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Filed Pursuant to Rule 424(b)(5)
Registration Statement No. 333-188407

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	Amount to be Registered(1)	Proposed Maximum Offering Per Price Unit	Proposed Maximum Aggregate Offering Price(1)	Amount of Registration Fee(2)
Common Stock, par value $0.001 per share	10,350,000	$19.00	$196,650,000.00	$26,823.06

(1) Assumes exercise in full of the underwriters' option to purchase up to 1,350,000 additional shares of Common Stock.

(2) Calculated in accordance with Rule 457(r) under the Securities Act of 1933, as amended. This "Calculation of Registration Fee" table shall be deemed to update the "Calculation of Registration Fee" table in the registrant's Registration Statement on Form S-3 (File No. 333-188407) in accordance with Rules 456(b) and 457(r) under the Securities Act of 1933, as amended.

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Prospectus Supplement to Prospectus dated May 7, 2013.

9,000,000 Shares

Isis Pharmaceuticals, Inc.

Common Stock

Isis Pharmaceuticals, Inc. is offering 9,000,000 shares to be sold in the offering.

The common stock is listed on The NASDAQ Global Select Market under the symbol "ISIS". The last reported sale price of our common stock on May 8, 2013 was $19.65 per share.

See "Risk Factors" beginning on page S-9 of this prospectus supplement to read about factors you should consider before buying shares of our common stock.

Neither the Securities and Exchange Commission nor any other regulatory body has approved or disapproved of these securities or passed upon the accuracy or adequacy of this prospectus supplement or the accompanying prospectus. Any representation to the contrary is a criminal offense.

	Per Share	Total
Initial price to public	$ 19.00	$ 171,000,000
Underwriting discount	$ 0.95	$ 8,550,000
Proceeds, before expenses, to Isis	$ 18.05	$ 162,450,000

To the extent that the underwriters sell more than 9,000,000 shares of common stock, the underwriters have the option to purchase up to an additional 1,350,000 shares from Isis at the initial price to public less the underwriting discount.

The underwriters expect to deliver the shares against payment in New York, New York on May 14, 2013.

Goldman, Sachs & Co. **J.P. Morgan**

Stifel

BMO Capital Markets **Cowen and Company** **Needham & Company**

Prospectus Supplement dated May 8, 2013.

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Prospectus Supplement

Prospectus

ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the terms of this offering of common stock and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus. The second part, the accompanying prospectus dated May 7, 2013, including the documents incorporated by reference therein, provides more general information. To the extent the information contained in this prospectus supplement, on the one hand, differs or varies from the information contained in the accompanying prospectus or in any document incorporated by reference that was filed with the Securities and Exchange Commission, or SEC, before the date of this prospectus supplement, on the other hand, you should rely on the information in this prospectus supplement. Generally, when we refer to the prospectus, we are referring to this prospectus supplement and the accompanying prospectus combined.

Neither we nor the underwriters have authorized anyone to provide you with information different from that contained in or incorporated by reference into this prospectus supplement, the accompanying prospectus or in any free writing prospectus that we have authorized for use in connection with this offering. We take no responsibility for, and can provide no assurance as to the reliability of, any information that others may give you. This document may only be used where it is legal to sell these securities. You should assume that the information appearing in this prospectus supplement, the accompanying prospectus, the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, and in any free writing prospectus that we have authorized for use in connection with this offering, is accurate only as of the date of those respective documents. Our business, financial condition, results of operations and prospects may have changed since that date.

Unless we indicate otherwise, references in this prospectus supplement to "Isis," "Company," "we," "our," and "us" refer to Isis Pharmaceuticals, Inc. and its consolidated subsidiaries.

This prospectus supplement and the accompanying prospectus, including the information incorporated by reference into this prospectus supplement and the accompanying prospectus, and any free writing prospectus that we have authorized for use in connection with this offering include trademarks, service marks and trade names owned by us or others. Isis Pharmaceuticals® is a registered trademark of Isis Pharmaceuticals, Inc. KYNAMRO™ is a trademark of Genzyme Corporation. Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc. All other trademarks, service marks and trade names included or incorporated by reference in this prospectus supplement and the accompanying prospectus and any free-writing prospectus that we have authorized for use in connection with this offering are the property of their respective owners.

FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the documents incorporated herein and therein by reference and any free writing prospectus that we have authorized for use in connection with this offering 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. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of KYNAMRO and the use of proceeds from this offering, is a forward-looking statement and should be considered an at-risk statement. 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, and in the endeavor of building a business around such drugs. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors known by us at the times the statements are made. As a result, you are cautioned not to rely on these forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in the section entitled "Risk Factors," as well as in our filings with the SEC.

We claim the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995 for all forward-looking statements.

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights selected information appearing elsewhere or incorporated by reference in this prospectus supplement and the accompanying prospectu and any free-writing prospectus that we have authorized for use in connection with this offering and may not contain all of the information that is important to you. This prospectus supplement and the accompanying prospectus include information about the shares we are offering as well as information regarding our business an financial data. You should read this prospectus supplement and the accompanying prospectus, including information incorporated by reference, and any free writing prospectus that we have authorized for use in connection with this offering, in their entirety. Investors should carefully consider the information set forth under "Risk Factors" in this prospectus supplement.

Isis Pharmaceuticals, Inc.

We are the leading company in antisense drug discovery and development, exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Antisense technology provides a direct route from genomics to drugs. Our strategy is to do what we do best—to discover and develop unique antisense drugs. The efficiency and broad applicability of our drug discovery platform allows us to discover and develop antisense drugs to treat a wide range of diseases, including cardiovascular, severe and rare, neurologic and metabolic diseases and cancer.

Our partnering strategy provides us the flexibility to license each of our drugs at the optimal time to maximize the near- and long-term value for each drug. In thi way, we can expand our and our partners' pipelines with antisense drugs that we design to address significant medical needs while remaining small and focused. We form traditional partnering alliances that enable us to discover and conduct early development of new drugs, outlicense our drugs to partners, such as Genzyme, and build a broad base of license fees, milestone payments and royalty income. We also form preferred partner transactions that provide us with a vested partner, such as AstraZeneca, Biogen Idec, GSK, and Roche, early in the development of a drug. Typically, the drugs we partner early in development are in therapeutic areas of high risk, like severe neurological diseases, or in areas where Phase 2 results would likely not provide a significant increase in value, like cancer. These preferred partner transactions allow us to develop select drugs that could have significant commercial potential with a knowledgeable and committed partner with the financial resource to fund later-stage clinical studies and expertise to complement our own development efforts. As in our other partnerships, we benefit financially from upfront payments, milestone payments, licensing fees and royalties. The cash generated from our partnering strategy provides us the financial flexibility to develop our drugs to potentially more valuable stages of clinical development, thereby increasing our share of our drugs' commercial revenues.

We also work with a consortium of smaller companies that can exploit our drugs and technologies. We call these smaller companies our satellite companies. We benefit from the disease-specific expertise of our satellite company partners, who are advancing drugs in our pipeline in areas that are outside of our core focus, or we maintain our broad RNA technology leadership through collaborations with satellite companies. All of these different types of relationships are part of our unique business model and create near and long-term shareholder value.

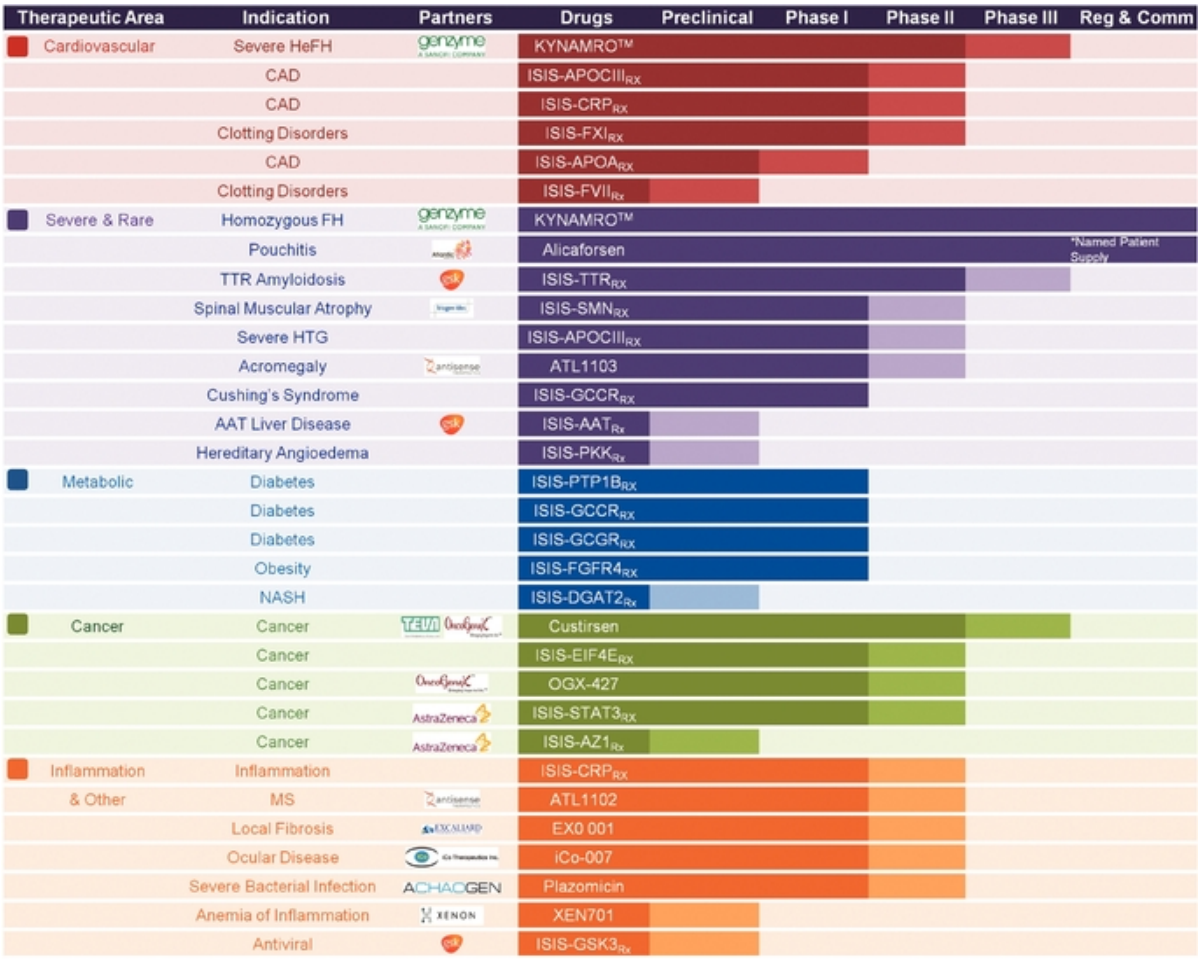
KYNAMRO™ (mipomersen sodium) injection

Our flagship product, KYNAMRO, is on the market in the United States as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol, or LDL-C, apolipoprotein B, total cholesterol and non-high density lipoprotein-cholesterol in patients with homozygous familial hypercholesterolemia, or HoFH. Patients with HoFH are at high cardiovascular risk and cannot reduce their LDL-C sufficiently with currently available lipid-lowering medications. In 2008, w licensed KYNAMRO to Genzyme Corporation, a Sanofi Company,and Genzyme has been responsible for the development and regulatory approvals and is responsib for commercialization of KYNAMRO on a

worldwide basis. In January 2013, the U.S. Food and Drug Administration, or FDA, approved Genzyme's New Drug Application for KYNAMRO. KYNAMRO is now available in the United States under a Risk Evaluation and Mitigation Strategy, or REMS, which is intended to monitor the incidence of adverse events and patie safety in compliance with FDA approval. Genzyme has substantial expertise in successfully marketing drugs in the United States for severe and rare diseases, and plans to leverage its infrastructure to commercialize KYNAMRO. In March 2013, following Genzyme's request for re-examination, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency, or EMA, confirmed its previous position and maintained a negative opinion regarding the marketing authorization application, or MAA, for KYNAMRO as a treatment for patients with homozygous and severe heterozygous familial hypercholesterolemia. Genzyme may consider reapplying for regulatory approval in Europe based on the results from the ongoing Phase III FOCUS FH study of KYNAMRO in patients with familial hypercholesterolemia.

Pipeline

Our pipeline goes well beyond KYNAMRO. We have a pipeline of 28 drugs in clinical and preclinical development that represents the potential for significant commercial opportunities in many therapeutic areas. We believe that several of the drugs in our pipeline could reach the market by 2017.



In addition, several of the drugs in our pipeline, including ISIS-APOCIII$_{Rx}$, ISIS-CRP$_{Rx}$ and ISIS-FXI$_{Rx}$, are advancing through Phase 2 clinical programs and could represent significant near and mid-term licensing opportunities.

Select examples of pipeline programs include:

- ISIS-APOCIII$_{Rx}$ targets the ApoC-III protein responsible for transporting triglycerides in the bloodstream. We are pursuing a staged development plan for ISIS-APOCIII$_{Rx}$ designed to shorten the time to bring this drug to patients at high-risk of cardiovascular disease and pancreatitis. ISIS-APOCIII$_{Rx}$ is currently in Phase 2 development for patients with high triglycerides and we plan to initiate Phase 3 studies for patients with severely elevated triglyceride levels (>880 mg/dL). These are the patients with the highest unmet medical need who have severely high triglyceride levels despite currently available therapies and are at the greatest risk. We estimate that there are over 200,000 patients with triglyceride levels above 880 mg/dL on maximum tolerated triglyceride lowering therapy in the United States and in Europe.

- ISIS-SMN$_{Rx}$ is an antisense drug we designed to treat spinal muscular atrophy, or SMA, a severe motor-neuron disease that is the leading genetic caus of infant mortality. We estimate that SMA affects approximately 30,000 to 35,000 patients in the United States, Europe and Japan. SMA is caused by a loss of, or defect in, the survival motor neuron 1, or SMN1, gene leading to a decrease in the protein, survival motor neuron, or SMN. SMN is critical to the health and survival of nerve cells in the spinal cord that are responsible for neuro-muscular growth and function. The severity of SMA correlates with the amount of SMN protein. Infants with Type I SMA, the most severe life-threatening form, produce very little SMN protein and have a shortened life expectancy. Children with Type II and Type III SMA have greater amounts of SMN protein and have less severe, but still life-altering, forms of SMA. In March 2013, we reported the results of an open-label study conducted in a small number of patients. In this study ISIS-SMN$_{Rx}$ was well tolerated in children with SMA, and improvements in the Hammersmith Functional Motor Scale-Expanded, a measure of muscle function, was observed in a number of these children. We are evaluating ISIS-SMN$_{Rx}$ in two multiple-dose, dose-escalation studies in children and infants with SMA. The FDA granted Orphan Drug Designation with Fast Track Status to ISIS-SMN$_{Rx}$ for the treatment of patients with SMA. In January 2012, w and Biogen Idec entered into a preferred partner alliance that provides Biogen Idec an option to develop and commercialize ISIS-SMN$_{Rx}$.

- ISIS-APOA$_{Rx}$ is an antisense drug we designed to reduce apolipoprotein(a) in the liver to offer a direct approach for reducing Lp(a), an independent risk factor for cardiovascular disease. High levels of Lp(a) are associated with an increased risk of atherosclerosis, coronary heart disease, heart attack and stroke. Even patients who can control their LDL-C levels remain at high-risk of cardiovascular events if they have high levels of Lp(a). There is a significant need for a highly specific drug that can lower Lp(a). We plan to develop ISIS-APOA$_{Rx}$ to treat patients with high Lp(a) levels who are at severe risk of experiencing cardiovascular events. We are currently evaluating ISIS-APOA$_{Rx}$ in a Phase 1 study in healthy volunteers.

- ISIS-PKK$_{Rx}$ is an antisense drug designed to prevent hereditary angioedema, or HAE, attacks. ISIS-PKK$_{Rx}$ inhibits the production of prekallikren, or PKK, a protein produced in the liver that plays an important role in the activation of inflammatory mediators associated with acute attacks of HAE. HAE is a rare genetic disease that is characterized by rapid and painful attacks of inflammation in the hands, feet, limbs, face, abdomen, larynx and trachea. We estimate HAE affects approximately 20,000 patients in the United States and Europe and can be fatal if swelling occurs in the larynx. In patients with frequent or severe attacks, doctors may use prophylactic treatment approaches to prevent and reduce the severity of HAE attacks. However,

current prophylactic treatment approaches are very limited and have tolerability issues due to challenging administration requirements leaving patients with few therapeutic options. By inhibiting the production of PKK, ISIS-PKK$_{Rx}$ could be an effective prophylactic approach to preventing HAE attacks.

Recent Developments

On May 7, 2013, we announced results for the first quarter of 2013. Our revenues for the three months ended March 31, 2013 were $43.4 million and our net los for the three months ended March 31, 2013 was $1.7 million. Our revenues were primarily driven by milestone payments we earned from our partners. As of March 31, 2013, we had cash, cash equivalents and short term investments of approximately $371.9 million.

Corporate Information

Our principal executive offices are located at 2855 Gazelle Court, Carlsbad, CA 92010, and our telephone number is (760) 931-9200. We incorporated in California in 1989, and in January 1991 we changed our state of incorporation to Delaware. We maintain a website at www.isispharm.com. The reference to our website does not constitute incorporation by reference into this prospectus supplement of any of the information contained on or accessible through our website.

The Offering

Common stock offered by Isis	9,000,000 shares.
Option to purchase additional shares	We have granted the underwriters an option to purchase up to an additional 1,350,000 shares of our common stock.
Common stock to be outstanding immediately after this offering	111,695,200 shares (or 113,045,200 shares if the underwriters' option to purchase additional shares is exercised in full).
Use of proceeds	Following this offering, we intend to use the net proceeds from this offering to increase our drug development activities, develop selec drugs in our pipeline to later stages of development prior to partnering, and use the remainder of the proceeds for general corporate an working capital purposes.
Risk factors	See "Risk Factors" beginning on page S-9 for a discussion of factors that you should consider before buying shares of our common stock.
NASDAQ Global Select Market symbol	Our common stock is listed on The NASDAQ Global Select Market under the symbol "ISIS".

The number of shares of our common stock to be outstanding immediately after this offering as shown above is based on 102,695,200 shares of common stock issued and outstanding as of March 31, 2013 and excludes as of that date:

- 11,068,845 shares of our common stock issuable upon exercise of outstanding options issued under our equity incentive plans at a weighted average exercise price of $11.44 per share;
- 2,301,153 additional shares of common stock reserved and available for future grants under our equity incentive plans;
- 388,765 shares of our common stock issuable upon the settlement of restricted stock units;
- 317,286 shares of our common stock available for purchase under our Employee Stock Purchase Plan;
- 12,102,531 shares of our common stock issuable upon the conversion of $201.3 million principal amount of our $2^{3}/_{4}$ percent convertible senior notes which mature in 2019, or the 2019 notes, that are outstanding as of March 31, 2013 (assuming that the 2019 notes had been converted as of March 31, 2013 and we elected to settle such conversions solely in shares of our common stock);
- Series B Convertible Exchangeable 5% Preferred Stock, 4,605 shares of which were authorized and none of which was issued and outstanding as of March 31, 2013; and
- Series C Junior Participating Preferred Stock, 1,000,000 shares of which were authorized and none of which was issued and outstanding as of March 31, 2013.

The discussion above also does not reflect the aggregate of 1,176,449 shares of our common stock issued pursuant to the exercise of outstanding options after March 31, 2013 and as of May 1, 2013, issued at a weighted average exercise price of $11.23 per share.

Summary Consolidated Financial Data

The following tables summarize our consolidated financial data. The statement of operations data for the years ended December 31, 2010, 2011 and 2012 are derived from our audited consolidated financial statements for those years which are incorporated by reference in this prospectus supplement. The statement of operations data for the three months ended March 31, 2012 and 2013 and the balance sheet data as of March 31, 2013 are derived from our unaudited consolidated financial statements for those periods which are incorporated by reference in this prospectus supplement. The following data should be read together with the financia statements, the related notes thereto and other financial information included in this prospectus supplement and incorporated herein by reference.

	Years Ended December 31,			Three Months Ended March 31, (Unaudited)	
	2012	2011	2010	2013	2012
	(In thousands, except per share data)				
Consolidated Statements of Operations Data:					
Total revenue	$ 102,049	$ 99,086	$ 108,473	$ 43,360	$ 23,235
Research and development expenses	$ 158,458	$ 157,397	$ 145,160	$ 38,312	$ 38,714
Net loss applicable to common stock	$ (65,478)	$ (84,801)	$ (61,251)	$ (1,672)	$ (23,995)
Basic and diluted net loss per share	$ (0.65)	$ (0.85)	$ (0.62)	$ (0.02)	$ (0.24)
Shares used in computing basic and diluted net loss per share	100,576	99,656	99,143	101,875	100,157

	As of March 31, 2013 (Unaudited)	
	Actual	As Adjusted(2)
	(In thousands)	
Consolidated Balance Sheet Data:		
Cash, cash equivalents and short-term investments	$ 371,911	$ 533,981
Working capital	$ 361,534	$ 523,604
Total assets	$ 552,961	$ 715,031
$2^{3}/_{4}$ percent convertible senior notes(1)	$ 145,533	$ 145,533
Long-term obligations, less current portion	$ 77,226	$ 77,226
Accumulated deficit	$ (908,638)	$ (908,638)
Stockholders' equity(1)	$ 201,091	$ 363,161

(1) Amounts shown reflect the application of Financial Accounting Standards Board ("FASB") Staff Position No. APB 14-1, as codified by Accounting Standards Codification ("ASC") 470-20, which requires issuers to separately account for the liability and equity components of convertible debt instruments that may be settled entirely or partially in cash. As of March 31, 2013, $201.3 million principal amount of the $2^{3}/_{4}$% convertible senior notes remained outstanding.

(2) The as adjusted column reflects the sale by us of 9,000,000 shares of our common stock in this offering at the public offering price of $19.00 per share, after deducting the underwriting discount and estimated offering expenses payable by us.

RISK FACTORS

Investing in our common stock involves a high degree of risk. Before deciding whether to invest in our common stock, you should consider carefully the risk factors described below and discussed in our filings with the SEC which are incorporated by reference in this prospectus supplement and accompanying prospectus in their entirety, together with the other information in this prospectus supplement, the accompanying prospectus, the information and documents incorporated by reference, and any free writing prospectus that we have authorized for use in connection with this offering. If any of these risks actually occur, it may materially harm our business, financial condition, operating results or cash flow. As a result, the market price of our common stock could decline, and you could lose all or part of your investment. Additional risks and uncertainties that are not yet identified or that we think are immaterial may also materially harm our business, operating results and financial condition and could result in a complete loss of your investment.

Risks Associated with our Drug Discovery and Development Business

If the market does not accept KYNAMRO or our other drugs, we are not likely to generate revenues or become consistently profitable.

Even though KYNAMRO is approved for HoFH in the United States, and if any of our other drugs is approved for marketing, our success will depend upon the medical community, patients and third party payors accepting our drugs as medically useful, cost-effective and safe. Even when the FDA or foreign regulatory authorities approve our or our partners' drugs for commercialization, doctors may not use our drugs to treat patients. We and our partners may not successfully commercialize additional drugs.

In particular, even though KYNAMRO is approved for HoFH in the United States it may not be commercially successful.

Additionally, in many of the markets where we may sell our drugs in the future, if we cannot agree with the government regarding the price we can charge for our drugs, then we may not be able to sell our drugs in that market.

The degree of market acceptance for KYNAMRO, and any of our other drugs, depends upon a number of factors, including the:

- receipt and scope of regulatory approvals;
- establishment and demonstration in the medical and patient community of the efficacy and safety of our drugs and their potential advantages over competing products;
- cost and effectiveness of our drugs compared to other available therapies;
- 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/or use any drugs that we may develop. In addition, cost control initiatives by governments or third party payors could decrease the price received for KYNAMRO or our other drugs or increase patient coinsurance to a level that makes KYNAMRO or our other drugs unaffordable.

If our drug discovery and development business fails to compete effectively, our drugs will not contribute significant revenues.

Our competitors engage in all areas of drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. Other companies engage in developing antisense technology. Our competitors may succeed in developing drugs that are:

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

These competitive developments could make our drugs, including KYNAMRO, 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 treat the same diseases our own collaborative programs target. 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, including KYNAMRO.

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 studies 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. Marketing and sales capability is another factor relevant to the competitive position of our drugs, and we will rely on our partners to provide this capability.

Regarding KYNAMRO, some competitors are pursuing a development or commercialization strategy that competes with our strategy for KYNAMRO. Other companies are currently developing products that could compete with KYNAMRO. Products such as microsomal triglyceride transfer protein inhibitors, or MTP inhibitors, and other lipid lowering drugs other companies are developing or commercializing could potentially compete with KYNAMRO. For example, Aegerion received approval from the FDA to market its MTP inhibitor, Juxtapid, as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol, total cholesterol, apolipoprotein B and non-high-density-lipoprotein cholesterol in patients with HoFH. Aegerion has also submitted a marketing authorization application for Juxtapid to the European Medicines Agency seeking approval of Juxtapid as an adjunct to a low fat diet and other lipid-lowering therapies to reduce cholesterol in patients with HoFH. Our revenues and financial position will suffer if KYNAMRO cannot compete effectively in the marketplace.

Following approval, KYNAMRO is, and any of our other drugs could be subject to regulatory limitations.

Following approval of a drug, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of drug products. Even if approved, we or our partners may not obtain the labeling claims necessary or desirable for successfully commercializing our drug products, including KYNAMRO.

The FDA and foreign regulatory authorities have the authority to impose significant restrictions on an approved drug product through the product label and on advertising, promotional and distribution activities. For example:

- KYNAMRO is approved in the United States as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, and non-high density lipoprotein-cholesterol in patients with HoFH;
- the KYNAMRO label contains a Boxed Warning citing a risk of hepatic toxicity; and
- KYNAMRO is available only through a Risk Evaluation and Mitigation Strategy called the KYNAMRO REMS.

In addition, when approved, the FDA or a foreign regulatory authority may condition approval on the performance of post-approval clinical studies or patient monitoring, which could be time consuming and expensive. If the results of such post-marketing studies are not satisfactory, the FDA or a foreign regulatory authority may withdraw marketing authorization or may condition continued marketing on commitments from us or our partners that may be expensive and/or time consuming to fulfill.

If we or others identify side effects after any of our drug products are on the market, or if manufacturing problems occur subsequent to regulatory approval, we or our partners may lose regulatory approval, or we or our partners may need to conduct additional clinical studies and/or change the labeling of our drug products including KYNAMRO.

We depend on our collaboration with Genzyme for the development and commercialization of KYNAMRO.

We have entered into a collaborative arrangement with Genzyme to develop and commercialize KYNAMRO.

We entered into this collaboration primarily to:

- fund some of our development activities for KYNAMRO;
- seek and obtain regulatory approvals for KYNAMRO; and
- successfully commercialize KYNAMRO.

In general, we cannot control the amount and timing of resources that Genzyme devotes to our collaboration. If Genzyme fails to further develop and commercialize KYNAMRO, or if Genzyme's efforts are not effective, our business may be negatively affected. We are relying on Genzyme to obtain additional marketing approvals for and successfully commercialize KYNAMRO. Our collaboration with Genzyme may not continue or result in the successful commercialization of KYNAMRO. Genzyme can terminate our collaboration at any time. If Genzyme stopped developing or commercializing KYNAMRO, we would have to seek additional sources for funding and may have to delay or reduce our development and commercialization programs for KYNAMRO. If Genzyme does not successfully commercialize KYNAMRO, we may receive limited or no revenues for KYNAMRO. In addition, Sanofi's acquisition of Genzyme could disrupt Genzyme or distract it from performing its obligations under our collaboration.

If Genzyme cannot manufacture finished drug product for KYNAMRO or the post-launch supply of the active drug substance for KYNAMRO, KYNAMRO may not achieve or maintain commercial success.

We rely on Genzyme to manufacture the finished drug product for KYNAMRO, including the initial commercial launch supply. In addition, Genzyme is responsible for the long term supply of both KYNAMRO drug substance and finished drug product. Genzyme may not be able to reliably manufacture KYNAMRO drug substance and drug product to support the long term commercialization of KYNAMRO. If Genzyme cannot reliably manufacture KYNAMRO drug substance and drug

product, KYNAMRO may not achieve or maintain commercial success, which will harm our ability to generate revenue.

If we or our partners fail to obtain regulatory approval for our drugs, including additional approvals for KYNAMRO, we or our partners cannot sell them in the applicable markets.

We cannot guarantee that any of our drugs will be safe and effective, or will be approved for commercialization. In addition, we cannot guarantee that KYNAMRO will be approved outside the United States or for additional indications. We and our partners must conduct time-consuming, extensive and costly clinical studies to show the safety and efficacy of each of our drugs, including KYNAMRO, before a drug can be approved for sale. We must conduct these studies in compliance with FDA regulations and with comparable regulations in other countries.

We and our partners may not obtain necessary regulatory approvals on a timely basis, if at all, for any of our drugs. It is possible that other regulatory agencies will not approve KYNAMRO for marketing. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our drugs, including KYNAMRO, the agency will not approve the specific drug or will require additional studies, which can be time consuming and expensive and which will delay or harm commercialization of the drug. For example, in March 2013 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency maintained a negative opinion for Genzyme's marketing authorization application for KYNAMRO as a treatment for patients with HoFH.

Failure to receive marketing approval for our drugs, including KYNAMRO outside the United States, or delays in these approvals could prevent or delay commercial introduction of the drug, and, as a result, could negatively impact our ability to generate revenue from product sales.

If the results of clinical testing indicate that any of our drugs 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 drugs are a relatively new approach to therapeutics. If we cannot demonstrate that our drugs are safe and effective for human use, we may need to abandon one or more of our drug development programs. There are ongoing clinical studies for KYNAMRO and sales to patients, adverse events from which could negatively impact our pending or planned marketing approval applications and commercialization of KYNAMRO.

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

Even if our drugs are successful in preclinical and human clinical studies, the drugs may not be successful in late-stage clinical studies.

Successful results in preclinical or initial human clinical studies, including the Phase 3 results for KYNAMRO and the Phase 2 results for some of our other drugs in development, may not predict the results of subsequent clinical studies, including subsequent studies of KYNAMRO. There are a number of factors that could cause a clinical study to fail or be delayed, including:

- the clinical study 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 study due to adverse side effects of a drug on subjects in the trial;
- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical studies;
- enrollment in our clinical studies may be slower than we anticipate;
- the cost of our clinical studies may be greater than we anticipate; and
- the supply or quality of our drugs or other materials necessary to conduct our clinical studies may be insufficient, inadequate or delayed.

Any failure or delay in the clinical studies, including any further studies under the development program for KYNAMRO, could reduce the commercial potential or viability of our drugs.

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

To successfully commercialize any of our drugs, we or our partner would need 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 drug costs. We may not be able to manufacture our drugs 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 and similar regulations in foreign countries, which the applicable regulatory authorities enforce through facilities inspection programs. We and our contract manufacturers may not comply or maintain compliance with Good Manufacturing Practices, or similar foreign regulations. Non-compliance could significantly delay or prevent receipt of marketing approval for our drugs, including KYNAMRO, or result in enforcement action after approval that could limit the commercial success of our drugs, including KYNAMRO.

We depend on third parties to conduct our clinical studies 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 to conduct our clinical studies for our drugs and expect to continue to do so in the future. For example, Medpace is the primary clinical research organization for the ongoing clinical studies for KYNAMRO. We rely heavily on these parties for successful execution of our clinical studies, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that these third parties conduct each of our clinical studies in accordance with the general investigational plan and approved protocols for the study. Third parties may not complete activities on schedule, or may not conduct our clinical studies 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 any expanded product label for KYNAMRO.

Risks Associated with our Businesses as a Whole

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

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of March 31, 2013, we had an accumulated deficit of approximately $908.6 million and stockholders' equity of approximately $201.1 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from research grants and the sale or licensing of our patents, as well as interest income. We may 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 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 drug 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 unpartnered drugs. However, we may not be able to negotiate favorable collaborative arrangements for these drug programs. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drugs could suffer.

Our corporate partners are developing and/or funding many of the drugs in our development pipeline, including AstraZeneca, ATL, Atlantic Pharmaceuticals, Biogen Idec, iCo, Genzyme, GSK, OncoGenex, Pfizer and Teva Pharmaceutical Industries Ltd. If any of these pharmaceutical companies stops developing and/or funding these drugs, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these drugs on our own.

Our collaborators can terminate their relationships with us under certain circumstances, many of which are outside of our control. In the past, based on the disappointing results of Phase 3 clinical studies, we had a partner discontinue its investment in one of our drugs.

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 drug development programs.

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

- conduct clinical studies;
- seek and obtain regulatory approvals; and
- manufacture, market and sell our drugs.

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

For example, a collaborator such as AstraZeneca, Biogen Idec, Genzyme, or GSK, could determine that it is in its financial interest to:

- pursue alternative technologies or develop alternative products that may be competitive with the drug 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.

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, including KYNAMRO.

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 study, 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 our investors' expectations, including milestones for additional approvals or sales expectations of KYNAMRO, the price of our securities would likely decrease.

For example, in March 2013 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency maintained a negative opinion for Genzyme's marketing authorization application for KYNAMRO as a treatment for patients with HoFH.

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

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

From time to time we have to defend our intellectual property rights. In the event of an intellectual property dispute, we sometimes need to litigate to defend our rights or assert them against others. Disputes can 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 September 2011 we filed a patent infringement lawsuit against Santaris Pharma A/S and Santaris Pharma A/S Corp. in the United States District Court of the Southern District of California. This lawsuit may be costly and may not be resolved in our favor.

If a third party claims that our drugs 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 patent applications held by

others that relate to our business. This is especially true since patent applications in the United States are filed confidentially for the first 18 months. 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.

Many of our drugs are undergoing clinical studies or are in the early stages of research and development. All of our drug programs will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and/or commitment of significant additional resources prior to their successful commercialization. As of March 31, 2013, we had cash, cash equivalents and short-term investments equal to $371.9 million. If we do not meet our goals to commercialize KYNAMRO or our other drugs, 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:

- additional marketing approvals and successful commercial launch of KYNAMRO;
- 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 studies;
- 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; 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 the 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 terminated 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 or drugs.

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 studies may make it more challenging to recruit and retain qualified scientific personnel.

We are exposed to potential product liability claims, and insurance against these claims may not be available to us at a reasonable rate in the future or at all.

Our business exposes us to potential product liability risks that are inherent in the testing, manufacturing, marketing and sale of therapeutic products, including potential product liability claims related to KYNAMRO. We have clinical study insurance coverage and commercial product liability insurance coverage. However, this insurance coverage may not be adequate to cover claims against us, or be available to us at an acceptable cost, if at all. Regardless of their merit or eventual outcome, products liability claims may result in decreased demand for our drug products, injury to our reputation, withdrawal of clinical study volunteers and loss of revenues. Thus, whether or not we are insured, a product liability claim or product recall may result in losses that could be material.

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. We store these materials and various wastes resulting from their use 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 liability could exceed our resources. Although we carry insurance in amounts and types 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 the coverage or coverage limits of our insurance policies may not be adequate. If our losses exceed our insurance coverage, our financial condition would be adversely affected.

We depend on Regulus for development of our microRNA technology.

Regulus is a company that we and Alnylam established to focus on discovering, developing, and commercializing microRNA therapeutics. We exclusively licensed to Regulus our intellectual property rights covering microRNA technology. Regulus operates as an independent company and Regulus and its employees are ultimately responsible for researching and developing our microRNA technology. If Regulus is not successful, the value of our microRNA technology would be harmed and we would lose part or all of our investment in Regulus. In addition, Regulus' directors, executive management team, and strategic partners, including Alnylam, Isis, AstraZeneca, GSK, Biogen Idec and Sanofi have agreed that until October 4, 2013, subject to specified exceptions, not to offer, sell, contract to sell, pledge or otherwise dispose of, directly or indirectly, any shares of Regulus' common stock or securities convertible into or exchangeable or exercisable for any shares of Regulus' common stock.

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

We manufacture our research and clinical supplies in a manufacturing facility located in Carlsbad, California. The facilities and the equipment we use to research, develop and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Our facilities may be harmed by natural or man-made disasters, including, without limitation, earthquakes, floods, fires and acts of terrorism; and if our facilities 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.

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 may issue approximately 12.1 million shares of our common stock upon conversion of our convertible senior 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 continue to incur additional expenses and divert our management's time to comply with these regulations. 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, or PCAOB, or The NASDAQ Global Market. Any such action could adversely affect our financial results and the market price of our common stock.

The SEC and other regulators have continued to adopt new rules and regulations and make additional changes to existing regulations that require our compliance. On July 21, 2010, the Dodd-Frank Wall Street Reform and Protection Act, or the Dodd-Frank Act, was enacted. There are significant corporate governance and executive compensation-related provisions in the Dodd-Frank Act that require the SEC to adopt, or where the SEC has adopted, additional rules and regulations in these areas such as "say on pay" and proxy access. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business.

Negative conditions in the global credit markets and financial services and other industries may adversely affect our business.

The global credit markets, the financial services industry, the U.S. capital markets, and the U.S. economy as a whole have been experiencing a period of substantial turmoil and uncertainty characterized by unprecedented intervention by the U.S. federal government and the failure, bankruptcy, or sale of various financial and other institutions. The impact of these events on our business and the severity of the economic crisis are uncertain. It is possible that the crisis in the global credit markets, the U.S. capital markets, the financial services industry and the U.S. economy may adversely affect our business, vendors and prospects as well as our liquidity and financial condition.

More specifically, our insurance carriers and insurance policies covering all aspects of our business may become financially unstable or may not be sufficient to cover any or all of our losses and may not continue to be available to us on acceptable terms, or at all.

Risks Associated with This Offering and Our Common Stock

Our management will have broad discretion over the use of proceeds from this offering, and we may use the proceeds in ways that may not generate a favorable return for us or improve our operating results.

Our management has significant flexibility in applying the net proceeds that we receive from this offering. Following this offering, we intend to use the net proceeds from this offering to increase our drug development activities, develop select drugs in our pipeline to later stages of development prior to partnering, and use the remainder of the proceeds for general corporate and working capital purposes. Because the net proceeds are not required to be allocated to any specific investment or transaction, you cannot determine in advance the value or propriety of our management's application of the proceeds on our behalf. In addition, the net proceeds from this offering may not generate a favorable return for us or improve our operating results.

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. From January 1, 2012 through May 8, 2013, the market price of our common stock ranged from $7.02 to $22.90 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical study 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.

Investors in this offering will experience immediate and substantial dilution.

The offering price of our common stock will be substantially higher than the net tangible book value per share of our existing capital stock. As a result, purchasers of our common stock in this offering will incur immediate and substantial dilution of $15.98 in net tangible book value per share of common stock after giving effect to the sale of 9,000,000 shares being offered in this offering at the public offering price of $19.00 per share. Purchasers of our common stock will experience additional dilution upon the exercise of outstanding stock options.

In addition, our outstanding 2019 notes are convertible, at the option of the holder, at or prior to maturity into cash, shares of our common stock or a combination of both, at our election. If any or all conversions of the 2019 notes are settled in shares of our common stock, stockholders will experience immediate dilution and our common stock price may be subject to downward pressure.

See "Dilution" on page S-24 for a more detailed discussion of the dilution investors will incur in this offering.

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 $66^{2}/3$ percent of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any

holder of 15 percent 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 have in the past, and may in the future, implement 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. 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.

The provisions of our 2019 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.

In addition, our collaboration agreement with Genzyme regarding KYNAMRO provides that if we are acquired, Genzyme may elect to purchase all of our rights to receive payments under the KYNAMRO collaboration agreement for a purchase price to be mutually agreed to by us and Genzyme, or, if we cannot agree, a fair market value price determined by an independent investment banking firm. This provision may make it more difficult or complicated for us to enter into an acquisition agreement with a potential acquirer.

These provisions, as well as Delaware law, including Section 203 of the Delaware General Corporation 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.

We have never paid dividends on our capital stock, and we do not anticipate paying any cash dividends in the foreseeable future.

We have never declared or paid any dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance our operations and do not anticipate paying any cash dividends on our capital stock in the foreseeable future.

USE OF PROCEEDS

We estimate that the net proceeds from the sale of the 9,000,000 shares of common stock that we are offering will be approximately $162.1 million, or approximately $186.4 million if the underwriters exercise in full their option to purchase up to 1,350,000 additional shares of common stock, after deducting the underwriting discount and estimated offering expenses payable by us. We intend to use the net proceeds from this offering to increase our drug development activities, develop select drugs in our pipeline to later stages of development prior to partnering, and use the remainder of the proceeds for general corporate and working capital purposes. Pending the application of the net proceeds, we intend to invest the net proceeds in investment-grade, interest-bearing securities.

PRICE RANGE OF OUR COMMON STOCK

Our common stock is traded publicly through The NASDAQ Global Select 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 Select Market. These prices do not include retail markups, markdowns or commissions.

Year Ended December 31, 2011		
First quarter	$ 10.45	$ 8.52
Second quarter	$ 9.49	$ 8.25
Third quarter	$ 9.36	$ 6.55
Fourth quarter	$ 8.67	$ 6.25
Year Ended December 31, 2012		
First quarter	$ 9.28	$ 7.08
Second quarter	$ 12.00	$ 7.02
Third quarter	$ 15.61	$ 11.45
Fourth quarter	$ 14.36	$ 7.56
Year Ending December 31, 2013		
First quarter	$ 19.53	$ 10.36
Second quarter (through May 8, 2013)	$ 22.90	$ 15.92

The reported last sale price of our common stock on The NASDAQ Global Select Market on May 8, 2013 was $19.65 per share. As of March 31, 2013, we had 771 stockholders of record. In addition, we believe that a significant number of beneficial owners of our common stock hold their shares in street name.

We have never declared or paid any dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance our operations and do not anticipate paying any cash dividends on our capital stock in the foreseeable future. Any future determination related to dividend policy will be made at the discretion of our board of directors.

CAPITALIZATION

The following table sets forth our cash and cash equivalents, and short-term investments and capitalization as of March 31, 2013:

- on an actual basis; and
- on an as adjusted basis to give effect to the issuance of 9,000,000 shares of our common stock in this offering at the public offering price of $19.00 per share, after deducting the underwriting discount and estimated offering expenses payable by us (but excluding the underwriters' option to purchase additional shares).

The following information should be read in conjunction with our consolidated financial statements and related notes incorporated by reference in this prospectus supplement. For more details on how you can obtain our SEC reports and other information, you should read the section of this prospectus supplement entitled "Where You Can Find Additional Information."

	As of March 31, 2013 (Unaudited)	
	Actual	As Adjusted
	(In thousands)	
Cash, cash equivalents and short term investments(1)	$ 371,911	$ 533,981
Long-term debt:		
$2^{3}/_{4}$ percent convertible senior notes due 2019	145,533	145,533
Long-term obligations, less current portion	77,226	77,226
Total long-term debt	$ 222,759	$ 222,759
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized; 102,695,200 shares issued and outstanding actual and 111,695,200 as adjusted(1)	103	112
Additional paid-in capital	1,091,842	1,253,903
Accumulated other comprehensive income	17,784	17,784
Accumulated deficit	(908,638)	(908,638)
Total stockholders' equity	201,091	363,161
Total capitalization	$ 423,850	$ 585,920

(1) Amounts shown reflect the application of ASC 470-20. As of March 31, 2013, $201.3 million principal amount of the $2^{3}/_{4}$ percent convertible senior notes due 2019 remained outstanding.

The foregoing table excludes as of March 31, 2013:

- 11,068,845 shares of our common stock issuable upon exercise of outstanding options issued under our equity incentive plans at a weighted average exercise price of $11.44 per share;
- 2,301,153 additional shares of common stock reserved and available for future grants under our equity incentive plans;
- 388,765 shares of our common stock issuable upon the settlement of restricted stock units;
- 317,286 shares of our common stock available for purchase under our Employee Stock Purchase Plan;
- 12,102,531 shares of our common stock issuable upon the conversion of $201.3 million principal amount of our 2019 notes, that are outstanding as of March 31, 2013 (assuming that the 2019

notes had been converted as of March 31, 2013 and we elected to settle such conversions solely in shares of our common stock);

- Series B Convertible Exchangeable 5% Preferred Stock, 4,605 shares of which were authorized and none of which was issued and outstanding as of March 31, 2013; and

- Series C Junior Participating Preferred Stock, 1,000,000 shares of which were authorized and none of which was issued and outstanding as of March 31, 2013.

The discussion above also does not reflect the aggregate of 1,176,449 shares of our common stock issued pursuant to the exercise of outstanding options after March 31, 2013 and as of May 1, 2013, issued at a weighted average exercise price of $11.23 per share.

DILUTION

Our net tangible book value as of March 31, 2013 was approximately $175.5 million, or $1.71 per share. Net tangible book value per share is determined by dividing our total tangible assets, less total liabilities, by the number of shares of our common stock outstanding as of March 31, 2013. Dilution with respect to net tangible book value per share represents the difference between the amount per share paid by purchasers of shares of common stock in this public offering and the net tangible book value per share of our common stock immediately after this public offering.

After giving effect to the sale of 9,000,000 shares of our common stock in this offering at the public offering price of $19.00 per share and after deducting the underwriting discount and estimated offering expenses payable by us, our as adjusted net tangible book value as of March 31, 2013 would have been approximately $337.5 million, or $3.02 per share. This represents an immediate increase in net tangible book value of $1.31 per share to existing stockholders and immediate dilution of $15.98 per share to investors purchasing our common stock in this offering at the public offering price. The following table illustrates this dilution on a per share basis:

Public offering price per share		$ 19.00
Net tangible book value per share of as March 31, 2013	$ 1.71	
Increase in net tangible book value per share attributable to investors purchasing our common stock in this offering	1.31	
As adjusted net tangible book value per share after this offering		3.02
Dilution per share to new investors		$ 15.98

If the underwriters exercise in full their option to purchase up to 1,350,000 additional shares of common stock, the as adjusted net tangible book value after this offering would be $3.20 per share, representing an increase in net tangible book value of $1.49 per share to existing stockholders and immediate dilution of $15.80 per share to investors purchasing our common stock in this offering at the public offering price.

The above discussion and table are based on 102,695,200 shares outstanding as of March 31, 2013, and exclude as of that date:

- 11,068,845 shares of our common stock issuable upon exercise of outstanding options issued under our equity incentive plans at a weighted average exercise price of $11.44 per share;
- 2,301,153 additional shares of common stock reserved and available for future grants under our equity incentive plans;
- 388,765 shares of our common stock issuable upon the settlement of restricted stock units;
- 317,286 shares of our common stock available for purchase under our Employee Stock Purchase Plan;
- 12,102,531 shares of our common stock issuable upon the conversion of $201.3 million principal amount of our 2019 notes, that are outstanding as of March 31, 2013 (assuming that the 2019 notes had been converted as of March 31, 2013 and we elected to settle such conversions solely in shares of our common stock);
- Series B Convertible Exchangeable 5% Preferred Stock, 4,605 shares of which were authorized and none of which was issued and outstanding as of March 31, 2013; and
- Series C Junior Participating Preferred Stock, 1,000,000 shares of which were authorized and none of which was issued and outstanding as of March 31, 2013.

To the extent that outstanding options or warrants are exercised or other shares issued, investors purchasing our common stock in this offering may experience further dilution. For example, the discussion above does not reflect the aggregate of 1,176,449 shares of our common stock issued pursuant to the exercise of outstanding options after March 31, 2013 and as of May 1, 2013, issued at a weighted average exercise price of $11.23 per share. In addition, we may choose to raise additional capital due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or equity-linked securities, the issuance of these securities could result in further dilution to our stockholders.

MATERIAL U.S. FEDERAL INCOME TAX CONSIDERATIONS FOR NON-U.S. HOLDERS OF COMMON STOCK

The following is a discussion of the material federal income tax considerations to non-U.S. Holders (as defined below) with respect to their ownership and disposition of our common stock issued pursuant to this offering.

This discussion is based on current provisions of the Internal Revenue Code, U.S. Treasury Regulations promulgated under the Internal Revenue Code, judicial opinions, published positions of the Internal Revenue Service, or IRS, and all other applicable authorities, all of which are subject to change, possibly with retroactive effect. No ruling has been or will be sought from the IRS with respect to the matters discussed below, and there can be no assurance that the IRS will not take a contrary position or that any such contrary position would not be sustained by a court. This discussion assumes that the non-U.S. Holder will hold our common stock as a capital asset (generally property held for investment).

This discussion does not address all aspects of U.S. federal income taxation (including alternative minimum and Medicare contribution taxation) or any aspects of estate, state, local, or non-U.S, taxation. It also does not consider any specific facts or circumstances that may apply to particular non-U.S. Holders that may be subject to special treatment under the U.S. federal income tax laws, including, but not limited to:

- U.S. expatriates and certain former citizens or long-term residents of the United States;
- persons subject to the alternative minimum tax;
- persons holding our common stock as part of a hedge, straddle or other risk reduction strategy or as part of a conversion transaction or other integrated investment;
- banks, insurance companies and other financial institutions;
- brokers, dealers or traders in securities;
- "controlled foreign corporations," "passive foreign investment companies" and corporations that accumulate earnings to avoid U.S. federal income tax;
- partnerships or other entities or arrangements treated as partnerships for U.S. federal income tax purposes;
- tax-exempt organizations or governmental organizations;
- persons deemed to sell our common stock under the constructive sale provisions of the Internal Revenue Code;
- persons who hold or receive our common stock pursuant to the exercise of any employee stock option or otherwise as compensation; and
- tax qualified retirement plans.

For purposes of this discussion, the term "non-U.S. Holder" means a beneficial owner of our shares that is not a partnership (or entity or arrangement treated as a partnership for U.S. federal income tax purposes) and is not:

- an individual who is a citizen or resident of the United States;
- a corporation created or organized in the United States or under the laws of the United States or of any state thereof or the District of Columbia;
- an estate, the income of which is subject to U.S. federal income tax regardless of its source; or

- a trust if (1) a U.S. court can exercise primary supervision over the trust's administration and one or more U.S. persons have the authority to control all of the trust's substantial decisions or (2) the trust has a valid election in effect under applicable U.S. Treasury Regulations to be treated as a U.S. person.

If a partnership or any other entity or arrangement taxed as a partnership for U.S. federal income tax purposes is a beneficial owner of our common stock, the treatment of a partner in the partnership will generally depend upon the status of the equity owner of such partnership and the activities of the partnership. Accordingly, partnerships (and entities and arrangements taxed as partnerships) that hold our common stock and owners in such partnerships (or other entities or arrangements taxed as partnerships) are urged to consult their tax advisors regarding the specific U.S. federal income tax consequences to them of acquiring, owning or disposing of our common stock.

PROSPECTIVE INVESTORS ARE URGED TO CONSULT THEIR TAX ADVISORS REGARDING THE PARTICULAR U.S. FEDERAL INCOME TAX CONSEQUENCES TO THEM OF ACQUIRING, OWNING AND DISPOSING OF SHARES OF OUR COMMON STOCK, AS WELL AS THE U.S. FEDERAL, STATE, LOCAL AND NON-U.S. INCOME AND OTHER TAX CONSIDERATIONS OF ACQUIRING, OWNING AND DISPOSING OF SHARES OF COMMON STOCK.

Distributions

We do not anticipate declaring or paying any cash distributions on our common stock in the foreseeable future. However, if we do make distributions on our common stock, those payments will constitute dividends for U.S. tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. To the extent those distributions exceed our current and accumulated earnings and profits, they will constitute a return of capital and will first reduce the recipient's adjusted tax basis in our common stock, but not below zero, and then will be treated as gain from the sale of stock as described below under the heading "Gain on Sale or Other Disposition of Common Stock."

Dividends paid to a non-U.S. Holder will be subject to U.S. federal withholding tax at a rate equal to 30 percent of the gross amount of the dividend, or a lower rate prescribed by an applicable income tax treaty, unless the dividends are effectively connected with a trade or business carried on by the non-U.S. Holder within the United States (and, if required by an applicable income tax treaty, are attributable to a U.S. permanent establishment maintained by the non-U.S. Holder). Under applicable Treasury Regulations, a non-U.S. Holder will be required to satisfy certain certification requirements, generally on IRS Form W-8BEN (or applicable successor form), directly or through an intermediary, in order to claim a reduced rate of withholding under an applicable income tax treaty. If tax is withheld in an amount in excess of the amount prescribed by an applicable income tax treaty, a refund of the excess amount may be obtained by the non-U.S. Holder by timely filing an appropriate claim for refund with the IRS.

Dividends that are effectively connected with such a U.S. trade or business (and, if required by an applicable income tax treaty, are attributable to a U.S. permanent establishment maintained by the recipient) will not be subject to U.S. withholding tax if the non-U.S. Holder files the required forms, generally an IRS Form W-8ECI (or applicable successor form), with the payor of the dividend, but instead will be subject to U.S. federal income tax on a net income basis in the same manner as if the non-U.S. Holder were a resident of the United States. A foreign corporation that receives dividends constituting effectively connected income may, under certain circumstances, be subject to an additional branch profits tax at a rate of 30 percent, or a lower rate prescribed by an applicable income tax treaty, with respect to such effectively connected income.

Gain on Sale or Other Disposition of Common Stock

A non-U.S. Holder will not be subject to U.S. federal income tax on any gain realized upon the sale or other taxable disposition of the non-U.S. Holder's shares of common stock unless:

- the gain is effectively connected with a trade or business carried on by the non-U.S. Holder within the United States (and, if required by an applicable tax treaty, is attributable to a U.S. permanent establishment or a fixed base maintained by the non-U.S. Holder), in which case the non-U.S. Holder generally will be required to pay tax on the net gain derived from the sale under regular graduated U.S. federal income tax rates and, if the non-U.S. Holder is a corporation, the branch profits tax may apply at a 30 percent rate or such lower rate as may be specified by an applicable income tax treaty;

- the non-U.S. Holder is a nonresident alien individual who is present in the United States for 183 days or more in the taxable year of disposition (and is not otherwise treated as a U.S. resident alien for U.S. federal income tax purposes) and certain other conditions are met, in which case the non-U.S. Holder will be required to pay a flat 30 percent tax (or such lower rate as may be specified by an applicable income tax treaty between the United States and such non-U.S. Holder's country of residence) on the net gain derived from the disposition, which tax may be offset by U.S. source capital losses, if any, provided that the non-U.S. Holder has timely filed U.S. federal income tax returns with respect to such losses; or

- our common stock constitutes a U.S. real property interest by reason of our status as a "United States real property holding corporation," or USRPHC, for U.S. federal income tax purposes at any time within the shorter of the five-year period preceding the disposition or the non-U.S. Holder's holding period for our common stock.

We believe that we are not currently and will not become a USRPHC. However, because the determination of whether we are a USRPHC depends on the fair market value of our U.S. real property relative to the fair market value of our other business assets, there can be no assurance that we will not become a USRPHC in the future. Even if we become a USRPHC, however, as long as our common stock is regularly traded on an established securities market, such common stock will be treated as U.S. real property interests only if the non-U.S. Holder actually or constructively held more than five percent of our common stock at any time during the shorter of the five-year period preceding the disposition or the non-U.S. Holder's holding period for our common stock.

Information Reporting and Backup Withholding

We must report annually to the IRS and to each non-U.S. Holder the amount of dividends on our common stock, the name and address of the recipient and the amount, if any, of tax withheld. These information reporting requirements apply even if withholding was not required because the dividends were effectively connected dividends or withholding was reduced by an applicable income tax treaty. Under tax treaties or other agreements, the IRS may make its reports available to tax authorities in the country in which the non-U.S. Holder resides or is established.

Dividend payments made to a non-U.S. Holder that is not an exempt recipient generally will be subject to backup withholding at the then applicable rate (currently 28 percent) unless the non-U.S. Holder certifies as to its foreign status, which certification may be made by providing the Company with an IRS Form W-8BEN or IRS Form W-8ECI, as applicable, and certain other requirements are met. Notwithstanding the foregoing, backup withholding may apply if either we or our paying agent has actual knowledge, or reason to know, that the holder is a U.S. person that is not an exempt recipient.

Proceeds from the sale or other disposition of common stock by a non-U.S. Holder effected by or through a U.S. office of a broker will generally be subject to information reporting and backup withholding, currently at a rate of 28 percent unless the non-U.S. Holder certifies to the payor under

penalties of perjury as to, among other things, its name, address and status as a non-U.S. Holder or otherwise establishes an exemption. Payment of disposition proceeds effected outside the United States by or through a non-U.S. office of a non-U.S. broker generally will not be subject to information reporting or backup withholding if the payment is not received in the United States. Information reporting, but generally not backup withholding, will apply to such a payment if the broker has certain connections with the United States unless the broker has documentary evidence in its records that the beneficial owner thereof is a non-U.S. Holder and specified conditions are met or an exemption is otherwise established.

Backup withholding is not an additional tax. Rather, the amount of tax withheld is applied to the U.S. federal income tax liability of persons subject to backup withholding. If backup withholding results in an overpayment of U.S. federal income taxes, a refund may be obtained, provided the required documents are timely filed with the IRS.

Foreign Accounts

The Internal Revenue Code generally will impose a U.S. federal withholding tax of 30 percent on dividends and the gross proceeds of a disposition of our common stock paid to a "foreign financial institution" (as specifically defined for this purpose) unless such institution enters into an agreement with the U.S. government to, among other things, withhold on certain payments and to collect and provide to the U.S. tax authorities substantial information regarding U.S. account holders of such institution (which includes certain equity and debt holders of such institution, as well as certain account holders that are foreign entities with U.S. owners), or otherwise establishes an exemption. A U.S. federal withholding tax of 30 percent also applies to dividends and the gross proceeds of a disposition of our common stock paid to a non-financial foreign entity unless such entity provides the withholding agent with a certification that it does not have any substantial direct or indirect U.S. owners, provides information regarding direct and indirect U.S. owners of the entity or otherwise establishes an exemption. The withholding provisions described above will generally apply to dividends on our common stock paid on or after January 1, 2014 and with respect to gross proceeds of a sale or other disposition of our common stock on or after January 1, 2017. Under certain circumstances, a non-U.S. Holder might be eligible for refunds or credits of such taxes.

UNDERWRITING

We will enter into an underwriting agreement with Goldman, Sachs & Co. and J.P. Morgan Securities LLC, as representatives of the underwriters listed in the table below. Subject to certain conditions, each underwriter has severally agreed to purchase the number of shares indicated in the following table.

Underwriters	Number of Shares
Goldman, Sachs & Co.	3,060,000
J.P. Morgan Securities LLC	3,060,000
Stifel, Nicolaus & Company, Incorporated	1,080,000
BMO Capital Markets Corp.	720,000
Cowen and Company, LLC	720,000
Needham & Company, LLC	360,000
Total	9,000,000

The underwriters are committed to take and pay for all of the shares being offered, if any are taken, other than the shares covered by the option described below unless and until this option is exercised.

The underwriters have an option to buy up to an additional 1,350,000 shares of common stock from us to cover sales by the underwriters of a greater number of shares than the total number set forth in the table above. They may exercise that option during the 30-day period beginning on the date of this prospectus supplement. If any shares are purchased pursuant to this option, the underwriters will severally purchase shares in approximately the same proportion as set forth in the table above.

The following table shows the per share and total underwriting discounts and commissions to be paid to the underwriters by us. Such amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase additional shares.

	Paid by the Company	
	No Exercise	Full Exercise
Per Share	$ 0.95	$ 0.95
Total	$ 8,550,000.00	$ 9,832,500.00

Shares sold by the underwriters to the public will initially be offered at the public offering price set forth on the cover of this prospectus supplement. Any shares sold by the underwriters to securities dealers may be sold at a discount of up to $0.57 per share from the public offering price. After the initial offering of the shares, the representatives may change the offering price and the other selling terms. The offering of the shares by the underwriters is subject to receipt and acceptance and subject to the underwriters' right to reject any order in whole or in part.

We and our directors and our executive officers have agreed with the underwriters, subject to certain exceptions, not to dispose of or hedge any of our common stock or securities convertible into or exchangeable for shares of common stock during the period from the date of this prospectus supplement continuing through the date 90 days after the date of this prospectus supplement, except with the prior written consent of the representatives. We have also agreed not to file any registration statement or sell common stock pursuant to the registration statement of which the accompanying prospectus forms a part during this 90-day period.

Notwithstanding the above, the underwriters have agreed in the underwriting agreement that the lock-up agreement applicable to us does not apply to (i) the sale of the securities in this offering; (ii) the issuance by us of any shares of our common stock or securities convertible into, or exercisable

or exchangeable for, our common stock pursuant to equity incentive plans existing on the date of the underwriting agreement; (iii) the issuance by us of any shares of our common stock pursuant to the terms of securities convertible, exercisable or exchangeable for our common stock or other substantially similar securities outstanding as of the date hereof; (iv) the filing of any registration statement on Form S-8 or any successor form; and (v) the entry into agreements providing for the issuance of, and the actual issuance of, shares of our common stock or securities convertible into, or exercisable or exchangeable for, our common stock in connection with license agreements, collaboration agreements or joint ventures in the aggregate not to exceed ten percent of our issued and outstanding shares of common stock as of the date hereof, provided that the recipients of such common stock or other securities agree to be bound by the lock-up restrictions otherwise applicable to our directors and executive officers described in the succeeding paragraph.

In addition, notwithstanding the lock-up agreements applicable to our directors and our executive officers, the underwriters have agreed that the lock-up agreements applicable to such directors and executive officers do not apply to (A) transfers of shares of our common stock (i) as a bona fide gift or gifts, (ii) to any trust for the direct or indirect benefit of such director or executive officer or his or her immediate family, provided that any such transfer shall not involve a disposition for value, or (iii) upon death by will or intestacy, provided that in the case of clauses (A)(i) - (A)(iii), the transferee agrees to be bound by the lock-up restrictions and as a result of any such transfer, no public reports, including but not limited to public reports pursuant to Section 16(a) of the Exchange Act are required to be or are voluntarily filed by any such director or executive officer in connection with such transfer during the 90 day lock-up period; (B) transfers of shares of our common stock pursuant to any contract, instruction or plan in effect on the date hereof complying with Rule 10b5-1 under the Exchange Act ("Rule 10b5-1") and of which the underwriters or their counsel have been made aware; (C) entry into a Rule 10b5-1 plan after the date hereof provided that such plan does not provide for the transfer of our common stock during the 90 day lock-up period (other than pursuant to clause (E) below) and no public announcement or filing under the Exchange Act regarding the establishment of such plan shall be required of or voluntarily made during the lock-up period; (D) transfers to us in connection with the repurchase of securities issued pursuant to our equity incentive plans or pursuant to agreements pursuant to which such securities were issued; (E) non-employee director transfers or sales of up to 10,000 shares of our common stock issued to such non-employee directors under stock options that are scheduled to expire on or before June 30, 2013 (or entry into Rule 10b5-1 plans during the 90-day lock-up period solely with respect to such transfers or sales), and (F) transfers to us pursuant to a cashless or net exercise of a security issued pursuant to our equity incentive plans to cover the exercise price or taxes due upon the exercise or vesting of securities. In addition, our non-employee directors may transfer shares of common stock by same-day-sales effectuated through a broker solely to cover the exercise price or taxes due upon the exercise or vesting of a security issued pursuant to our equity incentive plans, so long as any such transfers to cover exercise prices or taxes do not occur within 30 days of the date of their lock-up agreements. The lock-up agreements shall not restrict the receipt, exercise, vesting, forfeiture of, or removal or lapse of restrictions on any shares of our common stock or equity incentive awards pursuant to any equity incentive plan outstanding as of the date hereof, provided that such transaction does not involve the sale or transfers of shares of our common stock other than as provided in this paragraph.

In addition, each of our directors and our executive officers has agreed that, without the prior written consent of the representatives, he or she will not, during the period commencing on the date of his or her lock-up agreement and ending 90 days after the date of this prospectus supplement, make any demand for, or exercise any right with respect to, the registration of any shares of our common stock or any security convertible into or exercisable or exchangeable for shares of our common stock. The representatives, in their sole discretion, may release any of the securities subject to this lock-up agreement at any time without notice.

Our common stock is listed on The NASDAQ Global Select Market under the symbol "ISIS".

In connection with the offering, the underwriters may purchase and sell shares of common stock in the open market. These transactions may include short sales, stabilizing transactions and purchases to cover positions created by short sales. Short sales involve the sale by the underwriters of a greater number of shares than they are required to purchase in the offering, and a short position represents the amount of such sales that have not been covered by subsequent purchases. A "covered short position" is a short position that is not greater than the amount of additional shares for which the underwriters' option described above may be exercised. The underwriters may cover any covered short position by either exercising their option to purchase additional shares or purchasing shares in the open market. In determining the source of shares to cover the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase additional shares pursuant to the option described above. "Naked" short sales are any short sales that create a short position greater than the amount of additional shares for which the option described above may be exercised. The underwriters must cover any such naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in the offering. Stabilizing transactions consist of various bids for or purchases of common stock made by the underwriters in the open market prior to the completion of the offering.

The underwriters may also impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it because the representatives have repurchased shares sold by or for the account of that underwriter in stabilizing or short covering transactions.

Purchases to cover a short position and stabilizing transactions, as well as other purchases by the underwriters for their own accounts, may have the effect of preventing or retarding a decline in the market price of the Company's stock, and together with the imposition of the penalty bid, may stabilize, maintain or otherwise affect the market price of the common stock. As a result, the price of the common stock may be higher than the price that otherwise might exist in the open market. The underwriters are not required to engage in these activities and may end any of these activities at any time. These transactions may be effected on The NASDAQ Global Select Market, in the over-the-counter market or otherwise.

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive (each, a "Relevant Member State") an offer to the public of any shares which are the subject of the offering contemplated by this prospectus supplement (the "shares") may not be made in that Relevant Member State, except that an offer to the public in that Relevant Member State of any shares may be made at any time under the following exemptions under the Prospectus Directive, if they have been implemented in that Relevant Member State:

(a) to any legal entity which is a qualified investor as defined in the Prospectus Directive;

(b) to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representatives for any such offer; or

(c) in any other circumstances falling within Article 3(2) of the Prospectus Directive, provided that no such offer of shares shall result in a requirement for the publication by the Company or any representative of a prospectus pursuant to Article 3 of the Prospectus Directive.

For the purposes of this provision, the expression an "offer to the public" in relation to any shares in any Relevant Member State means the communication in any form and by any means of sufficient

information on the terms of the offer and any shares to be offered so as to enable an investor to decide to purchase any shares, as the same may be varied in that Member State by any measure implementing the Prospectus Directive in that Member State, the expression "Prospectus Directive" means Directive 2003/71/EC (and amendments thereto, including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member State), and includes any relevant implementing measure in the Relevant Member State, and the expression "2010 PD Amending Directive" means Directive 2010/73/EU.

Each underwriter has represented and agreed that:

(a) it has only communicated or caused to be communicated and will only communicate or cause to be communicated an invitation or inducement to engage in investment activity (within the meaning of Section 21 of the FSMA) received by it in connection with the issue or sale of the shares in circumstances in which Section 21(1) of the FSMA does not apply to the Company; and

(b) it has complied and will comply with all applicable provisions of the FSMA with respect to anything done by it in relation to the shares in, from or otherwise involving the United Kingdom.

The shares may not be offered or sold by means of any document other than:

(i) in circumstances which do not constitute an offer to the public within the meaning of the Companies Ordinance (Cap.32, Laws of Hong Kong);

(ii) to "professional investors" within the meaning of the Securities and Futures Ordinance (Cap.571, Laws of Hong Kong) and any rules made thereunder; or

(iii) in other circumstances which do not result in the document being a "prospectus" within the meaning of the Companies Ordinance (Cap.32, Laws of Hong Kong);

and no advertisement, invitation or document relating to the shares may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the laws of Hong Kong) other than with respect to shares which are or are intended to be disposed of only to persons outside Hong Kong or only to "professional investors" within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder.

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than:

(i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore (the "SFA");

(ii) to a relevant person, or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA; or

(iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

Where the shares are subscribed or purchased under Section 275 by a relevant person which is:

(a) a corporation (which is not an accredited investor) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or

(b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary is an accredited investor, shares, debentures and units of shares and debentures of that corporation or the beneficiaries' rights and interest in that trust shall not be transferable for 6 months after that corporation or that trust has acquired the shares under Section 275 except:

(1) to an institutional investor under Section 274 of the SFA or to a relevant person, or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA;

(2) where no consideration is given for the transfer; or

(3) by operation of law.

The securities have not been and will not be registered under the Financial Instruments and Exchange Law of Japan (the Financial Instruments and Exchange Law) and each underwriter has agreed that it will not offer or sell any securities, directly or indirectly, in Japan or to, or for the benefit of, any resident of Japan (which term as used herein means any person resident in Japan, including any corporation or other entity organized under the laws of Japan), or to others for re-offering or resale, directly or indirectly, in Japan or to a resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the Financial Instruments and Exchange Law and any other applicable laws, regulations and ministerial guidelines of Japan.

We estimate that the total expenses of this offering, excluding underwriting discounts and commissions, will be approximately $380,000 and will be payable by us.

We have agreed to indemnify the several underwriters against certain liabilities, including liabilities under the Securities Act of 1933, as amended.

The underwriters and their respective affiliates are full service financial institutions engaged in various activities, which may include sales and trading, commercial and investment banking, advisory, investment management, investment research, principal investment, hedging, market making, brokerage and other financial and non-financial activities and services. Certain of the underwriters and their respective affiliates have provided, and may in the future provide, a variety of these services to the Company and to persons and entities with relationships with the Company, for which they received or will receive customary fees and expenses.

In the ordinary course of their various business activities, the underwriters and their respective affiliates, officers, directors and employees may purchase, sell or hold a broad array of investments and actively trade securities, derivatives, loans, commodities, currencies, credit default swaps and other financial instruments for their own account and for the accounts of their customers, and such investment and trading activities may involve or relate to assets, securities and/or instruments of the Company (directly, as collateral securing other obligations or otherwise) and/or persons and entities with relationships with the Company. The underwriters and their respective affiliates may also communicate independent investment recommendations, market color or trading ideas and/or publish or express independent research views in respect of such assets, securities or instruments and may at any time hold, or recommend to clients that they should acquire, long and/or short positions in such assets, securities and instruments.

LEGAL MATTERS

The validity of the common stock offered by this prospectus supplement and the accompanying prospectus will be passed upon by Patrick R. O'Neill, our Senior Vice President, Legal and General Counsel. Certain legal matters relating to the common stock offered by this prospectus supplement and the accompanying prospectus will be passed upon for us by Cooley LLP, San Diego, California. Davis Polk & Wardwell LLP, Menlo Park, California and Ropes & Gray LLP, Boston, Massachusetts, are counsel for the underwriters in connection with this offering.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2012, and the effectiveness of our internal control over financial reporting as of December 31, 2012, as set forth in their reports, which are incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements and our management's assessment of the effectiveness of internal control over financial reporting as of December 31, 2012 are incorporated by reference in reliance on Ernst & Young LLP's reports, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND ADDITIONAL INFORMATION

This prospectus supplement and the accompanying prospectus are part of the registration statement on Form S-3 we filed with the SEC under the Securities Act of 1933, as amended, and do not contain all the information set forth or incorporated by reference in the registration statement. Whenever a reference is made in this prospectus supplement or the accompanying prospectus to any of our contracts, agreements or other documents, the reference may not be complete and you should refer to the exhibits that are a part of the registration statement or the exhibits to the reports or other documents incorporated by reference in this prospectus supplement and the accompanying prospectus for a copy of such contract, agreement or other document. Because we are subject to the information and reporting requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act, we file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's web site at www.sec.gov. You may also read and copy any document we file 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 SEC's public reference room in Washington, D.C. by calling the SEC at 1-800-SEC-0330.

The registration statement and the documents referred to below under "Incorporation of Certain Documents by Reference" are also available on our corporate website, www.isispharm.com . We have not incorporated by reference into this prospectus supplement the information on or accessible through our website, and you should not consider it to be a part of this prospectus supplement.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" in this prospectus supplement the information that we file with it. This means that we can disclose important information to you in this document by referring you to other filings we have made with the SEC. The information incorporated by reference is considered to be part of this prospectus supplement. The information incorporated by reference in this prospectus supplement is accurate only as of the date of the information on the front cover of the applicable document, or such earlier date as is expressly stated or otherwise apparent with respect to such incorporated information in the applicable document, regardless of the time of delivery of this prospectus supplement or any sale of securities.

This prospectus supplement incorporates by reference the documents listed below, which we have filed with the SEC:

- our Annual Report on Form 10-K for our fiscal year ended December 31, 2012, filed on February 28, 2013;
- our Quarterly Report on Form 10-Q for our quarter ended March 31, 2013, filed on May 7, 2013;
- portions of our Definitive Proxy Statement on Schedule 14A filed on April 26, 2013 incorporated by reference into the Annual Report on Form 10-K for our fiscal year ended December 31, 2012;
- our Current Reports on Form 8-K filed on January 2, 2013, January 30, 2013, February 13, 2013 and April 8, 2013; 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 quarter ended March 31, 2006.

We incorporate by reference any additional documents that we may file with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Exchange Act (other than the portions of those made pursuant to Item 2.02 or Item 7.01 of Form 8-K or other information "furnished" to the SEC) between the date that we initially filed the registration statement to which this prospectus supplement relates and the termination of the offering of the securities. These documents may include periodic reports, like Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q and Current Reports on Form 8-K, as well as Proxy Statements. Any material that we subsequently file with the SEC will automatically update and replace the information previously filed with the SEC.

This prospectus supplement may contain information that updates, modifies or is contrary to information in one or more of the documents incorporated by reference in this prospectus supplement. You should rely only on the information incorporated by reference or provided in this prospectus supplement. We have not authorized anyone else to provide you with different information. You should not assume that the information in this prospectus supplement is accurate as of any date other than the date of this prospectus supplement or the date of the documents incorporated by reference in this prospectus supplement.

We will provide to each person, including any beneficial owner, to whom this prospectus supplement is delivered, upon written or oral request, at no cost, a copy of any and all of the information that is incorporated by reference in this prospectus supplement.

Requests for such documents should be directed to:

Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, California 92010
(760) 931-9200
Attention: General Counsel

In addition, copies of our filings are available through our corporate website at www.isispharm.com as soon as reasonably practicable after we electronically file such material with the SEC.

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PROSPECTUS **May 7, 2013**

Common Stock

We may from time to time offer and sell common stock in amounts, at prices and on terms described in one or more supplements to this prospectus.

This prospectus describes some of the general terms that may apply to an offering of our common stock. The specific terms and any other information relating to a specific offering will be set forth in a post-effective amendment to the registration statement of which this prospectus is a part or in a supplement to this prospectus or may be set forth in one or more documents incorporated by reference in this prospectus.

Our securities may be offered and sold in the same offering or in separate offerings; to or through underwriters, dealers, and agents; or directly to purchasers. The names of any underwriter, dealer or agents involved in the sale of our securities and their compensation will be described in an applicable prospectus supplement. See "Plan of Distribution." You should read this prospectus and the applicable prospectus supplement before you invest in our common stock.

Our common stock is currently traded on The NASDAQ Global Select Market under the symbol "ISIS."

Investing in our common stock involves risks.

See "Risk Factors" on page 3 of this prospectus, in the applicable prospectus supplement and similar headings in documents incorporated by reference herein and therein before investing in our common stock.

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.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or the SEC, using the "shelf" registration process as a "well-known seasoned issuer," as defined in Rule 405 under the Securities Act of 1933, as amended, or the Securities Act. By using a shelf registration statement, we may offer and sell from time to time in one or more offerings the common stock described in this prospectus. No limit exists on the aggregate number of shares of common stock we may sell pursuant to the registration statement.

Neither we nor any underwriters named in any prospectus supplement have authorized anyone to provide you with information different from that contained in or incorporated by reference into this prospectus or any applicable prospectus supplement. We take no responsibility for, and can provide no assurance as to the reliability of, any information that others may give you. This document may only be used where it is legal to sell these securities. You should not assume that the information contained in this prospectus, any prospectus supplement or any free writing prospectus prepared by or on behalf of us to which we have referred you, is accurate as of any date other than their respective dates regardless of the time of delivery or any sale of the common stock. Our business, financial condition, results of operations and prospects may have changed since that date.

This prospectus and the information incorporated herein by reference include trademarks, service marks and trade names owned by us or other companies. All trademarks, service marks and trade names included or incorporated by reference in this prospectus are the property of their respective owners.

We urge you to read carefully both this prospectus and any prospectus supplement accompanying this prospectus, together with the information incorporated herein by reference as described under the heading "Where You Can Find More Information," before deciding whether to invest in any of the securities being offered.

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PROSPECTUS SUMMARY

The following summary does not contain all of the information that may be important to purchasers of our securities. Prospective purchasers of securities should carefully review the detailed information and financial statements, including the notes thereto, appearing elsewhere in or incorporated by reference into this prospectus and any prospectus supplement.

We are exploiting our leadership position in antisense technology to discover and develop novel drugs for our product pipeline and for our partners. Our broad pipeline consists of 28 drugs in various stages of development to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, and cancer. Our partner, Genzyme, is commercializing our lead product, KYNAMRO™, in the United States for the treatment of patients with homozygous familial hypercholesterolemia, or HoFH. Genzyme is also pursuing marketing approval of KYNAMRO in other markets. We maintain a website at www.isispharm.com. The reference to our website does not constitute incorporation by reference into this prospectus of any of the information contained on or accessible through our website.

Our principal executive offices are located at 2855 Gazelle Court, Carlsbad, CA 92010, and our telephone number is (760) 931-9200. We incorporated in California in 1989, and in January 1991 we changed our state of incorporation to Delaware.

In this prospectus, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals, Inc. and its consolidated subsidiaries.

Isis Pharmaceuticals® is a registered trademark of Isis Pharmaceuticals, Inc.

KYNAMRO™ is a trademark of Genzyme Corporation.

RISK FACTORS

Investing in our securities involves risks. Please see the risk factors described under the caption "Risk Factors" in our most recent Annual Report on Form 10-K and in our most recent Quarterly Report on Form 10-Q filed with the SEC, as well as any amendments thereto reflected in subsequent filings with the SEC, which are incorporated by reference in this prospectus and in any accompanying prospectus supplement. Before making an investment decision, you should carefully consider these risks as well as information we include or incorporate by reference in this prospectus and in any accompanying prospectus supplement. The risks and uncertainties we have described are not the only ones that we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our business or operations.

FORWARD-LOOKING STATEMENTS

This prospectus, each prospectus supplement and the documents incorporated herein and therein by reference contain forward-looking statements regarding our business, the therapeutic and commercial potential of our technologies and products in development, and our financial position. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of KYNAMRO, is a forward-looking statement and should be considered an at-risk statement. 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, and in the endeavor of building a business around such drugs. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors known by us at the times the statements are made. As a result, you are cautioned not to rely on these forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in the section entitled "Risk Factors", as well as in our most recent Annual Report on Form 10-K and in our most recent Quarterly Report on Form 10-Q filed with the SEC.

We claim the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995 for all forward-looking statements.

USE OF PROCEEDS

Unless otherwise indicated in an applicable prospectus supplement, we will use the net proceeds from the sale of the securities for general corporate purposes and to fund our capital expenditures and working capital requirements. Pending the application of the net proceeds, we intend to invest the net proceeds in investment-grade, interest-bearing securities.

DESCRIPTION OF CAPITAL STOCK

Our authorized capital stock consists of:

- Series B Convertible Exchangeable 5% Preferred Stock, 4,605 shares of which were authorized and none of which was issued and outstanding as of March 31, 2013;
- Series C Junior Participating Preferred Stock, 1,000,000 shares of which were authorized and none of which was issued and outstanding as of March 31, 2013; and
- Common stock, 200,000,000 shares of which were authorized and 102,695,200 shares of which were outstanding as of March 31, 2013.

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, 2013, 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. Each one one-hundredth of a share of the Series C Preferred Stock 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 our common stock.

Common Stock

As of March 31, 2013, we had 200,000,000 shares of common stock authorized, of which 102,695,200 were issued and outstanding. As of March 31, 2013, 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 23,560,141.

Voting Rights

Holders of our common stock are entitled to one vote per share on all matters to be voted upon by stockholders.

Dividend Rights

Subject to preferences that may apply to shares of preferred stock outstanding at the time, the holders of outstanding shares of common stock are entitled to receive dividends out of assets legally available at the times and in the amounts that our board of directors may determine from time to time.

No Preemptive or Redemption Rights; Right to Receive Liquidation Distributions

Our common stock is not entitled to preemptive rights and is not subject to redemption or sinking fund provisions. Upon our liquidation, dissolution or winding-up, the holders of common stock are entitled to share equally in all of our assets remaining after payment of all liabilities and the liquidation preferences of any outstanding preferred stock.

Classified Board of Directors

Our certificate of incorporation provides for classified terms for the members of our board of directors. The board of directors is divided into three classes. Presently, the board of directors has six members with one class consisting of three directors, one class consisting of two directors, and one class consisting of one director. Each class serves a three-year term.

Size of the Board of Directors; Removal of Directors; Vacancies

Our certificate of incorporation and bylaws authorize our board of directors to fix the number of directors from time to time without stockholder approval. The board of directors is currently comprised of six members. Directors may be removed with cause by a majority of the outstanding shares entitled to vote or without cause upon the approval of at least $66^{2}/_{3}$ percent of the outstanding shares entitled to vote. All vacancies on the board of directors are to be filled by the directors then in office.

Power to Call Special Stockholder Meetings; Stockholder Action by Written Consent; Advance Notice of Stockholder Business and Nominees

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. Only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. In addition, our certificate of incorporation and bylaws require advance notice for nominations for election to our board of directors or for proposing matters that can be acted upon by stockholders at a stockholder meeting.

Amendment of Bylaws

Our board of directors is authorized to adopt, alter or repeal our bylaws, while our bylaws may be adopted, amended or repealed by stockholders only through the approval of at least $66^{2}/_{3}$ percent of the outstanding shares entitled to vote.

Fair Price Provision; Anti-takeover Effects of Delaware Law

Our certificate of incorporation includes a provision that requires at least $66^{2}/_{3}$ percent of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15 percent 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.

In addition, we are subject to Section 203 of the Delaware General Corporation Law (the "DGCL"), which prohibits a Delaware corporation from engaging in any business combination with any

interested stockholder for a period of three years after the date that such stockholder became an interested stockholder, unless:

- the transaction is approved by the board before the date the interested stockholder attained that status;
- upon consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced; or
- on or after the date the business combination is approved by the board and authorized at a meeting of stockholders by at least two-thirds of the outstanding voting stock that is not owned by the interested stockholder.

A "business combination" is defined to include mergers, asset sales and other transactions resulting in financial benefit to a stockholder. In general, an "interested stockholder" is a person who, together with affiliates and associates, owns (or within three years prior to the determination of interested stockholder status, did own) 15% or more of a corporation's voting stock.

The fair price provision and Section 203 of the DGCL could prohibit or delay mergers or other takeover or change in control attempts with respect to us and, accordingly, may discourage attempts to acquire us even though such a transaction may offer our stockholders the opportunity to sell their stock at a price above the prevailing market price.

Limitation of Liability and Indemnification Matters

Our certificate of incorporation and bylaws include provisions to eliminate the personal liability of our directors for monetary damages resulting from breaches of their fiduciary duty to the extent permitted under Delaware law. Delaware law provides that directors of a company will not be personally liable for monetary damages for breach of their fiduciary duty as directors, except for liabilities:

- for any breach of their duty of loyalty to us or our stockholders;
- for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law;
- for unlawful payment of dividend or unlawful stock repurchase or redemption, as provided under Section 174 of the DGCL; or
- for any transaction from which the director derived an improper personal benefit.

In addition, our bylaws provide that we will indemnify our directors and executive officers to the fullest extent not prohibited by Delaware law or any other applicable law, except that we will generally not be required to indemnify a director or executive officer in connection with any proceeding initiated by such director or executive officer. In addition, we have entered into indemnity agreements with each of our executive officers and directors and certain non-executive officers which provide, among other things, that we will indemnify such officer or director, under the circumstances and to the extent provided for therein, for expenses, damages, judgments, fines and settlements he or she may be required to pay in actions or proceedings which he or she is or may be made a party by reason of his or her position as a director, officer or other agent of Isis, and otherwise to the fullest extent permitted under Delaware law and our bylaws.

Equity Incentive Plans

1989 Stock Option Plan

In March 2004, our board of directors adopted, and our stockholders subsequently approved an amendment and restatement of our 1989 Stock Option Plan that provides for the issuance of non-qualified and incentive stock options for the purchase of up to 20,000,000 shares of common stock to our employees, directors, and consultants. In 2012 our board of directors adopted, and our stockholders subsequently approved an amendment to the 1989 Stock Option Plan such that the plan expires in January 2024. 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 generally vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options we granted after May 26, 2004 have a term of seven years while options we granted before May 26, 2004 have a term of ten years. As of March 31, 2013, a total of 8,739,799 options were outstanding under the 1989 Stock Option Plan, of which options to purchase 4,829,078 shares were exercisable, and 321,295 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, as amended, provided for the issuance of non-qualified stock options for the purchase of up to 5,990,000 shares of common stock to our employees, directors, and consultants. Typically options expire seven or ten years from the date of grant. Options granted under this plan generally vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. As of March 31, 2013, a total of 1,839,046 options were outstanding, of which 1,823,793 shares were exercisable, and no shares were available for future grant under the 2000 Plan. The 2000 Plan expired on January 5, 2010, so we may no longer grant new options 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 1989 Plan and the 2000 Plan or will substitute similar stock awards (including an award to acquire the same consideration paid to the stockholders in the transaction for those outstanding under the 1989 Plan and the 2000 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 1989 Plan and the 2000 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.

2011 Equity Incentive Plan

In March 2011, our board of directors adopted, and our stockholders subsequently approved, a stock option plan that provides for the issuance of stock options, stock appreciation rights, restricted

stock awards, restricted stock unit awards, and performance cash awards. The plan provides for the purchase of up to 2,000,000 shares of common stock for issuance to our employees, directors, and consultants. The plan expires in June 2021. The 2011 Plan does not allow us to reduce the exercise price of any outstanding stock options or stock appreciation rights or cancel any outstanding stock options or stock appreciation rights that have an exercise price or strike price greater than the current fair market value of the common stock in exchange for cash or other stock awards unless our stockholders approve such action. Currently we anticipate awarding only options and restricted stock units awards to our employees, directors and consultants. Under the 2011 Plan, stock options generally cannot vest in a period of less than two years and restricted stock unit awards cannot vest in a period of less than three years, subject to certain exceptions. Starting in 2012, we also grant restricted stock unit awards to our employees under the 2011 Plan which vest annually over a four year period. As of March 31, 2013, no options were outstanding or exercisable, 383,765 restricted stock unit awards were outstanding, and 1,577,858 shares were available for future grant under the 2011 Plan. As part of our Proxy Statement for our 2013 Annual Meeting of Stockholders, we included a proposal recommending our stockholders approve an amendment to the 2011 Plan to increase the shares available for issuance under the 2011 Plan to a total of 5,500,000 shares.

Under the 2011 Plan, we may issue a stock award with additional acceleration of vesting and exercisability upon or after a change in control. In the absence of such provisions, no such acceleration will occur. The stock options and restricted stock unit awards we issue to our chief executive officer and chief operating officer will accelerate upon a change of control, as defined in the 2011 Plan.

Corporate Transactions and Change in Control under 2011 Plan

In the event of certain significant corporate transactions, our board of directors has the discretion to take one or more of the following actions with respect to outstanding stock awards under the 2011 Plan:

- arrange for assumption, continuation, or substitution of a stock award by a surviving or acquiring entity (or its parent company);
- arrange for the assignment of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award to the surviving or acquiring corporation (or its parent company);
- accelerate the vesting and exercisability of a stock award followed by the termination of the stock award;
- arrange for the lapse of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award;
- cancel or arrange for the cancellation of a stock award, to the extent not vested or not exercised prior to the effective date of the corporate transaction, in exchange for cash consideration, if any, as the Board, in its sole discretion, may consider appropriate; and
- arrange for the surrender of a stock award in exchange for a payment equal to the excess of (a) the value of the property the holder of the stock award would have received upon the exercise of the stock award, over (b) any exercise price payable by such holder in connection with such exercise.

2002 Non-Employee Directors' Stock Option Plan

In March 2012, our board of directors adopted, and our stockholders subsequently approved, an amendment and restatement of the 2002 Non-Employee Directors' Stock Option Plan (the "2002

Plan"). The 2002 Plan provides for the issuance of stock options and restricted stock unit awards to our non-employee directors for the purchase of up to 1,200,000 shares of our common stock.

Options under this plan expire ten years from the date of grant. Options granted become exercisable, and restricted stock unit awards vest in four equal annual installments beginning one year after the date of grant. As of March 31, 2013, a total of 490,000 options were outstanding, of which 355,000 shares issued were exercisable, 5,000 restricted stock unit awards were outstanding, and 402,000 shares were available for future grant under the 2002 Plan.

Corporate Transactions and Change of Control Under 2002 Plan

With respect to the 2002 Plan, in the event of:

- a sale or other disposition of all or substantially all of our assets;
- a sale or other disposition of at least 90% of our outstanding securities;
- a merger or consolidation in which we are not the surviving corporation; or
- a 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 2002 Plan or will substitute similar awards (including an award to acquire the same consideration paid to the stockholders in the transaction for those outstanding under the 2002 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar awards for those outstanding under the 2002 Plan, then with respect to awards held by participants whose continuous service has not terminated, such awards automatically vest in full and the awards will terminate if not exercised (if applicable) at or prior to such event.

In addition, in the event (other than a dissolution or liquidation):

- any person becomes the owner of our securities representing more than 50% of the combined voting power of our outstanding securities other than by virtue of a merger;
- consolidation or similar transaction and other than by a purchase of securities directly from us;
- of a merger or consolidation in which our stockholders immediately prior to the merger or consolidation no longer own outstanding voting securities representing 50% of the combined voting power of the entity surviving the merger or consolidation;
- of a sale, lease or other disposition of all or substantially all of our assets; or
- a majority of our board of directors is replaced by individuals who are not nominated by members of our current board of directors or members nominated by our current board of directors or their nominees,

then notwithstanding the assumption or substitution of awards, the vesting and exercisability of awards held by participants whose continuous service has not terminated automatically accelerate in full.

Employee Stock Purchase Plan

In June 2009, our board of directors adopted, and our stockholders subsequently approved, the amendment and restatement of the 2000 ESPP and we reserved an additional 150,000 shares of common stock for issuance thereunder. In each of the subsequent years, we reserved an additional 150,000 shares of common stock for the ESPP resulting in a total of 317,286 shares authorized in the plan as of March 31, 2013. The ESPP permits full-time employees to purchase common stock through

payroll deductions (which cannot exceed 10 percent of each employee's compensation) at the lower of 85 percent of fair market value at the beginning of the purchase period or the end of each six-month purchase period. Under the amended and restated ESPP, employees must hold the stock they purchase for a minimum of six months from the date of purchase beginning with the offering ending in January 1, 2010. During 2012, employees purchased and we issued to employees 124,001 shares under the ESPP at $6.13 per share. As of March 31, 2013, a total of 317,286 shares were available for purchase under the ESPP.

Listing

Our common stock is listed on The NASDAQ Global Select Market under the symbol "ISIS."

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer and Trust. Its address is 59 Maiden Lane, Plaza Level, New York, New York 10038 and its telephone number is (718) 921-8124.

DESCRIPTION OF CONVERTIBLE SENIOR NOTES

In August 2012, we completed a $201.3 million convertible debt offering. The $201.3 million of convertible senior notes mature in 2019 and bear interest at $2^{3}/_{4}$ percent, which is payable semi-annually. The $2^{3}/_{4}$ percent notes are convertible under certain conditions, at the option of the note holders, into approximately 12.1 million shares of our common stock at a conversion price of $16.63 per share. We will settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both. We can redeem the $2^{3}/_{4}$ percent notes at our option, in whole or in part, on or after October 5, 2016 if the last reported sale price of our common stock for at least 20 trading days (whether or not consecutive) during the period of 30 consecutive trading days ending on the trading day immediately preceding the date we provide the redemption notice exceeds 130 percent of the applicable conversion price for the $2^{3}/_{4}$ percent notes on each such day. The redemption price for the $2^{3}/_{4}$ percent notes will equal 100 percent of the principal amount being redeemed, plus accrued and unpaid interest, plus $90 per each $1,000 principal amount being redeemed. Holders of the $2^{3}/_{4}$ percent notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indenture governing the $2^{3}/_{4}$ percent notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest.

PLAN OF DISTRIBUTION

We may sell the offered securities in one or more of the following ways, or any manner specified in a prospectus supplement:

- to or through an underwriter or underwriters;
- through dealers;
- through agents;
- directly to one or more purchasers, including affiliates of ours; or
- through a combination of any of these methods of sale.

The applicable prospectus supplement will contain the terms of the offerings of any securities. The public offering price and any discount or concessions allowed or reallowed to dealers may be changed from time to time. The applicable prospectus supplement will contain the expected time of delivery of the securities for which this prospectus is delivered.

Unless otherwise indicated in the applicable prospectus supplement, if underwriters are used in the sale of the securities, the underwriting agreement will provide that the obligations of the underwriters are subject to certain conditions precedent and that the underwriters will be obligated to purchase all of the securities if any are purchased. In connection with the sale of securities, underwriters may receive compensation from us or purchasers of securities for whom they may act as agents in the form of discounts, concessions or commissions. Underwriters may sell securities to or through dealers, and dealers may receive compensation in the form of discounts, concessions or commissions from the underwriters and/or commissions from the purchasers for whom they may act as agent.

Underwriters, agents or dealers participating in the distribution of securities may be deemed to be underwriters, and any discounts and commissions received by them and any profit realized by them on resale of the securities may be deemed to be underwriting discounts and commissions under the Securities Act. The securities may be sold in one or more transactions either at a fixed price or at prices which may be changed based on market prices prevailing at the time of sale, at prices related to the prevailing market prices or at negotiated prices. Any underwriter, dealer or agent will be acting on a best efforts basis or, if indicated in the applicable prospectus supplement, on a firm commitment basis.

We may indemnify the underwriters, agents or dealers who participate in the distribution of securities against certain liabilities, including liabilities under the Securities Act. We may also contribute to payments that the underwriters, dealers or agents or any of their controlling persons may be required to make in respect of such liabilities. Underwriters, agents or dealers may be customers of, engage in transactions with or perform services for us or our subsidiaries in the ordinary course of business.

If so indicated in a prospectus supplement, we will authorize underwriters, dealers and agents to solicit offers by certain institutions to purchase securities from us pursuant to delayed delivery contracts providing for payment and delivery on the date stated in the prospectus supplement. These contracts will be subject only to those conditions contained in the prospectus supplement. The prospectus supplement will also contain the commission payable for solicitation of any of these contracts.

Offers to purchase securities may be solicited directly by us and sales of securities may be made by us directly to institutional investors or others who may be deemed to be underwriters within the meaning of the Securities Act, with respect to any resale of the securities. The terms of any such sales will be described in the prospectus supplement relating to the securities. Except as contained in the applicable prospectus supplement, no director, officer or employee of ours will solicit or receive a commission in connection with the direct sales by us of the securities, although these persons may respond to inquiries by potential purchasers and perform ministerial and clerical work in connection with any such direct sales.

LEGAL MATTERS

The validity of the issuance of the common stock offered hereby will be passed upon for us by Patrick R. O'Neil, our Senior Vice President, Legal and General Counsel.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2012, and the effectiveness of our internal control over financial reporting as of December 31, 2012, as set forth in their reports, which are incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements and our management's assessment of the effectiveness of internal control over financial reporting as of December 31, 2012 are incorporated by reference in reliance on Ernst & Young LLP's reports, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND ADDITIONAL INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's web site at www.sec.gov. You may also read and copy any document we file 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 SEC's public reference room in Washington, D.C. by calling the SEC at 1-800-SEC-0330.

We have filed with the SEC a registration statement under the Securities Act relating to the offering of these securities. The registration statement, including the attached exhibits, contains additional relevant information about us and the securities. This prospectus does not contain all of the information set forth in the registration statement. You can obtain a copy of the registration statement (including the exhibits and schedules thereto), at prescribed rates, from the SEC at the address listed above or from the SEC's website.

The registration statement and the documents referred to below under "Incorporation by Reference" are also available on our corporate website, www.isispharm.com. We have not incorporated by reference into this prospectus the information on our website, and you should not consider it to be a part of this prospectus.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" in this prospectus the information that we file with it. This means that we can disclose important information to you in this document by referring you to other filings we have made with the SEC. The information incorporated by reference is considered to be part of this prospectus. The information incorporated by reference in this prospectus is accurate only as of the date of the information on the front cover of the applicable document, or such earlier date as is expressly stated or otherwise apparent with respect to such incorporated information in the applicable document, regardless of the time of delivery of this prospectus or any sale of securities.

This prospectus incorporates by reference the documents listed below, which we have filed with the SEC:

- our Annual Report on Form 10-K for our fiscal year ended December 31, 2012, filed on February 28, 2013;
- our Quarterly Report on Form 10-Q for our quarter ended March 31, 2013, filed on May 7, 2013;
- portions of our Definitive Proxy Statement on Schedule 14A filed on April 26, 2013 incorporated by reference into the Annual Report on Form 10-K for our fiscal year ended December 31, 2012;
- our Current Reports on Form 8-K filed on January 2, 2013, January 30, 2013, February 13, 2013 and April 8, 2013; 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 quarter ended March 31, 2006.

We incorporate by reference any additional documents that we may file with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Exchange Act (other than the portions of those made pursuant to Item 2.02 or Item 7.01 of Form 8-K or other information "furnished" to the SEC) prior to the termination of the offering of the securities. These documents may include periodic reports, like

Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q and Current Reports on Form 8-K, as well as Proxy Statements. Any material that we subsequently file with the SEC will automatically update and replace the information previously filed with the SEC.

This prospectus may contain information that updates, modifies or is contrary to information in one or more of the documents incorporated by reference in this prospectus. 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 of this prospectus or the date of the documents incorporated by reference in this prospectus.

We will provide to each person, including any beneficial owner, to whom this prospectus is delivered, upon written or oral request, at no cost, a copy of any and all of the information that is incorporated by reference in this prospectus.

Requests for such documents should be directed to:

Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, California 92010
(760) 931-9200
Attention: General Counsel

In addition, copies of our filings are available through our corporate website at www.isispharm.com as soon as reasonably practicable after we electronically file such material with the SEC.

9,000,000 Shares

Isis Pharmaceuticals, Inc.

Common Stock

Goldman, Sachs & Co. **J.P. Morgan**

Stifel

BMO Capital Markets **Cowen and Company** **Needham & Company**