

PROSPECTUS

4,250,000 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:

- 4,250,000 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 11 of this prospectus.

Our common stock is currently traded on the Nasdaq National Market under the symbol "ISIS." On August 15, 2006, the last reported sales price for our common stock was \$6.38 per share.

Investing in our common stock involves risks.
See "Risk Factors" beginning on page 4.

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 August 21, 2006

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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 associated with disease. Interference with RNA can keep the body from producing the proteins that are involved in disease. We are the leader in making drugs that target RNA, and have a strong proprietary position in RNA-based drug discovery technologies. With our primary technology, antisense, we create inhibitors, called oligonucleotides, designed to hybridize, with a high degree of specificity to their RNA target and modulate the production of specific proteins associated with disease. In our Ibis division, we have developed a revolutionary system, called TIGER, 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. Additionally, as an innovator in RNA-based drug discovery and development, we are the owner or exclusive licensee of approximately 1,500 issued patents worldwide.

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

Isis PharmaceuticalsTM and Ibis T5000TM are our trademarks. Vitravene[®] is a registered trademark of Novartis AG. AffinitakTM is a trademark of Eli Lilly and Company. This prospectus also contains trademarks and servicemarks of other companies.

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The Offering

Common stock covered hereby	4,250,000 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

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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 June 30, 2006, we had accumulated losses of approximately \$790.5 million and stockholders' equity of approximately \$6.7 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 T5000 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. 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 T5000 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

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 June 30, 2006, the market price of our common stock ranged from \$3.75 to \$9.50 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 T5000 biosensor system.

We are developing our Ibis T5000 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 T5000 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 or shares under our shelf registration statement are issued, 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 the warrant 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 the warrant, 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.

If we sell shares of our common stock under our equity line of credit arrangement, our existing common stockholders will experience immediate dilution and our stock price may fall.

We have entered into a common stock purchase agreement with Azimuth Opportunity Ltd., which provides that, upon the terms and subject to the conditions set forth therein, Azimuth is committed to purchase up to \$75 million of our common stock, or 14,578,970 shares, 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. The per share purchase price for these shares is at a discount ranging from 3.8% to 5.3%. As a result, our existing common stockholders will experience immediate dilution upon the purchase of any shares of our common stock by Azimuth.

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 products 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 the five-year warrant 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 substantially reduce our capital resources. A payment in shares of our common stock will 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 would 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. 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 T5000 biosensor system.

Our Ibis T5000 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 T5000 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 T5000 biosensor system business could fail to meet our business and financial objectives.

We will depend on Bruker Daltonics to manufacture the IbisT5000 biosensor system and any failure of Bruker to fulfill its obligations could harm or delay our commercialization efforts.

In July 2006, Ibis entered into a strategic alliance with Bruker Daltonics to manufacture and distribute the Ibis T5000 biosensor system. Bruker will be the exclusive worldwide manufacturer of the Ibis T5000 biosensor system and will also be responsible for order processing, system installations and service in North America, Europe and the Middle East. In Europe and the Middle East, Bruker will have exclusive rights to sell Ibis T5000 systems and Ibis infectious organism identification kits to government customers for defense, homeland security and other government applications, and non-exclusive rights to sell to all other customers, including clinical, pharmaceutical and academic researchers for all other applications, except diagnostics. As such, we rely heavily on Bruker to successfully manufacture and distribute our Ibis T5000 biosensor system, but do not control many aspects of Bruker's activities. If Bruker fails to carry out its obligations under our alliance, such failure could harm or delay the commercialization of our Ibis T5000 biosensor system.

If we fail to secure additional commercial partners for our Ibis T5000 biosensor system, our commercialization efforts for our Ibis T5000 biosensor system may be harmed or delayed.

In addition to Bruker, we may depend on third parties to commercialize our Ibis T5000 biosensor system, particularly in the areas of hospital-associated infection control and infectious disease diagnostics. If we are unable to reach agreements with suitable third parties, we may fail to meet our business objectives for the Ibis T5000 biosensor system. We may not successfully establish a relationship in these markets 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 revenue targets 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 six months ended June 30, 2006, Isis derived approximately 55% 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 T5000 biosensor system's reliability does not meet market expectations, we may be unable to retain our existing customers and attract new customers.

Complex instruments such as our Ibis T5000 biosensor system typically require operating and reliability improvements following their initial introduction. As we continue to develop our Ibis T5000 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 T5000 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 T5000 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 T5000 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 T5000 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 T5000 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 T5000 biosensor systems are lengthy, and we may expend substantial funds and management effort with no assurance of successfully selling our Ibis T5000 biosensor systems or services.

The sales cycles for Ibis T5000 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 T5000 biosensor system applications, we may not successfully obtain approval.

Depending on their intended use, our Ibis T5000 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.

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, including the documents incorporated by reference. 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.

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 \$8.93 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 4,250,000 shares of our common stock issuable upon exercise of warrants to purchase common stock. We issued the warrants in connection with our collaboration with Symphony GenIsis, Inc.

On April 7, 2006, we entered into a series of related agreements in connection with a transaction with Symphony Capital and a group of co-investors to provide \$75 million to fund the development of our cholesterol-lowering drug, ISIS 301012, and two novel drugs from our metabolic disease program. Symphony Capital formed Symphony GenIsis, capitalized with \$75 million, to provide funding for the development of these three drugs in collaboration with us. We licensed to Symphony GenIsis the intellectual property for our apoB-100, glucagon receptor (GCGR) and glucocorticoid receptor (GCCR) programs. We received an exclusive purchase option from Symphony GenIsis' investors that will allow us to reacquire the intellectual property by purchasing all of Symphony GenIsis' equity at a predetermined price that reflects a compounded annual rate of return that averages 32% and is 27% at the end of the anticipated four-year collaborative development period. The purchase option exercise price may be paid in cash or a combination of cash and our common stock (up to 33% of the purchase price), at our discretion.

In exchange for the purchase option, we granted to Symphony GenIsis Holdings LLC a five-year warrant to purchase 4.25 million shares of common stock at an exercise price of \$8.93 per share, a 25% premium over Isis' prior 60 day average trading price, which was \$7.14. To compensate Symphony Capital for structuring the transaction and to pay a portion of its expenses, Isis paid a structuring fee of \$3.75 million. The selling stockholders are members of Symphony GenIsis Holdings and/or hold interests in one of its members and received their Warrants from Symphony GenIsis Holdings or from a member of Symphony GenIsis Holdings.

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 October 4, 2006 and ending April 7, 2011.

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. Since the warrants held by the selling stockholders are exercisable beginning October 4, 2006 and the shares of common stock issuable upon exercise of the warrants are being offered in this prospectus, those shares of common held by the selling stockholders are included in the table below. The percentages of shares owned after the offering are based on 73,883,231 shares of our common stock outstanding as of August 15, 2006.

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 15, 2006.

Selling stockholders (1)(2)	Shares of Common Stock Beneficially Owned Prior to Offering			Shares of Common Stock Offered	Percentage Of Common Stock Outstanding After The Offering
	Shares of Common Stock Held	Shares of Common Stock Issuable Upon Exercise of Warrants	Total Number of Shares Beneficially Owned		
Symphony Capital Partners, L.P. 875 Third Avenue, 18 th Floor New York, NY 10022	—	3,141,934	3,141,934	3,141,934	—
Symphony Strategic Partners, LLC 875 Third Avenue, 18 th Floor New York, NY 10022	—	170,798	170,798	170,798	—
Howard Hughes Medical Institute 4000 Jones Bridge Road Chevy Chase, MD 20815	—	266,333	266,333	266,333	—
STORMLAUNCH & CO. for the benefit of Morgan Stanley Private Markets Fund III LP One Tower Bridge 100 Front Street, Suite 1100 West Conshohocken, PA 19428	—	213,067	213,067	213,067	—
MELLON BANK, N.A., solely in its capacity as trustee for the Weyerhaeuser Company Master Retirement Trust One Tower Bridge 100 Front Street, Suite 1100 West Conshohocken, PA 19428	—	133,167	133,167	133,167	—
SAILORSHELL & CO. for the benefit of Morgan Stanley AIP Global Diversified Fund LP One Tower Bridge 100 Front Street, Suite 1100 West Conshohocken, PA 19428	—	79,900	79,900	79,900	—
SAILORPASS & CO. for the benefit of Morgan Stanley Private Markets Fund I LP One Tower Bridge 100 Front Street, Suite 1100 West Conshohocken, PA 19428	—	53,267	53,267	53,267	—
Factory Mutual Insurance Company One Tower Bridge 100 Front Street, Suite 1100 West Conshohocken, PA 19428	—	21,307	21,307	21,307	—
Nuclear Electric Insurance Ltd. One Tower Bridge 100 Front Street, Suite 1100 West Conshohocken, PA 19428	—	21,307	21,307	21,307	—
STORMBAY & CO. for the benefit of Vijverpoort Huizen C.V. One Tower Bridge 100 Front Street, Suite 1100 West Conshohocken, PA 19428	—	10,653	10,653	10,653	—
UBS O'Conner LLC for the benefit of O'Connor PIPES Corporate Strategies Master Limited 299 Park Avenue New York, NY 10171	—	53,267	53,267	53,267	—
RRD International, LLC 7361 Calhoun Place, Suite 325 Rockville, MD 20850	—	85,000	85,000	85,000	—
Commerce and Industry Insurance Company 599 Lexington Ave., 25 th Floor New York, NY 10022	—	532,667	532,667	532,667	—
WHI Morula Fund 191 N. Wacker Drive, Suite 1500 Chicago, IL 60606	—	53,267	53,267	53,267	—
SAILORPIER & CO. for the benefit of Aurora Cayman Limited One Tower Bridge 100 Front Street, Suite 1100 West Conshohocken, PA 19428	—	46,875	46,875	46,875	—
STORMSTAR & CO. for the benefit of Morgan Stanley Private Markets Fund Employee Investors III LP One Tower Bridge 100 Front Street, Suite 1100 West Conshohocken, PA 19428	—	6,392	6,392	6,392	—

* 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.

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.

PLAN OF DISTRIBUTION

The selling stockholders, which as used herein includes donees, distributees, 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) such time as all of the shares covered by this prospectus have been disposed or (2) the date on which all the shares may be sold without restriction 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 15, 2006;
- Series C Junior Participating Preferred Stock, 1,000,000 shares of which were authorized and none of which was issued and outstanding at August 15, 2006; and
- Common stock, 200,000,000 shares of which were authorized and 73,883,231 shares of which were outstanding as of August 15, 2006.

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

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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.

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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

This prospectus "incorporates by reference" certain of our publicly-filed documents, 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, as amended on August 9, 2006;
- our Quarterly Report on Form 10-Q for the quarter ended March 31, 2006, as amended on August 9, 2006;
- our Quarterly Report on Form 10-Q for the quarter ended June 30, 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 27, 2006,
 - May 5, 2006;
 - May 31, 2006;and
 - July 31, 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.

**4,250,000 Shares
Common Stock**

ISIS PHARMACEUTICALS, INC.

Prospectus

August 21, 2006