

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM S-3
REGISTRATION STATEMENT
Under
THE SECURITIES ACT OF 1933**ISIS PHARMACEUTICALS, INC.**

(Exact name of Registrant as specified in its charter)

Delaware
(State or other jurisdiction
of incorporation or organization)33-0336973
(I.R.S. Employer
Identification Number)1896 Rutherford Road
Carlsbad, California 92008
(760) 931-9200

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

B. Lynne Parshall, Esq.
Executive Vice President
Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, California 92008
(760) 931-9200

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

*Copies to:*Julie M. Robinson, Esq.
Cooley Godward LLP
4401 Eastgate Mall
San Diego, CA 92121
(858) 550-6000Approximate date of commencement of proposed sale to the public:
From time to time after the effective date of this Registration Statement.If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box. If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box. If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box. If this is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box. **CALCULATION OF REGISTRATION FEE**

Title of each class of securities to be registered	Proposed maximum aggregate offering price	Amount of registration fee(3)
Common Stock, \$0.001 per share (1)	\$200,000,000(2)	\$21,400

- (1) An indeterminate number of shares of common stock of the registrant may be sold from time to time by the registrant. The common stock includes associated Series C Junior Participating Preferred Stock Rights pursuant to Rights Agreement dated as of December 8, 2000 between the Registrant and American Stock Transfer & Trust Company.
- (2) In no event will the aggregate offering price of all securities issued from time to time pursuant to this registration statement exceed \$200,000,000.00.
- (3) Calculated pursuant to Rule 457(o) of the Securities Act of 1933.

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment that specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the Registration Statement shall become effective on such date as the Commission, acting pursuant to said Section 8 (a), may determine.

The information in this prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and we are not soliciting offers to buy these securities in any state where the offer or sale is not permitted.

PRELIMINARY PROSPECTUS

\$200,000,000

ISIS PHARMACEUTICALS, INC.

Common Stock

We may from time to time sell common stock in one or more offerings for an aggregate initial offering price of \$200,000,000. This prospectus describes the general manner in which our common stock may be offered using this prospectus. We will specify in the accompanying prospectus supplement the terms of the securities to be offered and sold. We may sell these securities to or through underwriters or dealers and also to other purchasers or through agents. We will set forth the names of any underwriters, dealers or agents in the accompanying prospectus supplement.

Our common stock is currently traded on the Nasdaq National Market under the symbol "ISIS." On December 21, 2005, the last reported sales price for our common stock was \$5.25 per share.

**Investing in our common stock involves risks.
See "Risk Factors" beginning on page 3.**

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

This prospectus may not be used to consummate sales of securities unless it is accompanied by a prospectus supplement.

The date of this Prospectus is December 22, 2005

TABLE OF CONTENTS

	Page
About this Prospectus	1
About our Business	1
Risk Factors	3
Special Notice Regarding Forward-Looking Statements	8
Use of Proceeds	9
Plan of Distribution	9
Description of Capital Stock	10
Dividend Policy	11
Legal Matters	11
Experts	11
Where You Can Find More Information	12
Incorporation of Certain Documents by Reference	12

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission using a "shelf" registration process. Under this shelf registration process, we may, from time to time, sell common stock in one or more offerings up to a total dollar amount of \$200,000,000. This prospectus describes the general manner in which our common stock may be offered by this prospectus. Each time we sell common stock, we will provide a prospectus supplement that will contain specific information about the terms of that offering. If there is any inconsistency between the information in this prospectus and the accompanying prospectus supplement, you should rely on the information in the prospectus supplement. We may also add, update or change in the prospectus supplement any of the information contained in this prospectus. This prospectus, together with applicable prospectus supplements, includes all material information relating to this offering.

We encourage you to read this prospectus in its entirety, including the documents incorporated by reference. As used in this prospectus, unless otherwise specified or the context requires otherwise, the terms "Isis," "we," "our" and "us" refer to Isis Pharmaceuticals, Inc.

ABOUT OUR BUSINESS

We are a biopharmaceutical company exploiting proprietary RNA-based drug discovery technologies to identify and commercialize novel drugs to treat important diseases. RNA, or ribonucleic acid, is a molecule that provides to a cell the information the cell needs to produce proteins, including those proteins implicated in disease. Interference with RNA can keep the body from producing proteins that are involved in disease. We are the leader in exploiting RNA as a target for drugs, and have a strong proprietary position in RNA-based drug discovery technologies. With our primary technology, antisense, we create inhibitors, or oligonucleotides, designed to hybridize, with a high degree of specificity to their RNA target and modulate the production of specific proteins associated with disease. We also use our antisense technology internally and in collaborations with pharmaceutical companies to rapidly and efficiently identify and prioritize attractive gene targets for drug discovery. Within our Ibis division, we are expanding on our RNA expertise by creating a system that can rapidly and accurately identify a broad range of infectious organisms with a single test. Our ongoing development of this technology and a system related to this technology has been funded primarily by agencies within the United States government.

We successfully commercialized our first antisense drug, Vitravene. Vitravene demonstrates our ability to meet Food and Drug Administration, or FDA, and European regulatory requirements, and to commercially manufacture antisense drugs. We and our partners currently have 12 antisense products in preclinical and clinical development, the majority of which are in Phase I or Phase II human clinical trials. Our products in development address numerous therapeutic areas with major market potential, including inflammatory, metabolic, cardiovascular and ocular diseases, and cancer. We are expanding the therapeutic opportunities for antisense drugs by developing a variety of formulations to enhance patient convenience and compliance, including intravitreal, subcutaneous, topical cream, enema, aerosol and oral formulations. In addition, our pipeline has matured to consist primarily of drugs based on our proprietary second-generation chemistry. Our second-generation antisense drugs offer a number of advantages over prior chemistries. Specifically, these drugs offer the potential for improved safety, increased potency and a longer half-life, which correlates with durability of therapeutic response and the potential for less frequent dosing. Physicians may be able to dose our second-generation drugs as infrequently as once every two weeks to once a month. We are also making progress on developing oral formulations of our second-generation antisense drugs. Our oral formulations may increase the commercial value of our antisense drugs.

Within our Ibis division we have invented technology that has the potential to revolutionize the identification of infectious diseases. This technology is called Triangulation Identification for Genetic Evaluation of Risks, or TIGER. We have applied the TIGER technology to develop a system to identify from a sample a broad range of infectious organisms, including organisms that are newly-emerging, genetically altered and unculturable. We have successfully demonstrated proof-of-principle of the TIGER biosensor system with the identification of a variety of bacteria and viruses in both environmental and human clinical samples. In addition to bioweapons defense, Ibis has advanced the development of our TIGER biosensor system to include epidemiological surveillance, biological products screening and microbial forensics screening applications. These applications represent the first

1

of many we plan to add to the TIGER biosensor system to enhance its commercial value and opportunity in the government, research, medical and diagnostic markets.

We incorporated in California in 1989, and in 1991 we reincorporated as a Delaware corporation. Our principal offices are in Carlsbad, California. Our executive offices are located at 1896 Rutherford Road, Carlsbad, California 92008, and our telephone number is (760) 931-9200.

Isis PharmaceuticalsTM is our trademark. Vitravene® is a registered trademark of Novartis AG. AffinitakTM is a trademark of Eli Lilly and Company. This prospectus also contains trademarks and servicemarks of other companies.

2

RISK FACTORS

Investing in our securities involves a high degree of risk. In addition to the other information in this prospectus, you should carefully consider the risks described below before purchasing our securities. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment.

We have incurred losses, and our business will suffer if we fail to achieve profitability in the future.

Because drug discovery and development require substantial lead-time and money prior to commercialization, our expenses have exceeded our revenue since we were founded in January 1989. As of September 30, 2005, we had accumulated losses of approximately \$762.9 million and a stockholders' equity of approximately \$4.0 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from interest income and research grants and the sale or licensing of patents. We currently have only one product, Vitravene, approved for commercial use. This product has limited sales potential. We expect to incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or services, or achieve or sustain future profitability.

If we or our partners fail to obtain regulatory approval for our products, we will not be able to sell them.

We and our partners must conduct time-consuming, extensive and costly clinical trials to show the safety and efficacy of each of our drug candidates before a drug candidate can be approved for sale. We must conduct these trials in compliance with United States Food and Drug Administration regulations and with comparable regulations in other countries. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of our drug candidates, it will not approve them or will require additional studies, which can be time consuming and

expensive and which will delay commercialization of a drug candidate. We and our partners may not be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our drug candidates. Failure to receive these approvals or delays in these approvals could prevent or delay commercial introduction of a product and, as a result, could negatively impact our ability to generate revenue from product sales. In addition, following approval of a drug candidate, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute products. If we fail to comply with these regulations, regulators could force us to withdraw a drug candidate from the market or impose other penalties or requirements that also could have a negative impact on our financial results.

We have only introduced one commercial product, Vitravene. We cannot guarantee that any of our other drug candidates will be safe and effective, will be approved for commercialization or that our partners or we can successfully commercialize these drug candidates.

If the results of clinical testing indicate that any of our drugs under development are not suitable for commercial use, or if additional testing is required to demonstrate suitability, we may need to abandon one or more of our drug development programs.

Drug discovery and development has inherent risks, including the risk that molecular targets prove not to be important in a particular disease; the risk that compounds that demonstrate attractive activity in preclinical studies do not demonstrate similar activity in human beings; the risk that a compound is not safe or effective for use in humans; and the risk that successful results in early human clinical trials may not be indicative of results in late-stage clinical trials. Antisense technology in particular is relatively new and unproven. We are applying most of our resources to create safe and effective drugs for human use. Any of the risks described above could prevent us from meeting this goal. In the past, we have invested in clinical studies of drug candidates that have not met the primary clinical end points in their initial Phase III studies.

In March 2003, we reported the results of a Phase III clinical trial of Affinitak in patients with late stage non-small cell lung cancer and in October 2004, we reported the results of a second similar Phase III clinical trial. In each case, Affinitak failed to demonstrate improved survival sufficient enough to support an NDA filing. In December 2004, we reported the results of our Phase III clinical trials of alicaforsen in patients with active Crohn's disease, in which alicaforsen did not demonstrate statistically significant induction of clinical remissions compared to placebo.

Similar results could occur with the trials for our other drugs. If any of our drugs in clinical studies do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for this and other drugs and our stock price could decline.

If the market does not accept our products, we are not likely to generate revenues or become profitable.

Our success will depend upon the medical community, patients and third-party payors accepting our products as medically useful, cost-effective and safe. We cannot guarantee that, if approved for commercialization, doctors will use our products to treat patients. We currently have one commercially available product, Vitravene, a treatment for cytomegalovirus, or CMV, retinitis in AIDS patients, which addresses a small market. Our partners and we may not successfully commercialize additional products.

The degree of market acceptance for any of our products depends upon a number of factors, including:

- The receipt and scope of regulatory approvals;
- The establishment and demonstration in the medical and patient community of the efficacy and safety of our drug candidates and their potential advantages over competing products;
- The cost and effectiveness of our drug candidates compared to other available therapies;
- The patient convenience of the dosing regimen for our drug candidates; and
- Reimbursement policies of government and third party payors.

Based on the profile of our drug candidates, physicians, patients, patient advocates, payors or the medical community in general may not accept and use any products that we may develop.

If any of our collaborative partners fail to fund our collaborative programs or develop or sell any of our products under development, or if we cannot obtain additional partners, we may have to delay or stop progress on our product development programs.

To date, corporate partnering has played a key role in our strategy to fund our development programs and to add key development resources. We plan to continue to rely on additional collaborative arrangements to develop and commercialize our products. However, we may not be able to negotiate additional attractive collaborative arrangements, and, even if negotiated, the collaborative arrangements may not be successful.

We have entered into collaborative arrangements with third parties to develop many of our product candidates. We enter into these collaborations in order to:

- Fund our research and development activities;
- Access manufacturing by third parties;
- Seek and obtain regulatory approvals;
- Conduct clinical trials; and
- Successfully commercialize existing and future product candidates.

If any of our partners fails to develop or sell any drug in which we have retained a financial interest, our business may suffer. These collaborations may not continue or result in commercialized drugs. Our collaborators can terminate their relationships with us under certain circumstances, some of which are outside of our control. For example, in November 2004 based on the outcome of both Phase III trials, Lilly discontinued its investment in Affinitak.

Other drug candidates in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics Limited, iCo Therapeutics, Inc., OncoGenex Technologies Inc. and Lilly. We have received significant financial support from United States Government-

funded grants and contracts for our Ibis division and the development of our TIGER system. The United States Government can unilaterally terminate these contracts and grants at its convenience at any time, even if we have fully performed our obligations. If any of

these pharmaceutical companies or government partners stopped funding and/or developing these products, our business could suffer and we may not have the resources available to develop these products on our own.

Certain of our partners are pursuing other technologies or developing other drug candidates either on their own or in collaboration with others, including our competitors, to develop treatments for the same diseases targeted by our own collaborative programs. Competition may negatively impact a partner's focus on and commitment to our drug candidate and, as a result, could delay or otherwise negatively affect the commercialization of a drug candidate.

In addition, the disappointing results of the two Affinitak trials, our Phase III clinical trials of alicaforsen in patients with active Crohn's disease or any future clinical trial failures could impair our ability to attract new collaborative partners. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drug candidates could suffer.

We may not successfully develop or derive revenues from our business based on our TIGER system to identify infectious organisms.

Our TIGER system is subject to the risks inherent in developing tools based on innovative technologies. Our product is at an early stage of development and requires additional research and development prior to marketing. If our potential customers fail to purchase our TIGER system due to competition or other factors, or if we fail to develop applications that lead to market acceptance, we could lose our investment in this technology and our TIGER business could fail to meet our business and financial objectives.

If we fail to obtain timely funding, we may need to curtail or abandon some of our programs.

All of our product candidates are still undergoing clinical trials or are in the early stages of research and development. All of our products under development will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and a commitment of significant additional resources prior to their commercialization. Based on our current operating plan with reasonable assumptions for new sources of revenue and cash, we believe our resources will be sufficient to meet our anticipated requirements at least through 2007. If we do not meet our goals to commercialize our products, or to license our drugs and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- the profile and launch timing of our drugs;
- continued scientific progress in our research, drug discovery and development programs;
- the size of our programs and progress with preclinical and clinical trials;
- the time and costs involved in obtaining regulatory approvals;
- competing technological and market developments, including the introduction by others of new therapies that address our markets;
- success in developing and commercializing a business based on our TIGER system to identify infectious organisms; and
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and their price, as well as the price of our other securities, may decline. If adequate funds are not available, we may have to cut back on one or more of our research, drug discovery or development programs. For example, in January 2005 we decided to terminate the development of two lower priority drugs, ISIS 14803 and ISIS 104838. Alternatively, we may obtain funds through arrangements with collaborative partners or others, which could require us to give up rights to certain of our technologies, product candidates or products.

If we cannot manufacture our products or contract with a third party to manufacture our products at costs that allow us to charge competitive prices to buyers, we will not be able to market products profitably.

If we successfully commercialize any of our drug candidates, we may be required to establish large-scale commercial manufacturing capabilities. In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. We have limited experience manufacturing pharmaceutical products of the chemical class represented by our drug candidates, called oligonucleotides, on a commercial scale for the systemic administration of a drug. There are a small number of suppliers for certain capital equipment and raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our product costs. We may not be able to manufacture at a cost or in quantities necessary to make commercially successful products.

Also, manufacturers, including us, must adhere to the FDA's current Good Manufacturing Practices regulations which the FDA enforces through its facilities inspection program. We and our contract manufacturers may not be able to comply or maintain compliance with Good Manufacturing Practices regulations. Non-compliance could significantly delay our receipt of marketing approval for potential products or result in FDA enforcement action after approval that could limit the commercial success of our potential product.

If we fail to compete effectively, our products will not contribute significant revenues.

Our competitors are engaged in all areas of drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. Other companies are engaged in developing antisense technology or unique methods of identifying infectious organisms. Our competitors may succeed in developing drug candidates or technologies that are more effective than any drug candidates or technologies that we are developing. These competitive developments could make our products obsolete or non-competitive.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical trials of new pharmaceutical products and in obtaining FDA

and other regulatory approvals of products for use in health care. Accordingly, our competitors may succeed in obtaining regulatory approval for products earlier than we do. We will also compete with respect to marketing and sales capabilities, areas in which we have limited or no experience.

If we cannot protect our patents or our proprietary rights, others may compete more directly against us.

Our success depends to a significant degree upon our ability to continue to develop and secure intellectual property rights to proprietary products and services. However, we may not receive issued patents on any of our pending patent applications in the United States or in other countries. In addition, the scope of any of our issued patents may not be sufficiently broad to provide us with a competitive advantage. Furthermore, our issued patents or patents licensed to us may be successfully challenged, invalidated or circumvented so that our patent rights would not create an effective competitive barrier or revenue source.

Intellectual property litigation could be expensive and prevent us from pursuing our programs.

It is possible that in the future we may have to defend our intellectual property rights. In the event of an intellectual property dispute, we may be forced to litigate to defend our rights or assert them against others. Disputes could involve arbitration, litigation or proceedings declared by the United States Patent and Trademark Office or the International Trade Commission or foreign patent authorities. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business.

If a third party claims that our products or technology infringe their patents or other intellectual property rights, we may have to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to such intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of patents or applications held by others that relate to our business. This is especially true since patent applications in the United States are filed confidentially. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain unresolved.

If we do not progress in our programs as anticipated, the price of our securities could decrease.

For planning purposes, we estimate the timing of a variety of clinical, regulatory and other milestones, like when a certain product candidate will enter the clinic, when we will complete a clinical trial, or when we will file an

application for marketing approval. We base our estimates on present facts and a variety of assumptions. Many of the underlying assumptions are outside of our control. If we do not achieve milestones when we expect to, investors could be disappointed and the price of our securities would likely decrease.

The loss of key personnel, or the inability to attract and retain highly skilled personnel, could make it more difficult to run our business and reduce our likelihood of success.

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our executive officers. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. Failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel.

We depend on third parties in the conduct of our clinical trials for our product candidates and any failure of those parties to fulfill their obligations could adversely affect our development and commercialization plans.

We depend on independent clinical investigators, contract research organizations and other third party service providers in the conduct of our clinical trials for our product candidates and expect to continue to do so in the future. We rely heavily on these parties for successful execution of our clinical trials, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Third parties may not complete activities on schedule, or may not conduct our clinical trials in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations could delay or prevent the development, approval and commercialization of our product candidates.

If the price of our securities continues to be highly volatile, this could make it harder for you to liquidate your investment and could increase your risk of suffering a loss.

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding September 30, 2005, the market price of our common stock has ranged from \$2.76 to \$6.63 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial results, technological innovations or new drug products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

Provisions in our certificate of incorporation, other agreements and Delaware law may prevent stockholders from receiving a premium for their shares.

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66% of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15% or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. We also have implemented a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. These provisions, as well as Delaware law and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and

may limit the ability of our stockholders to approve transactions that they think may be in their best interests. In addition, our board of directors has the authority to fix the rights and preferences of and issue shares of preferred stock, which

may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

If registration rights that we have previously granted are exercised, then the price of our securities may be negatively affected.

We have granted registration rights to Eli Lilly and Company which cover approximately 2.5 million shares of our common stock which we issued to Lilly upon the conversion of outstanding convertible securities. In addition, we recently registered for resale 12,000,000 shares of our common stock and 2,999,998 shares of our common stock issuable upon the exercise of warrants, which we issued as part of our August 2005 private placement. The addition of these shares into the market, may have an adverse effect on the price of our securities.

Our business is subject to changing regulations for corporate governance and public disclosure that has increased both our costs and the risk of noncompliance.

Each year we are required to evaluate our internal controls systems in order to allow management to report on, and our Independent Registered Public Accounting Firm to attest to, our internal controls as required by Section 404 of the Sarbanes-Oxley Act. As a result, we will incur additional expenses and will suffer a diversion of management's time. In addition, if we cannot continue to comply with the requirements of Section 404 in a timely manner, we might be subject to sanctions or investigation by regulatory authorities, such as the Securities and Exchange Commission, the Public Company Accounting Oversight Board, or PCAOB, or the NASDAQ Stock Exchange. Any such action could adversely affect our financial results and the market price of our common stock.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated herein by reference contain forward-looking statements regarding our business, the financial position of Isis Pharmaceuticals, Inc. and the therapeutic and commercial potential of our technologies and products in development. Any statement describing our 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' clinical 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, in developing and commercializing technology and systems used to identify infectious agents, and in the endeavor of building a business around such products and services. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in the section entitled "Risk Factors" in this prospectus. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements.

USE OF PROCEEDS

Unless otherwise provided in the applicable prospectus supplement, we intend to use the net proceeds from the sale of our common stock under this prospectus for research, drug discovery and product development activities, including preclinical, clinical studies and the continued development of our TIGER system, capital expenditures and other general corporate purposes. We will set forth in the prospectus supplement our intended use for the net proceeds received from the sale of our common stock. Pending the application of the net proceeds, we intend to invest the net proceeds in investment-grade, interest-bearing securities.

PLAN OF DISTRIBUTION

We may sell our common stock through underwriters or dealers, through agents, or directly to one or more purchasers. The accompanying prospectus supplement will describe the terms of the offering of our common stock, including:

- the number of shares of common stock we are offering;
- the name or names of any underwriters;
- any securities exchange or market on which the common stock may be listed;
- the purchase price of our common stock being offered and the proceeds we will receive from the sale;
- any over-allotment options pursuant to which underwriters may purchase additional shares of common stock from us;
- any underwriting discounts or agency fees and other items constituting underwriters' or agents' compensation; and
- any discounts or concessions allowed or reallocated or paid to dealers.

If underwriters are used in the sale, they will acquire the common stock for their own account and may resell the common stock from time to time in one or more transactions at a fixed public offering price or at varying prices determined at the time of the sale. The obligations of the underwriters to purchase the common stock will be subject to the conditions set forth in the applicable underwriting agreement. We may offer the common stock to the public through underwriting syndicates represented by managing underwriters or by underwriters without a syndicate. Subject to certain conditions, the underwriters will be obligated to purchase all the shares of common stock offered by the prospectus supplement. We may change from time to time the public offering price and any discounts or concessions allowed or reallocated or paid to dealers.

We may sell our common stock directly or through agents we designate from time to time. We will name any agent involved in the offering and sale of our common stock, and we will describe any commissions we will pay the agent in the prospectus supplement. Unless the prospectus supplement states

otherwise, our agent will act on a best-efforts basis for the period of its appointment.

We may provide underwriters and agents with indemnification against civil liabilities related to this offering, including liabilities under the Securities Act, or contribution with respect to payments that the underwriters or agents may make with respect to these liabilities. Underwriters and agents may engage in transactions with, or perform services for, us in the ordinary course of business. We will describe such relationships in the prospectus supplement naming the underwriter and the nature of any such relationship.

Rules of the Securities and Exchange Commission may limit the ability of any underwriters to bid for or purchase shares of common stock before the distribution of the shares of common stock is completed. However, underwriters may engage in the following activities in accordance with the rules:

- *Stabilizing transactions* — Underwriters may make bids or purchases for the purpose of pegging, fixing or maintaining the price of the shares, so long as stabilizing bids do not exceed a specified maximum.
- *Over-allotments and syndicate covering transactions* — Underwriters may sell more shares of our common stock than the number of shares that they have committed to purchase in any underwritten offering. This over-allotment creates a short position for the underwriters. This short position may involve either

9

“covered” short sales or “naked” short sales. Covered short sales are short sales made in an amount not greater than the underwriters’ over-allotment option to purchase additional shares in any underwritten offering. The underwriters may close out any covered short position either by exercising their over-allotment option or by purchasing shares in the open market. To determine how they will close the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market, as compared to the price at which they may purchase shares through the over-allotment option. Naked short sales are short sales in excess of the over-allotment option. The underwriters must close out any naked position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that, in the open market after pricing, there may be downward pressure on the price of the shares that could adversely affect investors who purchase shares in the offering.

- *Penalty bids* — If underwriters purchase shares in the open market in a stabilizing transaction or syndicate covering transaction, they may reclaim a selling concession from other underwriters and selling group members who sold those shares as part of the offering.

Similar to other purchase transactions, an underwriter’s purchases to cover the syndicate short sales or to stabilize the market price of our common stock may have the effect of raising or maintaining the market price of our common stock or preventing or mitigating a decline in the market price of our common stock. As a result, the price of the shares of our common stock may be higher than the price that might otherwise exist in the open market. The imposition of a penalty bid might also have an effect on the price of shares if it discourages resales of the shares.

If commenced, the underwriters may discontinue any of these activities at any time.

Our common stock is quoted on the Nasdaq National Market. One or more underwriters may make a market in our common stock, but the underwriters will not be obligated to do so and may discontinue market making at any time without notice. We cannot give any assurance as to liquidity of the trading market for our common stock.

Any underwriters who are qualified market makers on the Nasdaq National Market may engage in passive market making transactions in the common stock on the Nasdaq National Market in accordance with Rule 103 of Regulation M, during the business day prior to the pricing of the offering, before the commencement of offers or sales of the common stock. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security; if all independent bids are lowered below the passive market maker’s bid, however, the passive market maker’s bid must then be lowered when certain purchase limits are exceeded.

In compliance with guidelines of the National Association of Securities Dealers, or NASD, the maximum consideration or discount to be received by any NASD member or independent broker dealer may not exceed 8% of the aggregate amount of the securities offered pursuant to this prospectus and any applicable prospectus supplement.

DESCRIPTION OF CAPITAL STOCK

Our authorized capital stock consists of

- Series B Convertible Exchangeable 5% Preferred Stock, 4,605 shares of which were authorized and none of which was issued and outstanding at September 30, 2005;
- Series C Junior Participating Preferred Stock, 1,000,000 shares of which were authorized and none of which was issued and outstanding at September 30, 2005; and
- Common stock, 100,000,000 shares of which were authorized and 72,201,505 shares of which were issued and outstanding as of September 30, 2005.

The description of our common stock is incorporated by reference to filings with the SEC. See “Incorporation by Reference.”

10

DIVIDEND POLICY

We have never declared or paid any cash dividends on our capital stock. We intend to retain any future earnings to support operations and to finance the growth and development of our business and we do not anticipate paying cash dividends for the foreseeable future.

LEGAL MATTERS

The validity of the issuance of the common stock offered hereby will be passed upon for us by Grantland E. Bryce our Vice President, Legal and General Counsel.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2004, and management's assessment of the effectiveness of our internal control over financial reporting as of December 31, 2004, as set forth in their reports, which are incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements and management's assessment are incorporated by reference in reliance on Ernst & Young LLP's reports, given on their authority as experts in accounting and auditing.

11

WHERE YOU CAN FIND MORE INFORMATION

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission. Certain information in the registration statement has been omitted from this prospectus in accordance with the rules of the SEC. We are a public company and file proxy statements and annual, quarterly and special reports and other information with the SEC. You can inspect and copy the registration statement as well as the reports, proxy statements and other information we have filed with the SEC at the public reference room maintained by the SEC at 100 F Street, N.E., Room 1580, Washington D.C. 20549. You can call the SEC at 1-800-732-0330 for further information about the public reference rooms. We are also required to file electronic versions of these documents with the SEC, which may be accessed from the SEC's World Wide Web site at <http://www.sec.gov>.

We make available, free of charge, on our web site, www.isispharm.com, our reports on 10-K, 10-Q, 8-K and amendments thereto, as soon as reasonably practical after we file such materials with the Securities and Exchange Commission. Any information that is included on or linked to our Internet site is not a part of this prospectus or any related registration statement.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

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

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

- our Annual Report on Form 10-K for the year ended December 31, 2004;
- our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2005, June 30, 2005 and September 30, 2005;
- our Current Reports on Form 8-K, filed with the SEC on:
 - April 8, 2005,
 - May 5, 2005,
 - May 24, 2005,
 - May 26, 2005,
 - June 29, 2005,
 - July 26, 2005,
 - July 27, 2005,
 - July 29, 2005,
 - August 5, 2005;
 - August 25, 2005; and
 - December 15, 2005.
- the description of our common stock in our Registration Statement on Form 8-A filed with the SEC on April 12, 1991, as updated by our Certificate of Amendment of our Restated Certificate of Incorporation filed with our Quarterly Report on Form 10-Q for the period ended June 30, 2001.

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

12

You should rely only on the information contained in this prospectus. We have not authorized anyone to provide you with information different from that contained in this prospectus or any prospectus supplement. This prospectus is not an offer of these securities in any jurisdiction where an offer and sale is not permitted. The information contained in this prospectus is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or any sale of our common stock.

\$200,000,000
Common Stock

ISIS PHARMACEUTICALS, INC.

Prospectus

December 22, 2005

Part II

INFORMATION NOT REQUIRED IN PROSPECTUS

Item 14. Other Expenses of Issuance and Distribution

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

SEC registration fee	\$	21,400
Legal fees and expenses	\$	10,000
Accounting fees and expenses	\$	10,000
Miscellaneous	\$	3,600
Total	\$	45,000

Item 15. Indemnification of Officers and Directors

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

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

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

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

II-1

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

Item 16. Exhibits

<u>Exhibit Number</u>	<u>Description of Document</u>
1.1	Form of Underwriting Agreement (To be filed as an Exhibit to a Current Report on Form 8-K and incorporated herein by reference).
4.1	— Amended and Restated Certificate of Incorporation filed June 19, 1991. (1)
4.2	— Certificate of Amendment to Restated Certificate of Incorporation filed April 9, 2001. (2)
4.3	— Bylaws. (2)
4.6	— Certificate of Designation of the Series C Junior Participating Preferred Stock. (3)
4.7	— Specimen Common Stock Certificate. (1)
4.10	— Form of Right Certificate. (3)
5.1	— Opinion of Grantland E. Bryce
23.1	— Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm. Reference is made to page II-3
23.2	— Consent of Grantland E. Bryce. Reference is made to Exhibit 5.1
24.1	— Power of Attorney. Reference is made to page II-4

- (1) Filed as an exhibit to the Registrant's Registration Statement on Form S-1 (No. 33-39640) or amendments thereto and incorporated herein by reference.
- (2) Filed as an exhibit to the Registrant's report on Form 10-Q/A for the quarter ended June 30, 2001 and incorporated herein by reference.
- (3) Filed as an exhibit to Registrant's Report on Form 8-K dated December 8, 2000 and incorporated herein by reference.

Item 17. Undertakings

(a) The undersigned registrant hereby undertakes:

- (1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement
 - (i) to include any prospectus required by Section 10(a)(3) of the Securities Act of 1933;
 - (ii) to reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20 percent change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective registration statement;
 - (iii) to include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement;

provided, however, that the undertakings set forth in paragraphs (1)(i), (1)(ii) and (1)(iii) above do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the Commission by the registrant pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 that are incorporated by reference in the registration statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is a part of the registration statement.

II-2

- (2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.
- (3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.
- (4) That, for the purpose of determining liability under the Securities Act of 1933 to any purchaser:

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

(B) Each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5), or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii), or (x) for the purpose of providing the information required by section 10(a) of the Securities Act of 1933 shall be deemed to be part of and included in the registration statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in the prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the registration statement relating to the securities in the registration statement to which that prospectus relates, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof. Provided, however, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date.

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

- (i) Any preliminary prospectus or prospectus of the undersigned registrant relating to the offering required to be filed pursuant to Rule 424;
- (ii) Any free writing prospectus relating to the offering prepared by or on behalf of the undersigned registrant or used or referred to by the undersigned registrant;
- (iii) The portion of any other free writing prospectus relating to the offering containing material information about the undersigned registrant or its securities provided by or on behalf of the undersigned registrant; and
- (iv) Any other communication that is an offer in the offering made by the undersigned registrant to the purchaser.

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

Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers, and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer, or controlling person of the registrant in the successful defense of any action, suit or proceeding)

II-3

is asserted by such director, officer, or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

The undersigned registrant hereby undertakes that:

- (1) For purposes of determining any liability under the Securities Act of 1933, the information omitted from the form of prospectus filed as part of this registration statement in reliance upon Rule 430A and contained in a form of prospectus filed by the registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act shall be deemed to be part of this registration statement as of the time it was declared effective.
- (2) For purposes of determining any liability under the Securities Act of 1933, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

The undersigned registrant hereby undertakes to file an application for the purpose of determining the eligibility of the trustee to act under subsection (a) of Section 310 of the Trust Indenture Act in accordance with the rules and regulations prescribed by the Securities and Exchange Commission under Section 305(b)(2) of the Trust Indenture Act.

II-4

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this Registration Statement to be signed on its behalf by the undersigned thereunto duly authorized, in the city of Carlsbad, County of San Diego, State of California, on the 20th day of December, 2005.

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints STANLEY T. CROOKE and B. LYNNE PARSHALL, and each of them, as his or her true and lawful attorney-in-fact and agents, with full power of substitution and resubstitution, for the undersigned and in his or her name, place and stead, in any and all capacities, to sign any or all amendments (including post-effective amendments) to this Registration Statement and to sign any Registration Statement that is to be effective on filing pursuant to Rule 462(b) promulgated under the Securities Act of 1933, and all post-effective amendments thereto, and to file the same, with all exhibits thereto, and all documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power of authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, each acting alone, or his or her substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

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

<u>Signatures</u>	<u>Title</u>	<u>Date</u>
<u>/s/ Stanley T. Croke</u> Stanley T. Croke	Chairman of the Board and Chief Executive Officer (Principal executive officer)	December 20, 2005
<u>/s/ B. Lynne Parshall</u> B. Lynne Parshall	Executive Vice President, Chief Financial Officer and Director (Principal financial and accounting officer)	December 20, 2005
<u>/s/ Spencer R. Berthelsen</u> Spencer R. Berthelsen	Director	December 20, 2005
<u>/s/ Richard D. DiMarchi</u> Richard D. DiMarchi	Director	December 20, 2005
<u>/s/ Christopher F.O. Gabrieli</u> Christopher F.O. Gabrieli	Director	December 20, 2005
<u>/s/ Frederick T. Muto</u> Frederick T. Muto	Director	December 20, 2005
<u>/s/ John C. Reed</u> John C. Reed	Director	December 20, 2005
<u>/s/ Joseph H. Wender</u> Joseph H. Wender	Director	December 20, 2005

II-5

EXHIBIT INDEX

<u>Exhibit Number</u>	<u>Description of Document</u>
1.1	Form of Underwriting Agreement (To be filed as an Exhibit to a Current Report on Form 8-K and incorporated herein by reference).
4.1	— Amended and Restated Certificate of Incorporation filed June 19, 1991. (1)
4.2	— Certificate of Amendment to Restated Certificate of Incorporation filed April 9, 2001. (2)
4.3	— Bylaws. (2)
4.6	— Certificate of Designation of the Series C Junior Participating Preferred Stock. (3)
4.7	— Specimen Common Stock Certificate. (1)
4.10	— Form of Right Certificate. (3)
5.1	— Opinion of Grantland E. Bryce
23.1	— Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm. Reference is made to page II-3
23.2	— Consent of Grantland E. Bryce. Reference is made to Exhibit 5.1
24.1	— Power of Attorney. Reference is made to page II-4

- (1) Filed as an exhibit to the Registrant's Registration Statement on Form S-1 (No. 33-39640) or amendments thereto and incorporated herein by reference.
- (2) Filed as an exhibit to the Registrant's report on Form 10-Q/A for the quarter ended June 30, 2001 and incorporated herein by reference.
- (3) Filed as an exhibit to Registrant's Report on Form 8-K dated December 8, 2000 and incorporated herein by reference.

OPINION OF GRANTLAND E. BRYCE

December 20, 2005

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

Ladies and Gentlemen:

This opinion is furnished to you in connection with the Registration Statement on Form S-3 (the "Registration Statement") to be filed with the Securities and Exchange Commission (the "Commission") under the Securities Act of 1933, as amended (the "Securities Act"), for the registration of common stock, \$.001 par value per share (the "Common Stock"), of Isis Pharmaceuticals, Inc. (the "Company"), which may be issued from time to time on a delayed or continuous basis pursuant to Rule 415 under the Securities Act at an aggregate initial offering price not to exceed \$200,000,000 (the "Shares").

I am acting as counsel for the Company in connection with the registration for sale by the Company of the Shares. I have examined a signed copy of the Registration Statement to be filed with the Commission. I have also examined and relied upon the minutes of meetings of the Board of Directors of the Company, as provided to me by the Company, the Certificate of Incorporation and By-Laws of the Company, each as amended to date (collectively, the "Charter Documents"), and such other documents as I have deemed necessary for purposes of rendering the opinions hereinafter set forth.

In my examination of the foregoing documents, I have assumed the genuineness of all signatures, the authenticity of all documents submitted to me as originals, the conformity to original documents of all documents submitted to me as copies, the authenticity of the originals of such latter documents and the legal competence of all signatories to such documents.

I assume that appropriate action will be taken, prior to the offer and sale of the Shares, to register and qualify the Shares for sale under all applicable state securities or "blue sky" laws.

I express no opinion herein as to the laws of any state or jurisdiction other than the state laws of the Commonwealth of Massachusetts, the General Corporation Law of the State of Delaware and the federal laws of the United States of America.

Based upon and subject to the foregoing, I am of the opinion that the Shares, when (i) specifically authorized for issuance by the Company's Board of Directors or an authorized committee thereof (the "Authorizing Resolutions"), (ii) the Registration Statement, as finally amended, has become effective under the Securities Act, (iii) an appropriate prospectus supplement with respect to the Shares has been prepared, filed and delivered in compliance with the Securities Act and the applicable rules promulgated thereunder, (iv) the terms of the sale of the Shares have been duly established in conformity with the Charter Documents and do not violate any applicable law or result in a default under or breach of any agreement or instrument binding on the Company and comply with any requirement or restriction imposed by any court or governmental body having jurisdiction over the Company, (v) the Shares have been issued and sold as contemplated by the Registration Statement, and (vi) the Company has received the consideration provided for in the Authorizing Resolutions and such consideration is not less than the par value of the Shares, will be validly issued, fully paid and nonassessable.

It is understood that this opinion is to be used only in connection with the offer and sale of the Shares while the Registration Statement is in effect.

Please note that I am opining only as to the matters expressly set forth herein, and no opinion should be inferred as to any other matters. This opinion is based upon currently existing statutes, rules, regulations and judicial decisions, and we disclaim any obligation to advise you of any change in any of these sources of law or subsequent legal or factual developments which might affect any matters or opinions set forth herein.

I consent to the reference to myself under the caption "Legal Matters" in the Prospectus included in the Registration Statement and to the filing of this opinion as an exhibit to the Registration Statement.

Sincerely,

/s/ Grantland E. Bryce

Grantland E. Bryce
Vice President, Legal and
General Counsel

CONSENT OF ERNST & YOUNG LLP, INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the reference to our firm under the caption "Experts" in the Registration Statement (Form S-3) to be filed on December 22, 2005, and related Prospectus of Isis Pharmaceuticals, Inc. for the registration of up to \$200,000,000 worth of its common stock and to the incorporation by reference therein of our reports dated March 3, 2005, with respect to the consolidated financial statements of Isis Pharmaceuticals, Inc., Isis Pharmaceuticals, Inc. management's assessment of the effectiveness of internal control over financial reporting, and the effectiveness of internal control over financial reporting of Isis Pharmaceuticals, Inc. included in its Annual Report (Form 10-K) for the year ended December 31, 2004, filed with the Securities and Exchange Commission.

/s/ ERNST & YOUNG LLP

San Diego, California

December 20, 2005
