PROSPECTUS

14,999,998 Shares

ISIS PHARMACEUTICALS, INC.

Common Stock

We are registering our common stock for resale by the selling stockholders identified in this prospectus. We are not selling any shares of our common stock under this prospectus and will not receive any of the proceeds from the sale of shares by the selling stockholders. Specifically, this prospectus relates to the resale of:

- 12,000,000 shares of our common stock that were issued to the selling stockholders in connection with a private placement in August, 2005; and
- 2,999,998 shares of our common stock issuable upon the exercise of warrants held by the selling stockholders.

For a description of the plan of distribution of the resale shares, see page 12 of this prospectus.

Our common stock is currently traded on the Nasdaq National Market under the symbol "ISIS." On October 31, 2005, the last reported sales price for our common stock was $4.34 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.

The date of this Prospectus is November 1, 2005

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SUMMARY

This summary highlights selected information appearing elsewhere in this prospectus and may not contain all of the information that is important to you. This prospectus includes information about the securities we are offering, as well as information regarding our business and detailed financial data. 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.

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, ocular and cardiovascular diseases, and cancer. We are expanding the therapeutic opportunities for antisense drugs by developing a variety of formulations to enhance patient convenience and compliance. 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 system with the identification of a variety of bacteria and viruses in both environmental and human clinical samples. During 2004, we advanced the development of our TIGER system to include application development for epidemiological surveillance and biological products screening. These applications represent the first of many we plan to develop to enhance the TIGER system's 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 Pharmaceuticals™ is our trademark. Vitravene® is a registered trademark of Novartis AG. Affinitac™ is a trademark of Eli Lilly and Company. This prospectus also contains trademarks and servicemarks of other companies.

The Offering

Common stock covered hereby	• 12,000,000 shares of our common stock held by the selling stockholders; and • 2,999,998 shares of our common stock issuable upon the exercise of warrants held by the selling stockholders.
Use of proceeds	We will not receive any proceeds from the sale or other disposition of the shares of our common stock by the selling stockholders. However, upon any cash exercise of the warrants described herein, the selling stockholders will pay us the exercise price of the warrants, which we will use for working capital.
Nasdaq National Market symbol	ISIS

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 June 30, 2005, we had accumulated losses of approximately $747.8 million and a stockholders' deficit of approximately $124.2 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, 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 through at least mid 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 June 30, 2005, the market price of our common stock has ranged from $2.76 to $6.67 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 we issued to Lilly upon the conversion of outstanding convertible securities. 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 Registered Independent 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

We will not receive any proceeds from the sale or other disposition of the shares of our common stock covered hereby, or interests therein, by the selling stockholders.

The selling stockholders will pay any underwriting discounts and commissions and expenses incurred by the selling stockholders for brokerage, accounting, tax or legal services or any other expenses incurred by the selling stockholders in disposing of the shares. We will bear all other costs, fees and expenses incurred in effecting the registration of the shares covered by this prospectus, including, without limitation, all registration and filing fees, Nasdaq National Market listing fees and fees and expenses of our counsel and our accountants.

A portion of the shares covered by this prospectus are issuable upon exercise of warrants to purchase common stock. Upon any cash exercise of the warrants, the selling stockholders will pay us the exercise price of the warrants. The cash exercise price of the warrants is $5.2395 per share. We will use the cash we receive upon the exercise of the warrants for working capital.

SELLING STOCKHOLDERS

The shares of common stock covered hereby consist of:

- 12,000,000 shares of our common stock that we issued to the selling stockholders in a private placement in August 2005; and
- 2,999,998 shares of our common stock issuable upon exercise of warrants to purchase common stock. We issued the warrants to the selling stockholders in connection with their purchase of shares of our common stock in the private placement.

In connection with the registration rights we granted to the selling stockholders, we filed with the Securities and Exchange Commission a registration statement on Form S-3, of which this prospectus forms a part, with respect to the resale or other disposition of the shares of common stock offered

by this prospectus or interests therein from time to time on The Nasdaq National Market, in privately negotiated transactions or otherwise. We have also agreed to prepare and file amendments and supplements to the registration statement to the extent necessary to keep the registration statement effective for the period of time required under our agreements with the selling stockholders. The warrants held by the selling stockholders are exercisable at any time in whole or in part beginning February 19, 2006 and ending August 23, 2010.

The actual number of shares of common stock covered by this prospectus, and included in the registration statement of which this prospectus forms a part, includes additional shares of common stock that may be issued with respect to the shares of common stock or the warrants described herein as a result of stock splits, stock dividends, reclassifications, recapitalizations, combinations or similar events.

Beneficial ownership is determined in accordance with the rules of the Securities and Exchange Commission, or SEC and is based upon information provided by each respective selling stockholder, Schedules 13D and 13G and other public documents filed with the SEC. Although the warrants held by the selling stockholders are not exercisable until February 19, 2006, the shares of common stock issuable upon exercise of the warrants held by the selling stockholders are included in the table below since those shares of common stock are being offered in this prospectus. The percentages of shares owned after the offering are based on 72,202,052 shares of our common stock outstanding as of August 25, 2005, which includes the outstanding shares of common stock offered by this prospectus but excludes all warrant shares since the related warrants are not currently exercisable and are not exercisable within 60 days from the date hereof.

Unless otherwise indicated below, to our knowledge, all persons named in this table have sole voting and investment power with respect to their shares of common stock, except to the extent authority is shared by spouses under applicable law. The inclusion of any shares in this table does not constitute an admission of beneficial ownership for the person named below.

We do not know when or in what amounts a selling stockholder may offer shares for sale or other disposition. The selling stockholders might not sell or dispose of any or all of the shares offered by this prospectus. Because the selling stockholders may offer all or some of the shares pursuant to this offering, and because there are currently no agreements, arrangements or understandings with respect to the sale of any of the shares, we cannot estimate the number of the shares that will be held by the selling stockholders after completion of the offering. However, for purposes of this table, we have assumed that, after completion of the offering, none of the shares covered by this prospectus will be held by the selling stockholders.

The following table sets forth, to our knowledge, information about the selling stockholders as of August 25, 2005.

	Shares of Common Stock Beneficially Owned Prior to Offering				
Selling stockholders (1)(2)	Shares of Common Stock Held	Shares of Common Stock Issuable Upon Exercise of Warrants	Total Number of Shares Beneficially Owned	Shares of Common Stock Offered	Percentage Of Common Stock Outstanding After The Offering
Federated Kaufmann Fund, a portfolio of Federated Equity Funds (3)	8,743,160	1,176,470	8,743,160	5,882,352	5.59%
Farallon Capital Partners, L.P.(4)	934,118	233,529	934,118	1,167,647	—
Farallon Capital Institutional Partners, L.P.(4)	904,927	226,231	904,927	1,131,158	—
Farallon Capital Institutional Partners II, L.P. (4)	204,338	51,085	204,338	255,423	—
Farallon Capital Institutional Partners III, L.P. (4)	204,338	51,085	204,338	255,423	—
Farallon Special Situation Partners II, L.P. (4)	671,397	167,849	671,397	839,246	—
Caduceus Capital Master Fund Limited	460,000	115,000	460,000	575,000	—
Caduceus Capital II, LP	232,000	58,000	232,000	290,000	—
UBS Eucalyptus Fund LLC	380,000	95,000	380,000	475,000	—
PW Eucalyptus Fund Ltd	38,000	9,500	38,000	47,500	—
HFR SHC Aggressive Master Trust	90,000	22,500	90,000	112,500	—
Perceptive Life Sciences Master Fund, LTD .	1,000,000	250,000	1,000,000	1,250,000	—
Special Situations Private Equity Fund, L.P. (5)	380,000	95,000	380,000	475,000	—
Special Situations Life Sciences Fund, L.P. (5)	120,000	30,000	120,000	150,000	—
Special Situations Fund III, L.P. (5)	500,000	125,000	500,000	625,000	—
WHI Growth Fund, L.P.	2,528,000	187,500	2,528,000	937,500	2.46%
WPG-Farber Fund, L.P.	84,000	21,000	84,000	105,000	—
WPG-Farber QP Fund, L.P.	32,550	8,137	32,550	40,687	—
WPG-Farber Institutional Fund, L.P.	28,050	7,012	28,050	35,062	—
WPG-Farber Overseas, L.P.	5,400	1,350	5,400	6,750	—
Kamunting Street Master Fund, Ltd.	150,000	37,500	150,000	187,500	—
D3 LifeScience Ltd.	100,000	25,000	100,000	125,000	—
Bash Enterprises Limited Partnership	5,000	1,250	5,000	6,250	—
Jocelyn Bash Roth IRA	10,000	1,250	10,000	6,250	*
J. Moffat and P. Moffat Trust	4,500	750	4,500	3,750	*
R. Charles Dombrow IRA	10,000	1,750	10,000	8,750	*
David Kersten IRA	7,000	1,250	7,000	6,250	*

* Less than one percent

(1) The term “selling stockholders” includes donees, pledgees, transferees or other successors-in-interest selling shares received after the date of this prospectus from a selling stockholder as a gift, pledge, partnership distribution or other non-sale related transfer.

(2) For those selling stockholders which may be considered affiliates of broker dealers, each selling stockholder has represented and warranted that it has purchased in the ordinary course of business and that, at the time of the purchase, it had no agreements or understandings to distribute the securities.

(3) Includes 31,300 shares held by the Federated Kaufmann Fund II and 5,978 shares held by the Federated Mini-Cap Index Fund.

(4) As the general partner of each of the noted Farallon partnerships, Farallon Partners, L.L.C. may, for purposes of Rule 13d-3 under the Securities Exchange Act of 1934, as amended (the "Exchange Act"), be deemed to own beneficially the shares held by such Farallon partnerships. As the managing members of Farallon Partners, L.L.C., each of Chun R. Ding, Joseph F. Downes, William F. Duhamel, Charles E. Ellwein, Richard B. Fried, Monica R. Landry, William F. Mellin, Stephen L. Millham, Rajiv A. Patel, Derek C. Schrier, Thomas F. Steyer and Mark C. Wehrly may each, for purposes of Rule 13d-3 under the Exchange Act, be deemed to own beneficially the shares held by such Farallon partnerships. Each of Farallon Partners, L.L.C. and each of its managing members disclaims any beneficial ownership of such shares. All of the above-mentioned entities and persons disclaim group attribution.

(5) MGP Advisors Limited ("MGP") is the general partner of Special Situations Fund III, L.P. AWM Investment Company, Inc. ("AWM") is the general partner of MGP. MG Advisers, L.L.C. ("MG") is the general partner of and investment adviser to the Special Situations Private Equity Fund, L.P. LS Advisers, LLC ("LS") is the general partner and investment adviser to the Special Situations Life Sciences Fund, L.P. Austin W. Marxe and David M. Greenhouse are the principal owners of MGP, AWM, SSTA, MG and LS. Through their control of MGP, AWM, SSTA, MG and LS, Messrs. Marxe and Greenhouse share voting and investment control over the portfolio securities of each of the funds listed above.

Relationship with Selling Stockholders

To our knowledge, no selling stockholder has held any position or office or otherwise had a material relationship with us within the past three years.

Federated Kaufman Fund, a portfolio of Federated Equity Funds, which, together with its affiliates, held more than 5% of our 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

PLAN OF DISTRIBUTION

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.

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 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.

We will pay all costs, expenses and fees associated with the registration of the resale shares, estimated to be $25,000.

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 were issued and outstanding at August 25, 2005;
- Series C Junior Participating Preferred Stock, 1,000,000 shares of which were authorized and none of which was issued and outstanding at August 25, 2005; and
- Common stock, 100,000,000 shares of which were authorized and 72,202,052 shares of which were outstanding as of August 25, 2005.

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

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.

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 at1-800-732-0330 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.

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 and June 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; and
    - August 25, 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.

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.

14,999,998 Shares
Common Stock

ISIS PHARMACEUTICALS, INC.

Prospectus

November 1, 2005
