the Holder.

**12. NOTICES, ETC.** All notices required or permitted hereunder shall be in writing and shall be deemed effectively given: (a) upon personal delivery to the party to be notified, (b) when sent by confirmed facsimile if sent during normal business hours of the recipient, if not, then on the next business day, (c) five days after having been sent by registered or certified mail, return receipt requested, postage prepaid, or (d) one business day after deposit with a nationally

recognized overnight courier, specifying next day delivery, with written verification of receipt. All communications shall be sent to the Company at the address listed on the signature page and to the Holder at the addresses on the Company records, or at such other address as the Company or Holder may designate by ten days' advance written notice to the other party hereto.

13. **ACCEPTANCE.** Receipt of this Warrant by the Holder shall constitute acceptance of and agreement to all of the terms and conditions contained herein.

14. **GOVERNING LAW.** This Warrant and all rights, obligations and liabilities hereunder shall be governed by the laws of the State of New York without regard to the principles of conflict of laws. The Company and, by accepting this Warrant, the Warrantholder, each irrevocably submits and consents to the exclusive jurisdiction of the courts of the State of New York located in New York County and the United States District Court for the Southern District of New York for the purpose of any suit, action, proceeding or judgment relating to or arising out of this Warrant and the transactions contemplated hereby. The Company and, by accepting this Warrant, the Warrantholder, each irrevocably waives any objection to the laying of venue of any such suit, action or proceeding brought in such courts and irrevocably waives any claim that any such suit, action or proceeding brought in any such court has been brought in an inconvenient forum. **EACH OF THE COMPANY AND, BY ITS ACCEPTANCE HEREOF, THE WARRANTHOLDER HEREBY WAIVES ANY RIGHT TO REQUEST A TRIAL BY JURY IN ANY LITIGATION WITH RESPECT TO THIS WARRANT AND REPRESENTS THAT COUNSEL HAS BEEN CONSULTED SPECIFICALLY AS TO THIS WAIVER.**

15. **DESCRIPTIVE HEADINGS.** The descriptive headings of the several paragraphs of this Warrant are inserted for convenience only and do not constitute a part of this Warrant. The language in this Warrant shall be construed as to its fair meaning without regard to which party drafted this Warrant.

16. **SEVERABILITY.** The invalidity or unenforceability of any provision of this Warrant in any jurisdiction shall not affect the validity or enforceability of such provision in any other jurisdiction, or affect any other provision of this Warrant, which shall remain in full force and effect.

17. **REGISTRATION RIGHTS.** The holder of this Warrant and of the Exercise Shares shall be entitled to the registration rights and other applicable rights as and to the extent set forth in the Purchase Agreement.

18. **ENTIRE AGREEMENT.** This Warrant constitutes the entire agreement between the parties pertaining to the subject matter contained in it and supersedes all prior and contemporaneous agreements, representations, and undertakings of the parties, whether oral or written, with respect to such subject matter.

[Signature Page Follows]

IN WITNESS WHEREOF, the Company has caused this Warrant to be executed by its duly authorized officer as of August , 2005.

**ISIS PHARMACEUTICALS, INC.**

By: \_\_\_\_\_

Name: \_\_\_\_\_

Title: \_\_\_\_\_

Address: 1896 Rutherford Road  
Carlsbad, CA 92008-7208  
Attn: B. Lynne Parshall  
Facsimile: (760) 603-4650

W/copy to: General Counsel  
Facsimile: (760) 268-4922

**NOTICE OF EXERCISE**

**TO: ISIS PHARMACEUTICALS INC.**

(1) The undersigned hereby elects to (check one box only):

purchase \_\_\_\_\_ shares of the Common Stock of Isis Pharmaceuticals, Inc. (the "**Company**") pursuant to the terms of the attached Warrant, and tenders herewith payment of the exercise price in full for such shares.

purchase the number of shares of Common Stock of the Company by cashless exercise pursuant to the terms of the Warrant as shall be issuable upon cashless exercise of the portion of the Warrant relating to \_\_\_\_\_ shares.

(2) Please issue a certificate or certificates representing said shares of Common Stock in the name of the undersigned or in such other name as is specified below:

\_\_\_\_\_  
(Name)  
\_\_\_\_\_  
\_\_\_\_\_  
(Address)

(3) If the Warrant is not being exercised in full, please issue a certificate representing a new Warrant evidencing the right of the Holder to purchase the balance of the Exercise Shares purchasable under the Warrant, such certificate to be registered in the name of the undersigned or in such other name as is specified below:

\_\_\_\_\_  
(Name)  
\_\_\_\_\_  
\_\_\_\_\_  
(Address)

(4) The undersigned represents that (i) the aforesaid shares of Common Stock are being acquired for the account of the undersigned not with a view to, or for resale in connection with, the distribution thereof in violation of the Securities Act of 1933, as amended (the "**Securities Act**") and that the undersigned has no present intention of distributing or reselling such shares in violation of the Securities Act; (ii) the undersigned is aware of the Company's business affairs and financial condition and has acquired sufficient information about the Company to reach an informed and knowledgeable decision regarding its investment in the Company; (iii) the undersigned is experienced in making investments of this type and has such knowledge and background in financial and business matters that the undersigned is capable of evaluating the merits and risks of this investment and protecting the undersigned's own interests; (iv) the undersigned understands that the shares of Common Stock issuable upon exercise of this Warrant must be held indefinitely unless subsequently registered under the Securities Act or an exemption from such registration is

available, and (v) the undersigned agrees not to make any disposition of all or any part of the aforesaid shares of Common Stock unless and until there is then in effect a registration statement under the Securities Act covering such proposed disposition and such disposition is made in accordance with said registration statement, or the undersigned has provided the Company with an opinion of counsel satisfactory to the Company, stating that such registration is not required.

\_\_\_\_\_  
(Date) (Signature)  
\_\_\_\_\_  
(Print name)

**ASSIGNMENT FORM**

(To assign the foregoing Warrant, subject to compliance with section 4.3 hereof, execute this form and supply required information. Do not use this form to purchase shares.)

**FOR VALUE RECEIVED**, the foregoing Warrant and all rights evidenced thereby are hereby assigned to

Name: \_\_\_\_\_  
(Please Print)

Address: \_\_\_\_\_  
(Please Print)

Dated: \_\_\_\_\_, 20

Holder's  
Signature: \_\_\_\_\_

Holder's  
Address: \_\_\_\_\_

**NOTE:** The signature to this Assignment Form must correspond with the name as it appears on the face of the Warrant, without alteration or enlargement or any change whatever. Officers of corporations and those acting in a fiduciary or other representative capacity should file proper evidence of authority to assign the foregoing Warrant.



## Isis Pharmaceuticals Raises \$51 Million in Private Offering

### Funding to Support Continued Development of Promising Drug Pipeline

CARLSBAD, Calif., Aug. 22 /PRNewswire-FirstCall/ — Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced that it has entered into an agreement for a \$51 million private placement of 12 million shares of its common stock at a price of \$4.25 per share, a 2.3% discount from its 60 day average trading price. Upon closing of this financing, expected to be on or before August 24, 2005, investors in the financing will also receive warrants to purchase approximately 3 million shares of common stock at an exercise price of \$5.23 per share. Needham & Company and Fortis Securities LLC are acting as the exclusive placement agents for the offering.

The net proceeds from the offering realized by the Company are approximately \$48 million, and will be used for research, drug discovery and development activities, including preclinical and clinical studies, capital expenditures and other general corporate purposes.

“This financing strengthens our balance sheet, providing sufficient cash to fund our operations, with reasonable assumptions for new sources of revenue and cash, at least through 2007,” said B. Lynne Parshall, Isis’ Executive Vice President and Chief Financial Officer. “In addition, it gives us the capital to negotiate potential drug discovery and development collaborations and other licensing arrangements from a position of financial strength. We are pleased with the support shown by our long term investors whose participation was an important element of this financing, and with the addition of several sophisticated biotech investors to our investor base.”

“Our recent achievements in the clinic demonstrate that our antisense drugs are working in man, and we are committed to the continued development of these drugs and the antisense technology platform. We believe antisense represents a new sector of the pharmaceutical industry that will provide benefit to patients in need of novel therapeutic alternatives,” said Stanley T. Croke, Isis’ Chairman and CEO. “We appreciate the support from our investors who participated in this transaction, providing us assistance in achieving our goals moving forward.”

The shares sold in the private placement and the shares issuable upon the exercise of the related warrants have not been registered under the Securities Act of 1933, as amended, or state securities laws, and may not be offered or sold in the United States without being registered with the Securities and Exchange Commission (SEC) or through an applicable exemption from SEC registration requirements. The shares were offered and will be sold only to qualified institutional buyers and a limited number of accredited investors. The Company has agreed to file a registration statement with the SEC covering the resale of the common stock issued in the private placement and issuable upon the exercise of the warrants.

### ABOUT ISIS PHARMACEUTICALS, INC.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel

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drugs for its product pipeline and for its partners. The Company has successfully commercialized the world’s first antisense drug and has 11 antisense drugs in development to treat metabolic, cardiovascular and inflammatory diseases, and cancer. In its Ibis division, Isis is developing and commercializing the TIGER biosensor system, a revolutionary system to identify infectious organisms. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of more than 1,500 issued patents worldwide. Additional information about Isis is available at [www.isispharm.com](http://www.isispharm.com).

This press release includes forward-looking statements regarding Isis Pharmaceuticals’ business, the financial position of Isis, and the therapeutic and commercial potential of the Company’s technologies and products in development. Any statement describing Isis’ goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis’ goals. 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 products. Isis’ forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis’ forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis’ programs are described in additional detail in Isis’ annual report on Form 10-K for the year ended December 31, 2004, and its quarterly report on Form 10-Q for the quarter ended June 30, 2005, which are on file with the SEC. Copies of these and other documents are available from the Company.

SOURCE Isis Pharmaceuticals, Inc.

08/22/2005

CONTACT: Claudine Prowse, Ph.D., of Isis Pharmaceuticals, Inc., +1-760-603-2331

Web site: <http://www.isispharm.com>

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