Filed Pursuant to Rule 424(b)(2)
Registration No. 333-130639

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 May 24, 2006, the last reported sales price for our common stock was $6.85 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 May 30, 2006

TABLE OF CONTENTS

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 15 antisense products in preclinical and clinical development, most of which are in Phase 1 or Phase 2 human clinical trials. Our internal drug development programs are aimed at treating cardiovascular, metabolic and inflammatory diseases. Our partners are focused in disease areas such as inflammatory, ocular, viral and neurodegenerative diseases, and cancer. We are expanding the therapeutic opportunities for antisense drugs by developing a variety of formulations to enhance patient convenience and compliance, such as oral and inhaled delivery, as well as infrequent dose administration. 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 first generation drugs. Specifically, second generation drugs offer the potential for improved safety and increased potency. In addition, because second generation drugs have a longer half-life, they have the potential to produce long-duration of therapeutic response and to support more convenient, less frequent dosing.

In our Ibis division, we have developed a revolutionary biosensor system, utilizing a U.S. government funded technology called T.I.G.E.R., or Triangulation Identification for Genetic Evaluation of Risk, that can, with a single test, simultaneously identify from a sample a broad range of infectious organisms without needing to know beforehand what might be present in the sample. During 2005 and the first quarter of 2006, our Ibis scientists advanced application development through contracts with our government partners in the areas of biowarfare defense, epidemiological surveillance, biological products screening and microbial forensics. This work has added value to us in that we can also apply much of this application development to non-government commercial opportunities. Further, this shift from basic instrument and system development to application development under our government contracts reflects the progression from technology development to commercial viability.

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. Affinitak™ is a trademark of Eli Lilly and Company. This prospectus also contains trademarks and servicemarks of other companies.

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.

Risks Associated with our Businesses as a Whole

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

Because product 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 March 31, 2006, we had accumulated losses of approximately $788.3 million and stockholders' deficit of approximately $8.2 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 fail to obtain timely funding, we may need to curtail or abandon some of our programs.

All of our product candidates are 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 reasonable assumptions for new sources of revenue and cash, we believe we have sufficient resources to meet our anticipated requirements through at least the end of 2008. 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:

- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements;
- 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 Ibis biosensor system to identify infectious organisms; and
- the profile and launch timing of our drugs.

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. In addition, if our stockholders do not approve an increase in our authorized capital stock, it may limit our ability to raise funds. 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, or not available on acceptable terms, 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 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 products.

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 3 trials, Lilly discontinued its investment in Affinitak.

Other drugs in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics Limited, iCo Therapeutics, Inc., ImQuest Pharmaceuticals, 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 Ibis biosensor 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 drugs 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 and, as a result, could delay or otherwise negatively affect the commercialization of our drug.

In addition, the disappointing results of the two Affinitak trials, our Phase 3 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 drugs could suffer.

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 needed 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.

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 March 31, 2006, the market price of our common stock ranged from $2.76 to $9.34 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 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.

If a natural or man-made disaster strikes our research and development facilities, it could delay our progress developing and commercializing our drugs or our Ibis biosensor system.

We are developing our Ibis biosensor system in our facility located in Carlsbad, California. Additionally, we manufacture our research and clinical supplies in a separate manufacturing facility located in Carlsbad, California. The facilities and the equipment we use to develop the Ibis biosensor system and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Either of our facilities may be harmed by natural or man-made disasters, including, without limitation, earthquakes, floods and fires, and in the event they are affected by a disaster, our development and commercialization efforts would be delayed. Although we possess insurance for damage to our property and the disruption of our business from casualties, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all.

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 Lilly and Symphony GenIsis Holdings LLC, which cover approximately 6.75 million shares of our common stock, which we issued to Lilly upon the conversion of outstanding convertible securities or are issuable upon the exercise of warrants we issued to Symphony GenIsis Holdings. We also 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. In addition, on December 22, 2005, we filed a Form S-3 shelf

registration statement with the SEC to register up to $200,000,000 worth of our common stock for possible issuance. 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 (PCAOB), or the NASDAQ Stock Exchange. Any such action could adversely affect our financial results and the market price of our common stock.

Risks Associated with our Drug Discovery and Development Business

If we or our partners fail to obtain regulatory approval for our drug candidates, 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 drugs before a drug 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 drugs, 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. We and our partners may not be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our drugs. 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, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute drug products. If we fail to comply with these regulations, regulators could force us to withdraw a drug 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 drug product, Vitravene. We cannot guarantee that any of our other drugs will be safe and effective, will be approved for commercialization or that our partners or we can successfully commercialize these drugs.

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 drugs that have not met the primary clinical end points in their Phase 3 studies.

In March 2003, we reported the results of a Phase 3 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 3 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 3 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.

We have licensed the intellectual property, including commercialization rights, to our apoB-100, GCGR, and GCCR programs to Symphony GenIsis, Inc. and will not receive any future royalties or revenues with respect to the product in these programs, including ISIS 301012 and ISIS 325568 unless we exercise our option to acquire all of these product candidates in the future. We may not have the financial resources to exercise this option or sufficient clinical data in order to determine whether we should exercise this option.

We have licensed to Symphony GenIsis our intellectual property rights, including commercialization rights, to our apoB-100, GCGR, and GCCR Programs in exchange for Symphony GenIsis' investment of $75.0 million to advance the clinical development of these programs. In exchange for this investment and for five-year warrants to purchase shares of our common stock, we received an exclusive purchase option to acquire all of the equity of Symphony GenIsis, thereby allowing us to reacquire our apoB-100, GCGR and GCCR programs, which include ISIS 301012 and ISIS 325568. The purchase option exercise price reflects a compounded annual rate of return that averages 32% and is 27% at the end of the anticipated four-year collaborative development period. We may pay the option exercise price in cash or a combination of cash and our common stock, at our sole discretion, provided that the common stock portion may not exceed 33% of the purchase option exercise price.

If we elect to exercise the repurchase option, we will be required to make a substantial cash payment and/or issue a substantial number of shares of our common stock, or enter into a financing arrangement or license arrangement with one or more third parties, or some combination of the foregoing. A payment in cash would reduce our capital resources. A payment in shares of our common stock could result in dilution to our stockholders at that time. Other financing or licensing alternatives may be expensive or impossible to obtain. If we do not exercise the purchase options prior to their expiration, we will lose our rights in our apoB-100, GCGR, and GCCR programs. We may not have the financial resources to exercise the repurchase option, which may result in our loss of these rights. Additionally, we may not have sufficient clinical data in order to determine whether we should exercise the options.

Disagreements between Symphony GenIsis and us regarding the development of our product candidates in our apoB-100, GCGR, and GCCR programs may cause significant delays and other impediments in the development of these product candidates, which could negatively affect the value of these product candidates.

We have licensed to Symphony GenIsis our intellectual property rights, including commercialization rights, to our product candidates in our apoB-100, GCGR, and GCCR programs in exchange for Symphony GenIsis' investment of $75.0 million to advance the clinical development of these programs. We are responsible for developing these product candidates in accordance with a specified development plan and related development budget. The Symphony GenIsis development committee supervises our development activities. The development committee is comprised of an equal number of representatives from Isis and Symphony GenIsis. If the development committee cannot resolve a particular development issue, the issue will be referred to the chief executive officers of Isis and Symphony GenIsis. Any disagreements between Symphony GenIsis and us regarding a development decision may cause significant delays in the development and commercialization of our product candidates within

our apoB-100, GCGR, and GCCR programs.

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 payers 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 drug 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 drugs and their potential advantages over competing products;
- The cost and effectiveness of our drugs compared to other available therapies;
- The patient convenience of the dosing regimen for our drugs; and
- Reimbursement policies of government and third party payers.

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

If we cannot manufacture our drug products or contract with a third party to manufacture our drug 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 drugs, 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 drugs, 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 our drug discovery and development business fails to compete effectively, our drugs 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 drugs or technologies that are more effective than any drugs 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.

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.

Risks Associated with our Ibis Division

We may not successfully develop or derive revenues from our business based on our Ibis biosensor system.

Our Ibis biosensor 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 Ibis biosensor 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 Ibis biosensor system business could fail to meet our business and financial objectives.

If we fail to secure commercial partners for our Ibis biosensor system, our commercialization efforts for our Ibis biosensor system may be harmed or delayed.

We expect to depend on third parties to commercialize our Ibis biosensor system, particularly in the areas of manufacturing, selling and servicing the instruments. In addition, we expect to depend on third parties to sell and distribute our infectious organism ID kits to non-government customers in the healthcare-associated infection control and infectious disease diagnostic markets. If we are unable to reach agreements with suitable third parties, we may fail to meet our business objectives for the Ibis biosensor system. We may not successfully establish a distribution, manufacturing, sale or service relationship or be able to make alternative arrangements. Moreover, these relationships may not succeed, may require us to give up a part of our ownership interest, or may diminish our profit margins on our Ibis instruments and ID kits.

We depend on government contracts for most of our revenues and the loss of government contracts or a decline in funding of existing or future government contracts could adversely affect our revenues and cash flows and our ability to fund our growth.

Virtually all of our Ibis business' revenue is from the sale of services and products to the United States government. The U.S. government may cancel these contracts at any time without penalty or may change its requirements, programs or contract budget or decline to exercise option periods, any of which could reduce our revenues and cash flows from U.S. government contracts. Our revenues and cash flow from U.S. government contracts could also be reduced by declines in U.S. defense, homeland security and other federal agency budgets.

For the three months ended March 31, 2006, Isis derived approximately 64% of its revenue from agencies of the United States government, including through our subcontract with SAIC. Because of the concentration of our contracts, we are vulnerable to adverse changes in our revenues and cash flows if a significant number of our United States Government contracts and subcontracts are simultaneously delayed or canceled for budgetary, performance or other reasons. If United States defense and other federal agencies choose to reduce their purchases under our contracts, exercise their right to terminate contracts, fail to exercise options to renew contracts or limit our ability to obtain new contract awards, our revenues and cash flows could be adversely affected.

We may be liable for penalties under a variety of procurement rules and regulations, and changes in government regulations could adversely impact our revenues, operating expenses and operating margins.

Under our agreements with the United States government, we must comply with and are affected by various government regulations that impact our operating costs, operating margins and our internal organization and operation of our businesses. These regulations affect how our customers and Isis do business and, in some instances, impose added costs on our businesses. Any changes in applicable laws could adversely affect the financial performance of our Ibis business. With respect to U.S. government contracts, any failure to comply with applicable laws could result in contract termination, price or fee reductions or suspension or debarment from contracting with

the U.S. government. Among the most significant regulations are the following:

- the U.S. Federal Acquisition Regulations, which comprehensively regulate the formation, administration and performance of government contracts;
- the U.S. Truth in Negotiations Act, which requires certification and disclosure of all cost and pricing data in connection with contract negotiations; and
- the U.S. Cost Accounting Standards, which impose accounting requirements that govern our right to reimbursement under certain cost-based government contracts.

If our Ibis biosensor system's reliability does not meet market expectations, we may be unable to retain our existing customers and attract new customers.

Complex diagnostic instruments such as our Ibis biosensor system typically require operating and reliability improvements following their initial introduction. As we continue to develop our Ibis biosensor system and its related applications we will need to make sure our customers are satisfied with the sensor's reliability. Our efforts to satisfy our customer's needs for instrument reliability could result in greater than anticipated service expenses or divert other resources. Additionally, if we fail to resolve reliability issues as they develop, we could materially damage our reputation, which could prevent us from retaining our existing customers and attracting new customers.

If we had to replace a supplier of one of the major hardware components of our Ibis biosensor system, it could delay our commercialization efforts and lengthen our sales cycle.

We have a single supplier for each major hardware component of our Ibis biosensor system. Although, we believe we would be able to find a replacement provider, if any of these suppliers stopped providing us with their respective components, identifying and securing a suitable replacement could delay our commercialization efforts and lengthen our sales cycle.

If our Ibis business fails to compete effectively, it may not succeed or contribute significant revenues.

Many of our competitors have, and in the future these and other competitors may have, significantly greater financial, marketing, sales, manufacturing, distribution and technological resources than us. Moreover, these companies may have substantially greater expertise in conducting clinical

trials and research and development, greater ability to obtain necessary intellectual property licenses and greater brand recognition than we do. In addition, our competitors may be in a better position to respond quickly to new or emerging technologies, may be able to undertake more extensive marketing campaigns, may adopt more aggressive pricing policies and may be more successful in attracting potential customers, employees and strategic partners than we are.

The diagnostics industry is highly competitive. Currently, large reference laboratories, public health laboratories and hospitals perform the majority of diagnostic tests used by physicians and other health care providers. We expect that these laboratories will compete vigorously to maintain their dominance in the diagnostic testing market. In order to achieve market acceptance of our Ibis biosensor system, we will be required to demonstrate that it provides accurate, cost-effective and/or time saving alternatives to tests performed by traditional laboratory procedures and products made by our competitors.

Improvements in preventing major diseases could reduce the need for our Ibis biosensor instruments and ID kits, which in turn could reduce our revenues.

We expect to derive a significant portion of our revenues from the sale of the infectious organism ID kits necessary to use our Ibis biosensor system. The need to quickly identify and contain major threats, such as the avian flu, could increase the demand for our infectious organism ID kits. Conversely, improvements in containing or treating a threat, such as vaccines, would significantly reduce the need to identify and contain the threat. Any reduction in the need to identify or contain a threat could diminish the need for our infectious organism ID kits, which could reduce our revenues.

If we cannot access or license rights to particular nucleic acid sequences for targeted diseases in the future, we may be limited in our ability to develop new products and access new markets.

Although our research staff seeks to discover particular nucleic acid sequences for targeted diseases, our ability to offer diagnostic tests for diseases may depend on the ability of third parties to discover particular sequences or markers and correlate them with disease, as well as the rate at which such discoveries are made. Our

ability to design products that target these diseases may depend on our ability to obtain the necessary access to raw materials or intellectual property rights from third parties who make any of these discoveries. If we are unable to access new technologies or the rights to particular sequences or markers necessary for additional diagnostic products on commercially reasonable terms, we may not be able to develop new diagnostic products or enter new markets.

The sales cycles for our Ibis biosensor systems are lengthy, and we may expend substantial funds and management effort with no assurance of successfully selling our Ibis biosensor systems or services.

The sales cycles for Ibis biosensor systems are typically lengthy. Our sales and licensing efforts, and those of our partners, will require the effective demonstration of the benefits, value, and differentiation and validation of our products and services, and significant training of multiple personnel and departments within a potential customer organization. We or our partners may be required to negotiate agreements containing terms unique to each prospective customer or licensee, which would lengthen the sales cycle. We may expend substantial funds and management effort with no assurance that we will sell our products. In addition, this lengthy sales cycle makes it more difficult for us to accurately forecast revenue in future periods and may cause revenues and operating results to vary significantly in future periods.

If we or our partners are required to obtain regulatory approval for our Ibis biosensor system applications, we may not successfully obtain approval.

Depending on their intended use, our Ibis biosensor systems may be regulated as a medical device by the FDA and comparable agencies of other countries and require either premarket approval (PMA) or 510(k) clearance from the FDA, prior to marketing. The 510(k) clearance process usually takes from three to twelve months from submission, but can take longer. The premarket approval process is much more costly, lengthy, uncertain and generally takes from six months to two years or longer from submission. In addition, commercialization of any diagnostic or other product that our licensees or collaborators or we develop would depend upon successful completion of preclinical testing and clinical trials. Preclinical testing and clinical trials are long, expensive and uncertain processes, and we do not know whether we, our licensees or any of our collaborators, would be permitted or able to undertake clinical trials of any potential products. It may take us or our licensees or collaborators many years to complete any such testing, and failure could occur at any stage. Preliminary results of trials do not necessarily predict final results, and acceptable results in early trials may not be repeated in later trials. We or our collaborators may encounter delays or rejections of potential products based on changes in regulatory policy for product approval during the period of product development and regulatory agency review.

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 development activities, capital expenditures and other general corporate purposes, including advancing ISIS 113715, ISIS 369645, and ISIS 353512. In addition, these funds will also be used to accelerate the commercialization of Isis' Ibis biosensor system, the IBIS T-5000. 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 reallowed 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 reallowed 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 "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.

Equity Line of Credit

On May 30, 2006, we entered into what is sometimes termed an equity line of credit arrangement with Azimuth Opportunity Ltd. ("Azimuth"). Specifically, we entered into a Common Stock Purchase Agreement with Azimuth (the "Purchase Agreement"), which provides that, upon the terms and subject to the conditions set forth therein, Azimuth is committed to purchase up to $75,000,000 of our common stock, or the number of shares which is one less than twenty percent (20%) of the issued and outstanding shares of our common stock as of May 30, 2006, whichever occurs first, over the 18-month term of the Purchase Agreement. From time to time over the term of the Purchase Agreement, and at our sole discretion, we may present Azimuth with draw down notices constituting offers to purchase our common stock over ten consecutive trading days or such other period mutually agreed upon by us and Azimuth. We are able to present Azimuth with up to 16 draw down notices during the term of the Purchase Agreement, with a minimum of five trading days required between each draw down period. Only one draw down is allowed in each draw down pricing period, unless otherwise mutually agreed upon by us and Azimuth.

Once presented with a draw down notice, Azimuth is required to purchase a pro rata portion of the shares on each trading day during the trading period on which the daily volume weighted average price for our common stock exceeds a threshold price determined by us for such draw down. The per share purchase price for these shares equals the daily volume weighted average price of our common stock on each date during the draw down period on which shares are purchased, less a discount ranging from 3.8% to 5.3%, based on our stock price. If the daily volume weighted average price of our common stock falls below the threshold price on any trading day during a draw down period, the Purchase Agreement provides that Azimuth will not be required to purchase the pro-rata portion of shares of common stock allocated to that day. However, at its election, Azimuth could buy the pro-rata portion of shares allocated to that day at the threshold price less the discount described above.

The Purchase Agreement also provides that from time to time and at our sole discretion we may grant Azimuth the right to exercise one or more options to purchase additional shares of our common stock during each draw down pricing period for an amount of shares specified by us. Upon Azimuth's exercise of the option, we would sell to Azimuth the shares of our common stock subject to the option at a price equal to the greater of the daily volume weighted average price of our common stock on the day Azimuth notifies us of its election to exercise its option or the threshold price for the option determined by us, less a discount calculated the same as in the draw down notices.

In addition to our issuance of shares of common stock to Azimuth pursuant to the Purchase Agreement, our Registration Statement on Form S-3 (File No. 333-130639) (the "Registration Statement") also covers the sale of those shares from time to time by Azimuth to the public. Azimuth is an "underwriter" within the meaning of Section 2(a)(11) of the Securities Act of 1933, as amended (the "Securities Act").

Azimuth has informed us that, unless it notifies us that it will use a different broker-dealer and we have filed a prospectus supplement to our Registration Statement, it will use an unaffiliated broker-dealer to effectuate all sales, if any, of common stock that it may purchase from us pursuant to the Purchase Agreement. Such sales will be made on the Nasdaq National Market at prices and at terms then prevailing or at prices related to the then current market price. Each such unaffiliated broker-dealer will be an underwriter within the meaning of Section 2(a)(11) of the Securities Act. Azimuth has informed us that each such broker-dealer will receive commissions from Azimuth which will not exceed customary brokerage commissions. Azimuth also will pay other expenses associated with the sale of the common stock it acquires pursuant to the Purchase Agreement.

The shares of common stock may be sold in one or more of the following manners:

- ordinary brokerage transactions and transactions in which the broker solicits purchasers; or
- a block trade in which the broker or dealer so engaged will attempt to sell the shares as agent, but may position and resell a portion of the block as principal to facilitate the transaction.

Azimuth has agreed that during the term of and for a period of ninety (90) days after the termination of the Purchase Agreement, neither Azimuth nor any of its affiliates will, directly or indirectly, sell any of our securities except the shares that it owns or has the right to purchase pursuant to the provisions of a draw down notice. Azimuth has agreed that during the periods listed above it will not enter into a short position with respect to shares of our common stock except that Azimuth may sell shares that it is obligated to purchase under a pending draw down notice but has not yet taken possession of so long as Azimuth covers any such sales with the shares purchased pursuant to such draw down notice. Azimuth has further agreed that during the periods listed above it will not grant any option to purchase or acquire any right to dispose or otherwise dispose for value of any shares of our common stock or any securities convertible into, or exchangeable for, or warrants to purchase, any shares of our common stock, or enter into any swap, hedge or other agreement that transfers, in whole or in part, the economic risk of ownership of our common stock, except for the sales permitted by the prior two sentences.

In addition, Azimuth and any unaffiliated broker-dealer will be subject to liability under the federal securities laws and must comply with the requirements of the Securities Act and the Securities Exchange Act of 1934, as amended (the "Exchange Act"), including without limitation, Rule 10b-5 and Regulation M

under the Exchange Act. These rules and regulations may limit the timing of purchases and sales of shares of common stock by Azimuth or any unaffiliated broker-dealer. Under these rules and regulations, Azimuth and any unaffiliated broker-dealer:

- may not engage in any stabilization activity in connection with our securities;
- must furnish each broker which offers shares of our common stock covered by the prospectus that is a part of our Registration Statement with the number of copies of such prospectus and any prospectus supplement which are required by each broker; and
- may not bid for or purchase any of our securities or attempt to induce any person to purchase any of our securities other than as permitted under the Exchange Act.

These restrictions may affect the marketability of the shares of common stock by Azimuth and any unaffiliated broker-dealer.

We have agreed to indemnify and hold harmless Azimuth, any unaffiliated broker-dealer and each person who controls Azimuth or any unaffiliated broker-dealer against certain liabilities, including liabilities under the Securities Act. We have agreed to pay up to $35,000 of Azimuth's reasonable attorneys' fees and expenses (exclusive of disbursements and out-of-pocket expenses) incurred by Azimuth in connection with the preparation, negotiation, execution and delivery of the Purchase Agreement. We have also agreed to pay all reasonable fees and expenses incurred by Azimuth in connection with any amendments, modifications or waivers of the Purchase Agreement. Further, we have agreed that if we issue a draw down notice and fail to deliver the shares to Azimuth on the applicable settlement date, and such failure continues for ten trading days, we will pay Azimuth liquidated damages in cash or restricted shares of our common stock, at the option of Azimuth.

Azimuth has agreed to indemnify and hold harmless us and each of our directors, officers and persons who control us against certain liabilities, including liabilities under the Securities Act, which may be based upon written information furnished by Azimuth to us for inclusion in a prospectus or prospectus supplement related to this transaction.

Upon each sale of our common stock to Azimuth under the Purchase Agreement, we have also agreed to pay Reedland Capital Partners, an Institutional Division of the Financial West Group, member NASD/SIPC, a placement fee equal to one fifth of one percent of the aggregate dollar amount of common stock purchased by Azimuth. We have agreed to indemnify and hold harmless Reedland Capital Partners against certain liabilities, including liabilities under the Securities Act.

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 May 10, 2006;
- Series C Junior Participating Preferred Stock, 1,000,000 shares of which were authorized and none of which was issued and outstanding at May 10, 2006; and
- Common stock, 200,000,000 shares of which were authorized and 72,883,902shares of which were outstanding as of May 10, 2006.

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, 2005, and management's assessment of the effectiveness of our internal control over financial reporting as of December 31, 2005, 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 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.

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, 2005;
- our Quarterly Report on Form 10-Q for the quarter ended March 31, 2006;
- our Current Reports on Form 8-K, filed with the SEC on:
  - March 1, 2006,
  - April 10, 2006,
  - April 12, 2006,
  - April 20, 2006,
  - April 21, 2006, and
  - May 5, 2006.
- our Notice of Annual Meeting and Proxy Statement for the 2006 Annual Meeting of Stockholders, filed with the SEC on March 22, 2006;
- the description of our Preferred Share Purchase Rights Plan on Form 8-K filed with the SEC on December 13, 2000, as updated by our Form 8-K filed with the SEC on April 8, 2005; and
- the description of our common stock 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.

$200,000,000
Common Stock

ISIS PHARMACEUTICALS, INC.

Prospectus

May 30, 2006
