As filed with the Securities and Exchange Commission on May 21, 2008
Registration No. 333-

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM S-3

REGISTRATION STATEMENT
Under
THE SECURITIES ACT OF 1933

ISIS PHARMACEUTICALS, INC.

(Exact name of Registrant as specified in its charter)

Delaware	**33-0336973**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification Number)

1896 Rutherford Road
Carlsbad, California 92008
(760) 931-9200
(Address, including zip code, and telephone number, including area code, of Registrant's principal executive offices)

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Approximate date of commencement of proposed sale to the public: From time to time after this registration statement becomes effective.

If the only securities being registered on this form are being offered pursuant to dividend or interest reinvestment plans, please check the following box. o

If any of the securities being registered on this form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, as amended (the "Securities Act"), other than securities offered only in connection with dividend or interest reinvestment plans, check the following box. x

If this form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. o

If this form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. o

If this form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, please check the following box. x

If this form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, please check the following box. o

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer x	Accelerated filer ☐

Non-accelerated filer o (Don not check if a smaller reporting company) Smaller reporting company ☐

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered	Amount to be registered	Proposed maximum offering price per unit(1)	Proposed maximum aggregate offering price	Amount of registration fee
Common Stock, $0.001 per share	5,000,000	$ 12.950	$ 64,750,000	$ 2,545

(1) Estimated in accordance with Rule 457(c) of the Securities Act solely for the purpose of computing the amount of the registration fee based on the average of the high and low prices of the registrant's common stock as reported on the Nasdaq Global Market on May 19, 2008. Represents the number of shares of common stock held by the selling stockholders.

Isis Pharmaceuticals, Inc.

5,000,000 Shares of Common Stock

The common stock may be offered and sold from time to time pursuant to this prospectus by the holders of the common stock identified in this prospectus in the selling stockholder table. The selling stockholder may resell the shares of our common stock at fixed prices, at market prices prevailing at the time of sale, or at prices negotiated with purchases, to or through underwriters, broker-dealers, agents, or through any other means described in this prospectus under "Plan of Distribution". The selling stockholders will receive all of the net proceeds from the sale of the shares and will pay any applicable discounts, commission or concessions. The selling stockholders and any underwriters, broker-dealers or agents that participate in the sale of the shares may be "underwriters" within the meaning of the Securities Act of 1933, or Securities Act, and any discounts, commissions, concessions or profit they earn on any resale of the shares may be underwriting discounts or commissions under the Securities Act.

In January 2008, we announced a major strategic alliance with Genzyme Corporation in which Genzyme will develop and commercialize mipomersen. Mipomersen is our lipid lowering drug targeting apoB-100. As part of the strategic relationship, Genzyme has exclusively licensed mipomersen and will also have preferred access to our future drugs for CNS and certain rare diseases. As part of this transaction, Genzyme paid us $150 million to purchase five million shares of our common stock for $30 per share and upon the completion of the license agreement.

Genzyme has agreed that it will not sell its Isis stock until the earlier of 4 years from the date of our mipomersen license agreement, the first commercial sale of mipomersen and the termination of the our mipomersen license agreement. Thereafter, Genzyme will be subject to monthly limits on the number of shares it can sell. In addition, Genzyme has agreed that until the earlier of the 10 year anniversary of the mipomersen license agreement and the date Genzyme holds less than 2% of our issued and outstanding common stock, Genzyme will not acquire any additional shares of our common stock without our consent.

We issued and sold the shares in a private placement in reliance on an exemption from registration under the Securities Act.

Our common stock is listed on the Nasdaq Global Market under the symbol "ISIS." On May 20, 2008, the last reported bid price of our common stock was $12.95 per share.

Investing in our common stock involves risks.
See "Risk Factors" beginning on page 2

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 May 21, 2008

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You should rely only on the information incorporated by reference or provided in this prospectus. We have not authorized anyone else to provide you with different information. You should not assume that the information in this prospectus is accurate as of any date other than the date on the cover page of this prospectus.

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 herein. 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 the leading company in antisense technology, exploiting a novel drug discovery platform to create a broad pipeline of first-in-class drugs. Through our highly efficient and prolific drug discovery platform, we can expand our drug pipeline and our partners' drug pipelines with antisense drugs that address significant unmet medical needs. Our business strategy is to do what we do best—to discover unique antisense drugs and conduct early development on these drugs to key value inflection points. Because we can discover more drugs than we can develop, our plan is to discover new drugs, outlicense our drugs to partners and build a growing annuity of milestone payments and royalty income. In this way, we maximize the value of the drugs we discover by licensing our drugs to partners at key development points, which allows us to focus on utilizing our antisense technology platform to discover new drugs. At the same time, we benefit from our partners' expertise to develop, commercialize and market our drugs. For example, we partner our drugs with leading pharmaceutical companies as well as with smaller satellite companies that have expertise in specific disease areas. In addition to our cutting edge antisense programs, we maintain technology leadership beyond our core areas of focus through collaborations with other companies. We explore the technology beyond antisense with additional opportunities in infectious disease identification through our Ibis Biosciences, Inc. subsidiary.

We were incorporated in California in January 1989, and in April 1991 we changed our state of incorporation to Delaware. Our executive offices are located at 1896 Rutherford Road, Carlsbad, California 92008, and our telephone number is (760) 931-9200.

RISK FACTORS

Investing in our common stock 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 common stock. 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 common stock could decline, and you might lose all or part of your investment.

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

Because 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, 2008, we had accumulated losses of approximately $832.0 million and stockholders' equity of approximately $54.6 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from research grants and the sale or licensing of patents as well as interest income. We currently have only one product, Vitravene, approved for commercial use. This product has limited sales potential, and Novartis, our exclusive distribution partner for this product, no longer markets it. 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.

Since corporate partnering is a key part of our strategy to fund the development and commercialization of our development programs, if any of our collaborative partners fail to fund our collaborative programs, 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, including ISIS 113715. However, we may not be able to negotiate additional attractive collaborative arrangements.

Many of the drugs in our development pipeline are being developed and/or funded by corporate partners, including Altair Therapeutics Inc., Antisense Therapeutics Limited, Atlantic Healthcare (UK) Limited, BMS, iCo Therapeutics Inc., ImQuest Pharmaceuticals, Inc., Eli Lilly and Company, Merck & Co., Inc., OncoGenex Technologies Inc. and OMI. In addition, in January 2008 we entered a major strategic alliance with Genzyme in which Genzyme will develop and commercialize mipomersen. If any of these pharmaceutical companies stop funding and/or developing these products, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these products on our own.

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 disappointing results of the Phase 3 clinical trials, Lilly discontinued its investment in Affinitak.

In addition, the disappointing results of the two Affinitak clinical trials, our Phase 3 clinical trials of alicaforsen in patients with active Crohn's disease, or any future clinical trials 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.

Even with funding from corporate partners, if our partners do not effectively perform their obligations under our agreements with them, it would delay or stop the progress of our product development programs.

In addition to receiving funding, we enter into collaborative arrangements with third parties to:

- conduct clinical trials;

- seek and obtain regulatory approvals; and

- manufacture, market and sell existing and future products.

Once we have secured a collaborative arrangement to further develop and commercialize one of our development programs such as our collaborations with Genzyme, OMI and BMS, these collaborations may not continue or result in commercialized drugs, or may not progress as quickly as we anticipated.

For example, a collaborator such as Genzyme, OMI, or BMS, could determine that it is in its financial interest to:

- pursue alternative technologies or develop alternative products that may be competitive with the product that is part of the collaboration with us;

- pursue higher-priority programs or change the focus of its own development programs; or

- choose to devote fewer resources to our drugs than it does for its own drugs under development.

If any of these occur, it could affect our partner's commitment to the collaboration with us and could delay or otherwise negatively affect the commercialization of our drugs.

If we cannot protect our patents or our other proprietary rights, others may compete more effectively 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.

In addition, our Ibis business relies in part on trade secret laws and nondisclosure, confidentiality and other agreements to protect some of the proprietary technology that is part of the Ibis T5000 Biosensor System. However, these laws and agreements may not be enforceable or may not provide meaningful protection for Ibis' trade secrets or other proprietary information in the event of unauthorized use or disclosure or other breaches of these agreements.

Until recently, virtually all of Ibis' research and development activities have been funded under contracts from the U.S. government (either directly or through subcontracts from prime contractors or higher-tier subcontractors). As a general matter, subject to certain disclosure, notice, filing, acknowledgement and reporting obligations, Ibis is entitled to retain title to any inventions conceived or first reduced to practice under government contracts, but the government will have a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced these inventions for or on behalf of the United States.

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.

For example, in December 2006, the European Patent Office (EPO) Technical Board of Appeal reinstated with amended claims our Patent EP0618925 which claims a class of antisense compounds, any of which is designed to have a sequence of phosphorothioate-linked nucleotides having two regions of chemically modified RNA flanking a region of DNA. Prior to its reinstatement, this patent was originally opposed by several parties and revoked by an EPO Opposition Division in December of 2003. We intend to fully exercise our rights under this patent by pursuing licensing arrangements, but if licensing efforts are unsuccessful we may choose to assert our rights through litigation.

If a third party claims that our products or technology infringe its 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 fail to obtain timely funding, we may need to curtail or abandon some of our programs.

All of our drugs are undergoing clinical trials or are in the early stages of research and development. All of our drugs under development will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and a commitment of significant additional resources prior to their commercialization. Based on our existing cash and committed cash, including the $175 million mipomersen licensing fee from Genzyme, but not including the up to $210 million we could receive from Abbott, we expect that our 2008 year end cash balance will be greater than $450 million and will last for at least five years. 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, drugs or products.

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

For planning purposes, we estimate and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain drug will enter the clinic, when we anticipate completing a clinical trial, or when we anticipate filing an application for marketing approval. We base our estimates on present facts and a variety of assumptions. Many underlying assumptions are outside of our control. If we do not achieve milestones in accordance with our or investors' expectations, the price of our securities would likely decrease.

For example, in April 2008 the FDA provided guidance regarding approval requirements for mipomersen. The FDA indicated that reduction of LDL-cholesterol is an acceptable surrogate endpoint for accelerated approval of mipomersen for use in patients with homozygous familial hypercholesterolemia, or hoFH. The FDA will require data from two ongoing preclinical studies for carcinogenicity to be included in the hoFH filing, which is now anticipated to take place in 2010. The FDA also indicated that for broader indications in high risk, high cholesterol patients an outcome study would be required for approval. This FDA guidance caused us to revise our development plans and timelines to accelerate our planned outcome trial.

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 that would prevent them from leaving us. 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. In addition, 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, 2008, the market price of our common stock ranged from $8.79 to $20.15 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.

Because we use biological materials, hazardous materials, chemicals and radioactive compounds, if we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected.

Our research, development and manufacturing activities involve the use of potentially harmful biological materials as well as materials, chemicals and various radioactive compounds that could be hazardous to human health and safety or the environment. These materials and various wastes resulting from their use are stored at our facilities in Carlsbad, California pending ultimate use and disposal. We cannot completely eliminate the risk of contamination, which could cause:

- interruption of our research, development and manufacturing efforts;
- injury to our employees and others;
- environmental damage resulting in costly clean up; and
- liabilities under federal, state and local laws and regulations governing health and human safety, as well as the use, storage, handling and disposal of these materials and resultant waste products.

In such an event, we may be held liable for any resulting damages, and any such liability could exceed our resources. Although we carry insurance in amounts and type that we consider commercially reasonable, we do not have insurance coverage for losses relating to an interruption of our research, development or manufacturing efforts caused by contamination, and we cannot be certain that the coverage or coverage limits of our insurance policies will be adequate. In the event our losses exceed our insurance coverage, our financial condition would be adversely affected.

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, fires and acts of terrorism, 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.

In addition, the provisions of our convertible subordinated notes could make it more difficult or more expensive for a third party to acquire us. Upon the occurrence of certain transactions constituting a fundamental change, holders of the notes will have the right, at their option, to require us to repurchase all of their notes or a portion of their notes, which may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over the then current market prices.

Future sales of our common stock in the public market could adversely affect the trading price of our securities.

Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. For example, we 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 warrants we issued as part of our August 2005 private placement as well as 4.25 million shares of our common stock issuable upon the exercise of the warrant we issued to Symphony GenIsis Holdings. 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. Finally, we have registered for resale our $2^{5}/_{8}$% convertible subordinated notes, including the approximately 11,111,116 shares issuable upon conversion of the notes. The addition of any of these shares into the public 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 SEC, the Public Company Accounting Oversight Board (PCAOB) or the Nasdaq Global Market. 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 drugs, 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, including mipomersen and ISIS 113715, before a drug can be approved for sale. We must conduct these trials in compliance with FDA 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, including mipomersen and ISIS 113715, 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, including mipomersen and ISIS 113715. Failure to receive these approvals or delays in these approvals could prevent or delay commercial introduction of a product, including mipomersen and ISIS 113715, 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, including mipomersen and ISIS 113715, 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 we may need to abandon one or more of our drug development programs.

Drug discovery and development has inherent risks and the historical failure rate for drugs is high. Antisense technology in particular is relatively new and unproven. If we cannot demonstrate that our drugs, including mipomersen and ISIS 113715, are safe and effective drugs for human use, we may need to abandon one or more of our drug development programs.

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 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 clinical trials for our other drugs, including mipomersen and ISIS 113715. If any of our drugs in clinical studies, including mipomersen and ISIS 113715, do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for these and other drugs and our stock price could decline.

Even if our drugs are successful in preclinical and early human clinical studies, these results do not guarantee the drugs will be successful in late-stage clinical trials.

Successful results in preclinical or early human clinical trials, including the Phase 2 results for mipomersen and ISIS 113715, may not predict the results of late-stage clinical trials. There are a number of factors that could cause a clinical trial to fail or be delayed, including:

- the clinical trial may produce negative or inconclusive results;
- regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;
- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical trial due to adverse side effects of a drug on subjects or patients in the trial;
- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical trials;
- enrollment in our clinical trials may be slower than we anticipate;
- the cost of our clinical trials may be greater than we anticipate; and
- the supply or quality of our drugs or other materials necessary to conduct our clinical trials may be insufficient, inadequate or delayed.

Any failure or delay in one of our clinical trials, including our Phase 2 or Phase 3 development programs for mipomersen and ISIS 113715, could reduce the commercial viability of our drugs, including mipomersen and ISIS 113715.

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

Our success will depend upon the medical community, patients and third-party payors accepting our products as medically useful, cost-effective and safe. We cannot guarantee that, if approved for commercialization, doctors will use our products to treat patients. We currently have one commercially approved 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 payors.

Based on the profile of our drugs, physicians, patients, patient advocates, payors 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 would be required to establish large-scale commercial manufacturing capabilities either on our own or through a third party manufacturer. 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 or prevent 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 products.

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 that are:

- priced lower than our drugs;
- safer than our drugs; or
- more effective than our drugs.

These competitive developments could make our products obsolete or non-competitive.

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 drugs and, as a result, could delay or otherwise negatively affect the commercialization of our drugs.

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.

Disagreements between Alnylam and us regarding the development of our microRNA technology may cause significant delays and other impediments in the development of this technology, which could negatively affect the value of the technology and our investment in Regulus.

Regulus is our joint venture with Alnylam focused on the discovery, development, and commercialization of microRNA. As part of this joint venture, we exclusively licensed to Regulus our intellectual property rights covering microRNA. Regulus is operated as an independent company and governed by a managing board comprised of an equal number of directors appointed by each of Alnylam and us. Regulus researches and develops microRNA projects and programs pursuant to an operating plan that is approved by the managing board. Any disagreements between Alnylam and us regarding a development decision or any other decision submitted to Regulus' managing board may cause significant delays in the development and commercialization of our microRNA technology and could negatively affect the value of our investment in Regulus.

We depend on third parties in the conduct of our clinical trials for our drugs 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 drugs and expect to continue to do so in the future. For example, Medpace is the primary clinical research organization for clinical trials for mipomersen. 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 or a termination of our relationship with these third parties could delay or prevent the development, approval and commercialization of our drugs, including mipomersen.

Risks Associated With Our Ibis Biosciences Business

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 continued research and development to achieve our business objectives. For Ibis to be commercially successful, we must convince potential customers that our Ibis T5000 Biosensor System is an attractive alternative to existing methods of identifying pathogens. 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 may not recover our investment in this technology and our Ibis T5000 Biosensor System business could fail to meet our business and financial objectives.

If we fail to sell the Ibis T5000 Biosensor System to a minimum customer base, our ability to generate revenues from sales of assay kits will be negatively affected.

A key element of our business plan for Ibis calls for us to deploy the Ibis T5000 Biosensor System to a broad customer base. If we cannot create a broad installed base of our Ibis T5000 Biosensor System, our ability to sell assay kits, the consumables used to operate the system, may be significantly and adversely affected. Even if we successfully achieve broad installation of the Ibis T5000 Biosensor System, customers may not perform as many analyses as we anticipate, which may affect the assumptions underlying our business plan for Ibis and lead to lower-than-expected revenues.

We will depend on Bruker Daltonics to manufacture the Ibis T5000 Biosensor System and any failure of Bruker Daltonics to fulfill its obligations could harm or delay our commercialization efforts.

In July 2006, we entered into a strategic alliance with Bruker Daltonics to manufacture and distribute the Ibis T5000 Biosensor System. Bruker Daltonics 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 Daltonics will have exclusive rights to sell Ibis T5000 Biosensor Systems and Ibis assay kits for various government applications, and non-exclusive rights to sell to customers for all other applications except diagnostics. As such, we rely heavily on Bruker Daltonics to successfully manufacture, distribute and service our Ibis T5000 Biosensor System, but do not control many aspects of Bruker Daltonics activities. We believe Bruker Daltonics has failed to satisfactorily perform its obligations under the agreement. We have initiated the formal dispute resolution process under the agreement so that we can improve the manufacture, service and sales of our Ibis T5000 Biosensor Systems. If Bruker Daltonics continues to fail to carry out its obligations under our alliance, its failure could harm or delay the commercialization of our Ibis T5000 Biosensor System.

Ibis' strategic alliance with Abbott may restrict the way Ibis conducts its business and may not result in the ultimate sale of Ibis to Abbott.

On January 30, 2008, we and Ibis entered into a Strategic Alliance Master Agreement with Abbott. As part of this transaction, we granted Abbott an exclusive option to acquire from us all remaining Ibis capital stock. Under the exclusive option, we and Ibis must obtain Abbott's consent before we or Ibis can take specified actions, such as amending Ibis' certificate of incorporation, redeeming, repurchasing or paying dividends on Ibis capital stock, issuing any Ibis capital stock, entering into a transaction for the merger, consolidation or sale of Ibis, creating any Ibis indebtedness, or entering into any Ibis strategic alliance, joint venture or joint marketing agreement. These consent requirements may restrict the way Ibis conducts its business and may discourage others from trying to collaborate with or buy our Ibis subsidiary. Abbott's decision to exercise the exclusive option is at its sole discretion. As a result, we cannot guarantee that Abbott will exercise its option to acquire the remaining Ibis capital stock. If Abbott does not exercise its option to acquire the remaining Ibis capital stock, we will not realize the full benefit of the strategic alliance and we may need to secure a new partner to further expand the Ibis business into the areas of hospital associated infection control and infectious disease diagnostics.

We depend on government contracts for most of Ibis' 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.

Historically, most of Ibis' revenues were from the sale of services and products to the U.S. 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, even if we have fully performed our obligations. Since a large portion of Ibis' government contracts are milestone based, if Ibis fails to meet a specific milestone within the specified delivery date, our government partner may be more likely to reduce or cancel its contract with Ibis. Our revenues and cash flows 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, 2008 and 2007, we derived approximately 14% and 64%, respectively, of our revenue from agencies of the U.S. government. 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 U.S. government contracts and subcontracts are simultaneously delayed or canceled for budgetary, performance or other reasons.

If U.S. 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 U.S. 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 we do business and, in some instances, impose added costs on our businesses. Any changes in applicable laws could adversely affect the financial performance of Ibis. 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. For example, Bruker Daltonics supplies the mass spectrometer we use as part of our Ibis T5000 Biosensor System.

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

The market for products such as Ibis' 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. To remain competitive, we will need to continually improve Ibis' products so that, when compared to alternatives, its products:

- provide faster results;
- are cost-effective;
- deliver more accurate information;
- are more user friendly; and
- support a broad range of applications.

If Ibis cannot keep its products ahead of its competitors in these areas, Ibis' revenues will suffer and we may not meet our commercialization goals.

Many of Ibis' competitors have, and in the future these and other competitors may have, significantly greater financial, marketing, sales, manufacturing, distribution and technological resources than Ibis. 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 Ibis. In addition, Ibis' 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 Ibis.

Improvements in preventing major diseases could reduce the need for our Ibis T5000 Biosensor System and related assay kits, which in turn could reduce our revenues.

We expect to derive a significant portion of our Ibis revenues from the sale of assay 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 assay 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 assay kits, which could reduce our revenues.

Our plans to commercialize the Ibis T5000 Biosensor System internationally are subject to additional risks that could negatively affect our operating results.

Our success will depend in part on our ability and Bruker Daltonics' ability to market and sell the Ibis T5000 Biosensor System and assay kits in foreign markets. Expanding our international operations could impose substantial burdens on our resources, divert management's attention from domestic operations and otherwise adversely affect our business. Furthermore, international operations are subject to several inherent risks including:

- trade protective measures and import or export licensing requirements or other restrictive actions by U.S. and foreign governments could prevent or limit our international sales;
- reduced protection of intellectual property rights;
- changes in foreign currency exchange rates;
- changes in specific country's or region's political or economic conditions; and
- changes in tax laws.

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 or at all, 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, we may not successfully obtain approval.

Ibis' business plan assumes a significant portion of its revenues will come from Ibis T5000 Biosensor Systems and assay kits for *in vitro* diagnostic purposes, whose uses are regulated by the FDA and comparable agencies of other countries. In addition, customers may wish to utilize the Ibis T5000 Biosensor System and assay kits in manners that require additional regulatory approval. To access these markets, Ibis' products may require either premarket approval or 510(k) clearance from the FDA and other regulatory agencies 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, and 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 clinical trials do not necessarily predict final results, and acceptable results in early clinical trials may not be repeated in later clinical 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. If our Ibis T5000 Biosensor System is considered a medical device, after gaining market approval from the FDA, our Ibis T5000 Biosensor System may be subject to ongoing FDA requirements governing the labeling, packaging, storage, advertising, promotion, recordkeeping and reporting of safety and other post-market information.

If we become subject to product liability claims relating to Ibis, we may be required to pay damages that exceed our insurance coverage.

Any product liability claim brought against us with respect to Ibis, with or without merit, could result in the increase of our product liability insurance rates or the inability to secure coverage in the future. Expenses incurred by our insurance provider in defending these claims will reduce funds available to settle claims or pay adverse judgments. In addition, we could be liable for amounts in excess of policy limits, which would have to be paid out of our cash reserves, and our cash reserves may be insufficient to satisfy the liability. Finally, even a meritless or unsuccessful product liability claim could harm Ibis' reputation in the industry, lead to significant legal fees, and could result in the diversion of management's attention from managing our business.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference contain forward-looking statements regarding our business, the therapeutic and commercial potential of our technologies and products in development, and the financial position of Isis Pharmaceuticals, Inc., our Ibis Biosciences subsidiary and our Regulus Therapeutics joint venture. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' goals or projections. 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 systems to identify infectious organisms that are effective and commercially attractive, and in the endeavor of building a business around such products. Isis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. 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. As a result, you are cautioned not to rely on these forward-looking statements.

PRICE RANGE OF COMMON STOCK

Our common stock is traded publicly through the Nasdaq Global Market under the symbol "ISIS." The following table presents quarterly information on the price range of our common stock. This information indicates the high and low sale prices reported by the Nasdaq Global Market. These prices do not include retail markups, markdowns or commissions.

	HIGH	LOW
2008		
First Quarter	$ 20.15	$ 12.70
Second Quarter (through May 15, 2008)	$ 17.77	$ 10.91
2007		
First Quarter	$ 12.59	$ 8.30
Second Quarter	$ 10.58	$ 8.79
Third Quarter	$ 15.52	$ 9.52
Fourth Quarter	$ 18.23	$ 14.88
2006		
First Quarter	$ 9.34	$ 5.09
Second Quarter	$ 9.50	$ 5.76
Third Quarter	$ 7.89	$ 5.57
Fourth Quarter	$ 14.00	$ 7.06

As of May 15, 2008, there were approximately 879 stockholders of record of our common stock.

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.

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 Global Market listing fees and fees and expenses of our counsel and our accountants.

SELLING STOCKHOLDERS

The shares of common stock covered hereby consist of 5,000,000 shares of our common stock we issued to the selling stockholder as part of a private placement in January 2008.

In connection with the registration rights we granted to the selling stockholder, we filed with the Securities and Exchange Commission, or SEC, 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 Global 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 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 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 SEC and is based upon information provided by each respective selling stockholder, Schedules 13D and 13G and other public documents filed with the SEC. The percentages of shares owned after the offering are based on 95,388,877 shares of our common stock outstanding as of May 15, 2008.

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 stockholder 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 May 15, 2008.

Selling stockholders (1)	Shares of Common Stock Beneficially Owned Prior to Offering	Shares of Common Stock Offered	Shares Of Common Stock Beneficially Owned After The Offering
Genzyme Corporation 500 Kendall Street Cambridge, MA 02142	5,000,000	5,000,000	—

(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.

Relationship with Selling Stockholders

In January 2008, we announced a major strategic alliance with Genzyme Corporation in which Genzyme will develop and commercialize mipomersen. Mipomersen is our lipid lowering drug targeting apoB-100. As part of the strategic relationship, Genzyme has exclusively licensed mipomersen and will also have preferred access to our future drugs for CNS and certain rare diseases. Genzyme paid us $150 million to purchase five million shares of our common stock for $30 per share and upon the completion of the license agreement Genzyme will also pay us a $175 million upfront license fee for mipomersen. In addition to this initial $325 million, we also have the potential to receive development, regulatory and commercialization milestone payments. Under the agreement, we will also share profits with Genzyme on a pre-negotiated basis.

Genzyme has agreed that it will not sell its Isis stock until the earlier of 4 years from the date of our mipomersen license agreement, the first commercial sale of mipomersen and the termination of the our mipomersen license agreement. Thereafter, Genzyme will be subject to monthly limits on the number of shares it can sell. In addition, Genzyme has agreed that until the earlier of the 10 year anniversary of the mipomersen license agreement and the date Genzyme holds less than 2% of our issued and outstanding common stock, Genzyme will not acquire any additional shares of our common stock without our consent.

Except as described above, 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, 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, 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;

- 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.

We are not aware of any plans, arrangements, or understandings between the selling stockholder and any underwriter, broker-dealer or agent regarding the sale of the shares of our common stock.

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.

We cannot assure you that the selling stockholder will sell any or all of the shares of our common stock offered pursuant to this prospectus. In addition, we cannot assure you that the selling stockholder will not transfer the shares by means not described in this prospectus. The selling stockholder, for example, 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 stockholder 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, underwriter, or agent 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 stockholder to keep the registration statement of which this prospectus constitutes a part effective until the date all the shares held by the selling stockholder may be sold during any 90 period under Rule 144 of the Securities Act and any contractual agreements with Isis.

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 March 31, 2008;
- Series C Junior Participating Preferred Stock, 1,000,000 shares of which were authorized and none of which was issued and outstanding at March 31, 2008; and
- Common stock, 200,000,000 shares of which were authorized and 92,994,635 shares of which were outstanding as of March 31, 2008.

Preferred Stock

Blank Check Preferred Stock

We are authorized to issue up to 15,000,000 shares of "blank check" Preferred Stock. 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.

Series B Convertible Exchangeable 5% Preferred Stock

As of March 31, 2008, there were no Series B Convertible Exchangeable 5% Preferred Stock shares outstanding. We do not intend to issue any of the remaining authorized but unissued Series B Convertible Exchangeable 5% Preferred Stock.

Series C Junior Participating Preferred Stock

Series C Junior Participating Preferred Stock is designated but not outstanding. In December 2000, we adopted a Preferred Share Purchase Rights Plan ("Plan"). The Plan provides for a dividend distribution of one preferred stock purchase right ("Right") for each outstanding share of Isis common stock, par value $0.001 per share, held of record at the close of business on January 10, 2001, and on each subsequently issued share of Isis common stock. The Rights are not currently exercisable. Under certain conditions involving an acquisition or proposed acquisition by any person or group holding 20% or more of our common stock, the Rights permit the holders (except the 20 percent holder) to purchase one one-hundredth of a share of Series C Junior Preferred Stock, par value $0.001 per share ("Preferred Shares"), at a price of $85 per one one-hundredth of a Preferred Share, subject to adjustment. Each one one-hundredth of a share of Preferred Shares has designations and powers, preferences and rights, and qualifications, limitations and restrictions that make its value approximately equal to the value of a share of common stock. Certain conditions allow the Isis Board of Directors to redeem the Rights in whole, but not in part, at a price of $0.001 per Right.

Common Stock

At March 31, 2008, we had 200,000,000 shares of common stock authorized, of which 92,994,635 were issued and outstanding, respectively. As of March 31, 2008, total common shares reserved for future issuance upon the exercise or conversion of outstanding securities that are exercisable or convertible into shares of our common stock was approximately 26,923,679.

Equity Compensation Plans

1989 Stock Option Plan

In June 1989 and as amended, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that provides for the issuance of non-qualified and incentive stock options for the purchase of up to 13,200,000 shares of common stock to our employees, directors, and consultants. The term of the plan is scheduled to end in January 2014. The 1989 Plan does not allow us to grant stock bonuses or restricted stock awards and prohibits us from repricing any options outstanding under the plan unless our stockholders approve the repricing. Options granted after December 31, 1995 vest over a four-year period, with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted before January 1, 1996 generally vested over a five-year period. Options granted after May 26, 2004 have a term of seven years while options granted before May 26, 2004 have a term of ten years. At March 31, 2008, a total of 6,649,011 options were outstanding, options to purchase 3,263,727 shares were exercisable, and 42,683 shares were available for future grant under the 1989 plan.

2000 Broad Based Equity Incentive Plan

In January 2000, we adopted the 2000 Broad-Based Equity Incentive Plan (the "2000 Plan"), which provides for the issuance of non-qualified stock options for the purchase of up to 3,990,000 shares of common stock to our employees, directors, and consultants. In May 2002, our Board of Directors increased the 2000 Plan by 2,000,000 shares, authorizing up to 5,990,000 shares of common stock under the 2000 Plan for issuance to

employees, directors, and consultants. Typically options expire 10 years from the date of grant. Options granted under this plan generally vest over a four-year period, with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted under this plan pursuant to the April 2003 stock option exchange program became fully vested on January 1, 2007 and will expire on December 31, 2008. At March 31, 2008, a total of 2,871,488 options were outstanding, 1,432,624 shares were exercisable, and 804,588 shares were available for future grant under the 2000 Plan.

Change of Control Under 1989 Plan and 2000 Plan

With respect to both the 1989 Plan and 2000 Plan, in the event of:

- a sale, lease or other disposition of all or substantially all of our assets;
- a merger or consolidation in which we are not the surviving corporation; or
- reverse merger in which we are the surviving corporation but the shares of common stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise,

then any surviving corporation or acquiring corporation will assume any stock awards outstanding under the 2000 Plan and the 1989 Plan or will substitute similar stock awards (including an award to acquire the same consideration paid to the shareholders in the transaction for those outstanding under the 2000 Plan and the 1989 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar stock awards for those outstanding under the 2000 Plan and the 1989 Plan, then with respect to stock awards held by participants whose continuous service has not terminated, such stock awards automatically vest in full and the stock awards will terminate if not exercised (if applicable) at or prior to such event. With respect to any other stock awards outstanding under the 2000 Plan and the 1989 Plan, such stock awards will terminate if not exercised (if applicable) prior to such event. As of March 31, 2008, options to purchase approximately 1,967 shares granted under the 2000 Plan would have been accelerated in full if a transaction described above occurred at such date, even if the surviving corporation assumes such award. Beginning on May 16, 2007, new stock awards issued under the 2000 Plan will not be accelerated in full if a transaction described above occurs.

2002 Non-Employee Directors' Stock Option Plan

In September 2001, our Board of Directors adopted, and the stockholders subsequently approved, an amendment and restatement of the 1992 Non-Employee Directors' Stock Option Plan, which provides for the issuance of non-qualified stock options to our non-employee directors. The name of the resulting new plan is the 2002 Non-Employee Directors' Stock Option Plan (the "2002 plan"). In May 2006, after receiving approval from our stockholders, we amended our 2002 Plan to increase the total number of shares reserved for issuance under the 2002 Plan from 600,000 shares to 850,000 shares. Options under this plan expire 10 years from the date of grant. Options granted become exercisable in four equal annual installments beginning one year after the date of grant. At March 31, 2008, a total of 438,000 options were outstanding, 256,750 of the shares issued under this plan were exercisable and 303,000 shares were available for future grant.

Employee Stock Purchase Plan

In 2000, our Board of Directors adopted, and the stockholders subsequently approved, the 2000 Employee Stock Purchase Plan ("ESPP") and we reserved 200,000 shares of common stock for issuance thereunder. In each of the subsequent years, an additional 200,000 shares of common stock were reserved for the ESPP, resulting in a total of 1.8 million shares authorized in the plan as of March 31, 2008. The plan permits full-time employees to purchase common stock through payroll deductions (which cannot exceed 10% of each employee's compensation) at the lower of 85% of fair market value at the beginning of the purchase period or the end of each six-month purchase period.

Warrants

In August 2005, we raised $51.0 million in a private placement of 12 million shares of our common stock. Investors in the financing also received five-year warrants to purchase an aggregate of approximately 3 million shares of common stock at an exercise price of $5.2395 per share. The warrants issued in the private placement provide a call right in our favor to the extent that the price per share of our common stock exceeds $14.41 per share for twenty (20) consecutive trading days, subject to certain circumstances. We cannot exercise this call right prior to August 2008. As of March 31, 2008, approximately 2,274,998 shares of common stock under the warrants remained outstanding.

In April 2006, we granted the members of Symphony GenIsis Holdings LLC warrants to purchase 4.25 million shares of common stock at an exercise price of $8.93 per share. These warrants expire on April 7, 2011 and can be settled with unregistered shares of our common stock. As of March 31, 2008, approximately 3,579,066 shares of common stock under the warrants remained outstanding. If we enter into a merger or acquisition in which the surviving or resulting "parent" entity is an entity other than us, then the holders of these warrants may exchange the warrants for a new warrant exercisable in return for shares of common stock of the surviving entity as follows:

- if the terms of such merger or acquisition provide for consideration that consists solely of stock of the surviving entity, and the surviving entity has a class of common stock traded on a major national exchange or foreign exchange ("Public Common Shares"), then any replacement warrants issued to the holders will be solely for such publicly traded common shares, at an exchange ratio reflecting the stock consideration paid at the time of such change in control; or

- if the terms of such merger or acquisition shall provide for consideration that consists of cash or a combination of cash and Public Common Shares of the surviving entity, then any replacement warrants issued to the holders will be solely for Public Common Shares of the surviving entity, at an exchange ratio reflecting the total consideration paid by the surviving entity at the time of such change in control, as if the total consideration (including cash) for each share of our common stock was instead paid only in Public Common Shares of the surviving entity at the time of such change of control; or

- if the surviving entity is a private corporation, closely held company or other entity that does not have a class of Public Common Shares, then the holders of the warrants may elect, to surrender all outstanding warrants to us in consideration of a cash payment for each share of our common stock subject to purchase under the warrants in an amount equal to 40% of the per share cash consideration to be received by a holder of one share of our common stock to be tendered in the merger or acquisition, subject to an aggregate limit of $22,000,000.

In connection with the issuance of the warrants, we entered into a registration rights agreement with Symphony GenIsis Holdings LLC. Pursuant to the registration rights agreement, we filed a registration statement with the SEC covering the shares of common stock issuable upon exercise of the warrants. We are required to use commercially reasonable efforts to maintain the effectiveness of the registration statement over the term of the warrant.

Convertible Subordinated Notes

In January 2007, we completed a $162.5 million convertible debt offering, which raised proceeds of approximately $157.1 million, net of $5.4 million in issuance costs. We include the issuance costs in our balance sheet and are amortizing these costs to interest expense over the life of the debt. The $162.5 million convertible subordinated notes mature in 2027 and bear interest at $2^5/_8$%, which is payable semi-annually. The $2^5/_8$% notes are convertible, at the option of the note holders, into approximately 11.1 million shares of our common stock at a conversion price of $14.63 per share. At March 31, 2008, the principal on the notes was $162.5 million.

We will be able to redeem the $2^5/_8$% notes at a redemption price equal to 100.75% of the principal amount between February 15, 2012 and February 14, 2013; 100.375% of the principal amount between February 15, 2013 and February 14, 2014; and 100% of the principal amount thereafter. Holders of the $2^5/_8$% notes also are able to require us to repurchase these notes on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100% of the principal amount of the $2^5/_8$% notes being repurchased plus accrued interest and unpaid interest.

LEGAL MATTERS

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

EXPERTS

Ernst and 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, 2007, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, 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 the SEC's public reference room at 100 F Street, N.E., Washington, D.C. 20549. You may obtain information on the operation of the public reference room by calling the SEC at 1-800-SEC-0330. The SEC also maintains an Internet site that contains reports, proxy statements and other information regarding registrants (including us) that file electronically with the SEC (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 the registration statement of which this prospectus is a part 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 the offering is completed.

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, 2007;

- our Quarterly Report on Form 10-Q for the quarter ended March 31, 2008;

- our Current Reports on Form 8-K, filed with the SEC on January 8, 2008 (as amended on February 7, 2008), January 31, 2008, April 17, 2008 and April 25, 2008;

- our Notice of Annual Meeting and Proxy Statement for the 2008 Annual Meeting of Stockholders, filed with the SEC on April 18, 2008;

- the description of our Preferred Share Purchase Rights Plan contained in our Current Report 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 contained 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 and our Certificate of Amendment of our Restated Certificate of Incorporation filed with our Quarterly Report on Form 10-Q for the period ended March 31, 2006.

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 our principal executive offices at 1896 Rutherford Road, Carlsbad, California 92008, telephone number (760) 931-9200.

Any statement contained in a document incorporated or deemed to be incorporated by reference in this prospectus will be deemed modified, superseded or replaced for purposes of this prospectus to the extent that a statement contained in this prospectus or in any subsequently filed document that also is or is deemed to be incorporated by reference in this prospectus modifies, supersedes or replaces such statement. Any statement so modified, superceded or replaced, will not be deemed, except as so modified, superceded or replaced, to constitute a part of this prospectus.

Part II

INFORMATION NOT REQUIRED IN PROSPECTUS

Item 14. Other Expenses of Issuance and Distribution

The following table sets forth all expenses payable by the Registrant in connection with the resales of the securities being registered. All the amounts shown are estimates except for the registration fee. None of the expenses listed below will be paid by the selling security holders.

SEC registration fee	$	2,545
Legal fees and expenses	$	10,000
Accounting fees and expenses	$	7,500
Miscellaneous	$	4,955
Total	$	25,000

Item 15. Indemnification of Officers and Directors

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

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

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

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

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

Item 16. Exhibits

Exhibit Number		Description of Document
1.1	–	Stock Purchase Agreement, dated January 7, 2008, among the Registrant and Genzyme Corporation.(8)
4.1	–	Amended and Restated Certificate of Incorporation filed June 19, 1991.(1)

4.2	–	Certificate of Amendment to Restated Certificate of Incorporation filed May 3, 2006.(2)
4.3	–	Bylaws.(3)
4.4	–	Certificate of Designation of the Series C Junior Participating Preferred Stock.(4)
4.5	–	Specimen Common Stock Certificate.(1)
4.6	–	Form of Right Certificate.(4)
4.7	–	Form of Warrant dated August 23, 2005.(5)
4.8	–	Identure, dated January 23, 2007, between the Registrant and Wells Fargo Bank, N.A., a national banking association, as trustee, including Form of 2 5/8% Convertible Subordinated Note due 2027. (6)
4.9	–	Registration Rights Agreement, dated January 23, 2007, among the Registrant and the Initial Purchasers identified therein. (6)
4.10	–	Registration Rights Agreement between the Registrant and Symphony GenIsis Holdings LLC dated April 7, 2006 (with certain confidential information deleted). (7)
4.11	–	Form of Warrant dated April 7, 2006 issued to Symphony GenIsis Holdings LLC. (7)
4.12		Stock Purchase Agreement, dated January 7, 2008, among the Registrant and Genzyme Corporation.(8)
5.1	–	Opinion of Grantland E. Bryce
23.1	–	Consent of Independent Registered Public Accounting Firm.
23.2	–	Consent of Grantland E. Bryce. Reference is made to Exhibit 5.1
24.1	–	Power of Attorney. Reference is made to page II-5

(1) Filed as an exhibit to the Registrant's Registration Statement on Form S-1 (No. 33-39640) or amendments thereto and incorporated herein by reference.
(2) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2006.
(3) Filed as an exhibit to the Registrant's report on Form 10-Q/A for the quarter ended June 30, 2001 and incorporated herein by reference.
(4) Filed as an exhibit to Registrant's Report on Form 8-K dated December 8, 2000 and incorporated herein by reference.
(5) Filed as an exhibit to Registrant's Current Report on Form 8-K dated August 22, 2005 and incorporated herein by reference.
(6) Filed as an exhibit to the Registrant's Current Report on Form 8-K, filed with the SEC on May 5, 2006 and incorporated herein by reference.
(7) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2006.
(8) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2008.

Item 17. Undertakings

(a) The undersigned registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement

(i) to include any prospectus required by Section 10(a)(3) of the Securities Act of 1933;

(ii) to reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. However any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20 percent change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective registration statement;

(iii) to include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement;

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

(2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment will be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time will be deemed to be the initial bona fide offering thereof.

(3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

(4) That, for the purpose of determining liability under the Securities Act of 1933 to any purchaser:

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

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

prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date.

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

(i) Any preliminary prospectus or prospectus of the undersigned registrant relating to the offering required to be filed pursuant to Rule 424;

(ii) Any free writing prospectus relating to the offering prepared by or on behalf of the undersigned registrant or used or referred to by the undersigned registrant;

(iii) The portion of any other free writing prospectus relating to the offering containing material information about the undersigned registrant or its securities provided by or on behalf of the undersigned registrant; and

(iv) Any other communication that is an offer in the offering made by the undersigned registrant to the purchaser.

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

Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers, and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer, or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer, or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

The undersigned registrant hereby undertakes that:

(1) For purposes of determining any liability under the Securities Act of 1933, the information omitted from the form of prospectus filed as part of this registration statement in reliance upon Rule 430A and contained in a form of prospectus filed by the registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act will be deemed to be part of this registration statement as of the time it was declared effective.

(2) For purposes of determining any liability under the Securities Act of 1933, each post-effective amendment that contains a form of prospectus will be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time will be deemed to be the initial bona fide offering thereof.

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

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this Registration Statement to be signed on its behalf by the undersigned thereunto duly authorized, in the city of Carlsbad, County of San Diego, State of California, on the 20th day of May, 2008.

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall
B. Lynne Parshall
Chief Operating Officer and Chief Financial Officer

POWER OF ATTORNEY

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

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

Signatures	Title	Date
/s/ Stanley T. Crooke Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board and Chief Executive Officer (Principal executive officer)	May 20, 2008

/s/ B. Lynne Parshall B. Lynne Parshall	Chief Operating Officer, Chief Financial Officer and Director (Principal financial and accounting officer)	May 20, 2008
/s/ Spencer R. Berthelsen Spencer R. Berthelsen	Director	May 20, 2008
/s/ Richard D. DiMarchi Richard D. DiMarchi	Director	May 20, 2008
/s/ Joseph Klein Joseph Klein	Director	May 20, 2008
/s/ Frederick T. Muto Frederick T. Muto	Director	May 20, 2008
/s/ John C. Reed John C. Reed	Director	May 20, 2008
/s/ Joseph H. Wender Joseph H. Wender	Director	May 20, 2008

EXHIBIT INDEX

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EXHIBIT 5.1

May 21, 2008

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

Ladies and Gentlemen:

You have requested my opinion with respect to certain matters in connection with the filing by Isis Pharmaceuticals, Inc. (the "Company") of a Registration Statement on Form S-3 (the "Registration Statement") with the Securities and Exchange Commission, covering the registration of 5,000,000 shares of the Company's Common Stock (the "Shares") for resale on behalf of a certain selling stockholder.

In connection with this opinion, I have examined and relied upon the Registration Statement, the Company's Certificate of Incorporation and Bylaws, as amended, and the originals or copies certified to my satisfaction, of such records, documents, certificates, memoranda and other instruments as in my judgment are necessary or appropriate to enable me to render the opinion expressed below.

On the basis of the foregoing, and in reliance thereon, I am of the opinion that the Shares are validly issued, fully paid and nonassessable.

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

Very truly yours,

/s/ Grantland E. Bryce

Grantland E. Bryce
Vice President, Legal and
General Counsel

EXHIBIT 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the reference to our firm under the caption "Experts" in the Registration Statement (Form S-3) to be filed on or about May 21, 2008, and related Prospectus of Isis Pharmaceuticals, Inc. for the registration of 5,000,000 shares of its common stock and to the incorporation by reference therein of our reports dated March 11, 2008, with respect to the consolidated financial statements of Isis Pharmaceuticals, Inc. and the effectiveness of internal control over financial reporting of Isis Pharmaceuticals, Inc. included in its Annual Report (Form 10-K) for the year ended December 31, 2007, filed with the Securities and Exchange Commission.

/s/ ERNST & YOUNG LLP

San Diego, California
May 19, 2008