

**SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

**FORM S-3****REGISTRATION STATEMENT  
Under  
THE SECURITIES ACT OF 1933****ISIS PHARMACEUTICALS, INC.**

(Exact name of Registrant as specified in its charter)

Delaware  
(State or other jurisdiction  
of incorporation or organization)33-0336973  
(I.R.S. Employer  
Identification Number)1896 Rutherford Road  
Carlsbad, California 92008  
(760) 931-9200

(Address, including zip code, and telephone number, including area code, of Registrant's principal executive offices)

B. Lynne Parshall, Esq.  
Executive Vice President  
Isis Pharmaceuticals, Inc.  
1896 Rutherford Road  
Carlsbad, California 92008  
(760) 931-9200

(Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies to:  
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(858) 550-6000**Approximate date of commencement of proposed sale to the public:** From time to time after this registration statement becomes effective.If the only securities being registered on this form are being offered pursuant to dividend or interest reinvestment plans, please check the following box. If any of the securities being registered on this form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, as amended (the "Securities Act"), other than securities offered only in connection with dividend or interest reinvestment plans, check the following box. If this form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. If this form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. If this form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, please check the following box. If this form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, please check the following box. **CALCULATION OF REGISTRATION FEE**

Title of each class of securities to be registered	Amount to be registered	Proposed maximum offering price per unit(2)	Proposed maximum aggregate offering price(2)	Amount of registration fee
2½% Convertible Subordinated Notes due 2027(1)	\$ 162,500,000	100%	\$ 162,500,000	\$ 4,989
Common Stock, \$0.001 per share	11,111,116(3)	—	—	—(4)

- (1) The 2½% convertible subordinated notes due 2027 were issued by the Registrant on January 23, 2007 in an offering exempt from registration under the Securities Act of 1933. Under a Registration Rights Agreement dated January 23, 2007 among the Registrant and the initial purchasers of the notes who resold the notes in offerings exempt from registration under Rule 144A of the Securities Act of 1933, the Registrant is obligated to file this Registration Statement to permit registered resales by the selling security holders of the notes and the shares of common stock underlying the notes.
- (2) Estimated solely for the purpose of calculating the registration fee pursuant to Rule 457(i) of the Securities Act of 1933 based upon the offering price of the notes when the Registrant originally sold the notes on January 23, 2007 in an offering that was exempt from registration under the Securities Act of 1933.
- (3) Represents the number of shares of common stock issuable upon conversion of the 2½% convertible subordinated notes due 2027 registered hereby. The notes are convertible into 68,3761 shares of our common stock, par value \$0.001 per share, per \$1,000 principal amount of notes, subject to adjustment in certain circumstances. Pursuant to Rule 416 under the Securities Act, such number of shares shall include an indeterminate number of shares of common stock as may be issuable from time to time upon the conversion of the notes as a result of a stock split, stock dividend, capitalization or similar event and the antidilution provisions thereof.
- (4) The shares of common stock issuable upon conversion of the notes will be issued for no additional consideration, and therefore no registration fee is required pursuant to Rule 457(i) of the Securities Act.

Isis Pharmaceuticals, Inc.

**\$162,500,000 2½% Convertible Subordinated Notes due 2027 and  
11,111,116 Shares of Common Stock Issuable Upon Conversion of the Notes**

The notes and the common stock issuable upon conversion of the notes may be offered and sold from time to time pursuant to this prospectus by the holders of those securities. The selling security holders will receive all of the net proceeds from the sale of the securities and will pay any applicable discounts, commission or concessions. The selling security holders and any underwriters, broker-dealers or agents that participate in the sale of the securities may be

“underwriters” within the meaning of the Securities Act, and any discounts, commissions, concessions or profit they earn on any resale of the securities may be underwriting discounts or commissions under the Securities Act.

In January 2007, we issued and sold \$162,500,000 aggregate principal amount of 2% Convertible Subordinated Notes due 2027 in a private placement in reliance on an exemption from registration under the Securities Act of 1933, or Securities Act. The initial purchasers of the notes in that offering resold the notes in offerings in reliance on an exemption from registration under Rule 144A of the Securities Act. The notes are convertible into 68.3761 shares of our common stock, par value \$0.001 per share, per \$1,000 principal amount of notes and subject to adjustment in specific circumstances. This results in an initial conversion price of approximately \$14.63 per share.

Upon conversion, we will have the right to deliver shares of our common stock, cash or a combination of cash and shares of our common stock. In the event of specific types of fundamental changes, we will increase the number of shares issuable upon conversion or, in lieu thereof, we may elect to adjust the conversion obligation and conversion rate so that the Notes are convertible into shares of the acquiring or surviving company, in each case as described herein.

The Notes bear interest at a rate of 2% per year, payable semi-annually in arrears, on February 15 and August 15 of each year, commencing August 15, 2007. The Notes mature on February 15, 2027.

We may redeem some or all of the Notes on or after February 15, 2012, for cash at the redemption prices described in this prospectus, plus accrued and unpaid interest to the redemption date.

You may require us to repurchase all or a portion of your Notes on February 15, 2014, February 15, 2017 and February 15, 2022 at a cash repurchase price equal to 100% of the principal amount plus accrued and unpaid interest, including additional interest, if any. In addition, you may require us to repurchase all or a portion of your Notes upon a fundamental change at a cash repurchase price equal to 100% of the principal amount plus accrued and unpaid interest, including additional interest, if any.

The Notes are our unsecured subordinated obligations. As of December 31, 2006, we and our subsidiaries had approximately \$15.0 million of senior indebtedness outstanding, all of which was secured indebtedness.

Our common stock is listed on the Nasdaq Global Market under the symbol “ISIS.” On March 12, 2007, the last reported bid price of our common stock was \$12.59 per share. The notes trade on the Private Offerings, Resales and Trading Through Automated Linkages, or “PORTAL,” Market of the National Association of Securities Dealers, Inc.

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**Investing in our common stock involves risks.  
See “Risk Factors” beginning on page 6**

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**Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.**

The date of this prospectus is March 20, 2007

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

### TREASURY DEPARTMENT CIRCULAR 230

TO ENSURE COMPLIANCE WITH TREASURY DEPARTMENT CIRCULAR 230, EACH PERSON RECEIVING THIS PROSPECTUS IS HEREBY NOTIFIED THAT: (A) ANY DISCUSSION OF FEDERAL TAX ISSUES IN THIS PROSPECTUS IS NOT INTENDED OR WRITTEN TO BE RELIED UPON, AND CANNOT BE RELIED UPON, BY HOLDERS FOR THE PURPOSE OF AVOIDING PENALTIES THAT MAY BE IMPOSED ON HOLDERS UNDER THE INTERNAL REVENUE CODE OF 1986, AS AMENDED; (B) SUCH DISCUSSION IS INCLUDED HEREIN BY US IN CONNECTION WITH THE PROMOTION OR MARKETING (WITHIN THE MEANING OF TREASURY DEPARTMENT CIRCULAR 230) OF THE TRANSACTIONS OR MATTERS ADDRESSED HEREIN; AND (C) PROSPECTIVE PURCHASERS SHOULD SEEK ADVICE BASED ON THEIR PARTICULAR CIRCUMSTANCES FROM AN INDEPENDENT TAX ADVISOR.

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### SUMMARY

*This summary highlights selected information appearing elsewhere in this prospectus and may not contain all of the information that is important to you. This prospectus includes information about the securities we are offering, as well as information regarding our business and detailed financial data. We encourage you to read this prospectus in its entirety, including the documents incorporated by reference herein. As used in this prospectus, unless otherwise specified or the context requires otherwise, the terms “Isis,” “we,” “our” and “us” refer to Isis Pharmaceuticals, Inc.*

### Our Business

We are a biopharmaceutical company exploiting proprietary RNA-based drug discovery technologies to identify and commercialize a new class of drugs to treat important diseases. RNA, or ribonucleic acid, is a molecule that provides to a cell the information the cell needs to produce proteins, including those proteins associated with disease. Interference with RNA can keep the body from producing the proteins that are involved in disease. We are the leader in making drugs that target RNA, and have a strong proprietary position in RNA-based drug discovery technologies. With our primary technology, antisense, we create inhibitors, called oligonucleotides, designed to hybridize, with a high degree of specificity to their RNA target and modulate the production of specific proteins associated with disease. Separately, within our Ibis Biosciences subsidiary, we have developed a revolutionary biosensor system, called the Ibis T5000 Biosensor System, that can simultaneously identify from a sample a broad range of infectious organisms without needing to know beforehand what might be present in the sample.

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

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### NOTES AND COMMON STOCK ISSUABLE UPON CONVERSION OF THE NOTES

<b>Issuer</b>	Isis Pharmaceuticals, Inc.
<b>Securities Offered</b>	\$162.5 million aggregate principal amount of 2½% Convertible Subordinated Notes due 2027, which we refer to as Notes, and shares of our common stock issuable upon conversion of the notes.
<b>Maturity</b>	February 15, 2027, unless earlier converted, redeemed or repurchased.
<b>Interest Rate</b>	2½% per year. Interest is payable in cash on February 15 and August 15 of each year, beginning August 15, 2007.
<b>Ranking</b>	The Notes are our unsecured subordinated obligations and are subordinated in right of payment to all of our existing and future senior unsecured indebtedness and all of our existing and future senior secured indebtedness. The Notes are structurally subordinated to indebtedness and other liabilities of our subsidiaries. The Notes are equal in right of payment with our 5 ½% convertible subordinated notes due 2009.
<b>Conversion Rights</b>	You may convert your Notes into shares of our common stock at any time on or prior to the close of business on the business day immediately preceding the maturity date only under the following circumstances: <ul style="list-style-type: none"><li>• prior to February 15, 2025, on any date during any fiscal quarter beginning after March 31, 2007 (and only during such fiscal quarter) if the closing sale price of our common stock was more than 120% of the then current conversion price for at least 20 trading days in the period of the 30 consecutive trading days ending on the last trading day of the previous fiscal quarter, as described below in more detail under “Description of Notes — Conversion Upon Satisfaction of Market Price Condition”;</li></ul>

- at any time on or after February 15, 2025, as described below in more detail under “Description of Notes — Conversion 2 Years Prior to Maturity”;
- with respect to any Notes called for redemption, until the close of business on the business day prior to the redemption date, as described below in more detail under “Description of Notes — Conversion Upon Notice of Redemption”;
- if we distribute to all or substantially all holders of our common stock rights or warrants entitling them to purchase, for a period of 45 calendar days or less, shares of our common stock at a price less than the average closing sale price for the ten trading days preceding the declaration date for such distribution, as described in more detail under “Description of Notes — Conversion Upon Specified Corporate Transactions”;
- if we distribute to all or substantially all holders of our common stock, cash or other assets, debt securities or

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rights to purchase our securities, which distribution has a per share value exceeding 5% of the closing sale price of our common stock on the trading day preceding the declaration date for such distribution, as described in more detail under “Description of Notes — Conversion Upon Specified Corporate Transactions”;

- during a specified period if a fundamental change occurs, as described in more detail under “Description of Notes — Conversion Upon a Fundamental Change”; or
- during the five consecutive business-day period following any five consecutive trading-day period in which the trading price for the Notes for each day during such five trading-day period was less than 98% of the closing sale price of our common stock multiplied by the then current conversion rate, as described in more detail under “Description of Notes — Conversion Upon Satisfaction of Trading Price Condition.”

The Notes are convertible into shares of our common stock at an initial conversion rate of 68.3761 shares of common stock per \$1,000 principal amount of the Notes (equivalent to an initial conversion price of approximately \$14.63 per share). The conversion rate, and thus the conversion price, may be adjusted under specific circumstances as described under “Description of Notes — Conversion Procedures — Conversion Rate Adjustments.”

Upon conversion, we will have the right to deliver shares of our common stock, cash or a combination of cash and shares of our common stock, in each case calculated as described under “Description of Notes — Conversion Procedures — Settlement Upon Conversion.”

At any time on or prior to the 26th trading day preceding the maturity date, we may irrevocably elect to satisfy our conversion obligation with respect to the principal amount of the Notes to be converted in cash, with any remaining amount to be satisfied in shares of our common stock or cash. See “Description of Notes — Conversion Procedures — Settlement Upon Conversion.”

Upon any conversion, subject to specific exceptions, you will not receive any cash payment representing accrued and unpaid interest. See “Description of Notes — Conversion Procedures.”

**Adjustment to Conversion Rate Upon a Non-Stock Change of Control**

Prior to February 15, 2012, if and only to the extent holders elect to convert the Notes in connection with a transaction described under the first clause or fourth clause of the definition of fundamental change as described in “Description of Notes — Repurchase at the Option of the Holder — Fundamental Change Put” pursuant to which 10% or more of the consideration for our common stock (other than cash payments for fractional shares and cash payments made in respect of dissenters’ appraisal rights) consists of cash or securities, or other property, that are not common equity interests traded or scheduled to be traded immediately following such transaction on a U.S. national securities exchange, the Nasdaq Global Select Market or the Nasdaq Global Market, which we refer to as a “non-stock change of control,” we will increase the conversion rate by a number of additional shares. The

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number of additional shares will be determined by reference to the table in “Description of Notes — Conversion Procedures — Adjustment to Conversion Rate Upon a Non-Stock Change of Control,” based on the effective date and the price paid per share of our common stock in such non-stock change of control.

If holders of our common stock receive only cash in the type of transaction described above, the price paid per share will be the cash amount paid per share. Otherwise, the price paid per share will be the average of the last reported sale prices of our common stock on the five trading days prior to but not including the effective date of such non-stock change of control.

## **Conversion After a Public Acquirer Change of Control**

In the case of a non-stock change of control constituting a public acquirer change of control, as defined in this prospectus, we may, in lieu of adjusting the conversion rate as described in “Description of Notes — Conversion Procedures — Adjustment to Conversion Rate Upon a Non-Stock Change of Control,” elect to adjust the conversion obligation and the conversion rate such that from and after the effective date of such public acquirer change of control, holders of the Notes will be entitled to convert their Notes, subject to the satisfaction of specific conditions, into a number of shares of public acquirer common stock by adjusting the conversion rate in effect immediately before the public acquirer change of control by a fraction:

- the numerator of which will be:
  - in the case of a share exchange, consolidation, merger or binding share exchange pursuant to which our common stock is converted into cash, securities or other property, the value of all cash and any other consideration as determined by our board of directors paid or payable per share of common stock, or
  - in the case of any other public acquirer change of control, the average of the closing sale prices of our common stock for the five consecutive trading days prior to but excluding the effective date of such public acquirer change of control; and
- the denominator of which will be the average of the last reported sale prices of the public acquirer common stock for the five consecutive trading days commencing on the trading day next succeeding the effective date of such public acquirer change of control.

## **Optional Redemption by Isis**

At any time on or after February 15, 2012, we may redeem all or a part of the Notes for cash at the redemption prices described in this prospectus, plus accrued and unpaid interest (including additional interest, if any) to, but not including, the redemption date. See “Description of Notes — Optional Redemption.”

## **Optional Repurchase Right of Holders**

You may require us to repurchase all or a portion of your Notes on February 15, 2014, February 15, 2017 and February 15, 2022 at a cash repurchase price equal to 100% of the principal amount of the Notes, plus accrued and unpaid interest, including additional interest, if any, to, but not including, the repurchase date.

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## **Fundamental Change Repurchase Right of Holders**

If we undergo a fundamental change, as defined in this prospectus, prior to maturity, you will have the right, at your option, to require us to repurchase for cash some or all of your Notes at a repurchase price equal to 100% of the principal amount of the Notes being repurchased, plus accrued and unpaid interest, including additional interest, if any, to, but not including, the repurchase date. See “Description of Notes — Repurchase at the Option of the Holder — Fundamental Change Put.”

## **Events of Default**

If an event of default on the Notes occurs, the principal amount of the Notes, plus accrued and unpaid interest (including additional interest, if any) may be declared immediately due and payable, subject to specific conditions set forth in the indenture. These amounts automatically become due and payable in the case of specific types of bankruptcy or insolvency events of default involving us.

## **Trading**

The notes trade on the Private Offerings, Resales and Trading Through Automated Linkages, or “PORTAL,” Market of the National Association of Securities Dealers, Inc.

## **Nasdaq Symbol for Our Common Stock**

Our common stock is listed on the Nasdaq Global Market under the symbol “ISIS.”

## **Use of Proceeds**

We will not receive any proceeds from the sale of the notes or common stock offered in this prospectus. See “Selling Security Holders.”

## **Certain U.S. Federal Tax Considerations**

The Notes and the common stock issuable upon conversion of the Notes will be subject to special and complex U.S. federal income tax rules. Holders are urged to consult their own tax advisors with respect to the federal, state, local and foreign tax consequences of purchasing, owning and disposing of the Notes and common stock issuable upon conversion of the Notes. See “Certain U.S. Federal Tax Considerations.”

## **Risk Factors**

In analyzing an investment in the convertible notes offered by this prospectus, prospective investors should carefully consider, along with other matters referred to in this prospectus, the information set forth under “Risk Factors.”

For a more complete description of the terms of the convertible notes, see “Description of Notes.” For a more complete description of the terms of our common stock, see “Description of Capital Stock,” including the documents incorporated by reference in this prospectus that are referred to therein.

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## RISK FACTORS

*Investing in our securities involves a high degree of risk. In addition to the other information in this prospectus, you should carefully consider the risks described below before purchasing our securities. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment.*

### RISKS RELATED TO OUR BUSINESS

#### Risks Associated with our Businesses as a Whole

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

Because product discovery and development require substantial lead-time and money prior to commercialization, our expenses have exceeded our revenue since we were founded in January 1989. As of December 31, 2006, we had accumulated losses of approximately \$816.8 million and stockholders' equity of approximately \$68.6 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from research grants and the sale or licensing of patents as well as interest income. We currently have only one product, Vitravene, approved for commercial use. This product has limited sales potential and Novartis, our exclusive distribution partner for this product no longer markets it. We expect to incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or services, or achieve or sustain future profitability.

##### **If we fail to obtain timely funding, we may need to curtail or abandon some of our programs.**

All of our drugs are undergoing clinical trials or are in the early stages of research and development. All of our drugs under development will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and a commitment of significant additional resources prior to their commercialization. Based on reasonable assumptions for new sources of revenue and cash, we believe we have sufficient resources to meet our anticipated requirements through at least the second half of 2010. If we do not meet our goals to commercialize our products, or to license our drugs and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements;
- continued scientific progress in our research, drug discovery and development programs;
- the size of our programs and progress with preclinical and clinical trials;
- the time and costs involved in obtaining regulatory approvals;
- competing technological and market developments, including the introduction by others of new therapies that address our markets;
- success in developing and commercializing a business based on our Ibis T5000 Biosensor System to identify infectious organisms; and
- the profile and launch timing of our drugs.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and their price, as well as the price of our other securities, may decline. If adequate funds are not available or not available on acceptable terms, we may have to cut back on one or more of our research, drug discovery or development programs. For example, in January 2005 we decided to terminate the development of two lower priority drugs, ISIS 14803 and ISIS 104838. Alternatively, as in our

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transaction with Symphony GenSis, we may obtain funds through arrangements with collaborative partners or others, which could require us to give up rights to certain of our technologies, drugs or products.

**Since corporate partnering is a key part of our strategy to fund the development and commercialization of our development programs, if any of our collaborative partners fail to fund our collaborative programs, or if we cannot obtain additional partners, we may have to delay or stop progress on our product development programs.**

To date, corporate partnering has played a key role in our strategy to fund our development programs and to add key development resources. We plan to continue to rely on additional collaborative arrangements to develop and commercialize our products, including our two lead products ISIS 301012 and ISIS 113715. However, we may not be able to negotiate additional attractive collaborative arrangements.

Many of the drugs in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics Limited, iCo Therapeutics, Inc., ImQuest Pharmaceuticals, Inc., Merck & Co., Inc., OncoGenex Technologies Inc. and Lilly. If any of these pharmaceutical companies stopped funding and/or developing these products, our business could suffer and we may not have the resources available to develop these products on our own.

Our collaborators can terminate their relationships with us under certain circumstances, some of which are outside of our control. For example, in November 2004 based on the disappointing results of the Phase 3 clinical trials, Lilly discontinued its investment in Affinitak.

In addition, the disappointing results of the two Affinitak clinical trials, our Phase 3 clinical trials of alicaforsen in patients with active Crohn's disease, or any future clinical trials could impair our ability to attract new collaborative partners. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drugs could suffer.

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

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

- conduct clinical trials;
- seek and obtain regulatory approvals; and
- manufacture, market and sell existing and future products.

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

For example, a collaborator could determine that it is in its financial interest to:

- pursue alternative technologies or develop alternative products that may be competitive with the product that is part of the collaboration with us;
- pursue higher-priority programs or change the focus of its own development programs; or
- choose to devote fewer resources to our drugs than it does for drugs of its own development.

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

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

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

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

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

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

It is possible that in the future we may have to defend our intellectual property rights. In the event of an intellectual property dispute, we may be forced to litigate to defend our rights or assert them against others. Disputes could involve arbitration, litigation or proceedings declared by the United States Patent and Trademark Office or the International Trade Commission or foreign patent authorities. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business.

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

If a third party claims that our products or technology infringe their patents or other intellectual property rights, we may have to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to needed intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of

patents or applications held by others that relate to our business. This is especially true since patent applications in the United States are filed confidentially. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain unresolved.

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

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

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**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 Isis. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. In addition, failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel.

**If the price of our securities continues to be highly volatile, this could make it harder for you to liquidate your investment and could increase your risk of suffering a loss.**

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding December 31, 2006, the market price of our common stock ranged from \$5.09 to \$14.0 per share. On March 12, 2007, the closing price of our common stock on the Nasdaq Global Market was \$9.38. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial results, technological innovations or new products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

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

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

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

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

**If a natural or man-made disaster strikes our research and development facilities, it could delay our progress developing and commercializing our drugs or our Ibis T5000 Biosensor System.**

We are developing our Ibis T5000 Biosensor System in our facility located in Carlsbad, California. Additionally, we manufacture our research and clinical supplies in a separate manufacturing facility located in Carlsbad, California. The facilities and the equipment we use to develop the Ibis T5000 Biosensor System and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Either of our facilities may be harmed by natural or man-made disasters, including, without limitation, earthquakes, floods, fires

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and acts of terrorism, and in the event they are affected by a disaster, our development and commercialization efforts would be delayed. Although we possess insurance for damage to our property and the disruption of our business from casualties, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all.



**Provisions in our certificate of incorporation, other agreements and Delaware law may prevent stockholders from receiving a premium for their shares.**

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66% of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15% or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. We also have implemented a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. These provisions, as well as Delaware law and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests. In addition, our board of directors has the authority to fix the rights and preferences of and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

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

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

Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. We have granted registration rights to Lilly, which cover approximately 2.5 million shares of our common stock, which we issued to Lilly upon the conversion of outstanding convertible securities. We also registered for resale 12,000,000 shares of our common stock and 2,999,998 shares of our common stock issuable upon the exercise of the warrants we issued as part of our August 2005 private placement as well as 4.25 million shares of our common stock issuable upon the exercise of the warrant we issued to Symphony GenSis Holdings. In addition, on December 22, 2005, we filed a Form S-3 shelf registration statement with the SEC to register up to \$200,000,000 worth of our common stock for possible issuance. Finally, we have granted registration rights to the holders of our 2 5/8% convertible subordinated notes that include the approximately 11,111,116 shares issuable upon conversion of the notes. The addition of any of these shares into the market may have an adverse effect on the price of our securities.

**Our business is subject to changing regulations for corporate governance and public disclosure that has increased both our costs and the risk of noncompliance.**

Each year we are required to evaluate our internal controls systems in order to allow management to report on and our Independent Registered Public Accounting Firm to attest to, our internal controls as required by Section 404 of the Sarbanes-Oxley Act. As a result, we will incur additional expenses and will suffer a diversion of management's time. In addition, if we cannot continue to comply with the requirements of Section 404 in a timely manner, we might be subject to sanctions or investigation by regulatory authorities, such as the Securities and Exchange Commission, the Public Company Accounting Oversight Board (PCAOB) or the NASDAQ Stock Market. Any such action could adversely affect our financial results and the market price of our common stock.

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**Risks Associated with our Drug Discovery and Development Business**

**If we or our partners fail to obtain regulatory approval for our drugs, we will not be able to sell them.**

We and our partners must conduct time-consuming, extensive and costly clinical trials to show the safety and efficacy of each of our drugs, including ISIS 301012 and ISIS 113715, before a drug can be approved for sale. We must conduct these trials in compliance with FDA regulations and with comparable regulations in other countries. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of our drugs, including ISIS 301012 and ISIS 113715, it will not approve them or will require additional studies, which can be time consuming and expensive and which will delay commercialization of a drug. We and our partners may not be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our drugs, including ISIS 301012 and ISIS 113715. Failure to receive these approvals or delays in these approvals could prevent or delay commercial introduction of a product, including ISIS 301012 and ISIS 113715, and, as a result, could negatively impact our ability to generate revenue from product sales. In addition, following approval of a drug, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute drug products. If we fail to comply with these regulations, regulators could force us to withdraw a drug from the market or impose other penalties or requirements that also could have a negative impact on our financial results.

We have only introduced one commercial drug product, Vitravene. We cannot guarantee that any of our other drugs, including ISIS 301012 and ISIS 113715, will be safe and effective, will be approved for commercialization or that our partners or we can successfully commercialize these drugs.

**If the results of clinical testing indicate that any of our drugs under development are not suitable for commercial use we may need to abandon one or more of our drug development programs.**

Drug discovery and development has inherent risks and the historical failure rate for drugs is high. Antisense technology in particular is relatively new and unproven. If we cannot demonstrate that our drugs, including ISIS 301012 and ISIS 113715, are safe and effective drugs for human use, we may need to abandon one or more of our drug development programs.

In the past, we have invested in clinical studies of drugs that have not met the primary clinical end points in their Phase 3 studies. In March 2003, we reported the results of a Phase 3 clinical trial of Affinitak in patients with late-stage non-small cell lung cancer and in October 2004, we reported the results of a second similar Phase 3 clinical trial. In each case, Affinitak failed to demonstrate improved survival sufficient to support an NDA filing. In December 2004, we reported the results of our Phase 3 clinical trials of alicaforsen in patients with active Crohn's disease, in which alicaforsen did not demonstrate statistically

significant induction of clinical remissions compared to placebo. Similar results could occur with the clinical trials for our other drugs. If any of our drugs in clinical studies do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for this and other drugs and our stock price could decline.

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

Successful results in preclinical or early human clinical trials, including the recently announced Phase 2 results for ISIS 301012 and ISIS 113715, may not predict the results of late-stage clinical trials. There are a number of factors that could cause a clinical trial to fail or be delayed, including:

- the clinical trial may produce negative or inconclusive results;
- regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;
- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical trial due to adverse side effects of a drug on subjects or patients in the trial;
- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical trials;

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- enrollment in our clinical trials may be slower than we currently anticipate;
  - the cost of our clinical trials may be greater than we anticipate; and
  - the supply or quality of our drugs or other materials necessary to conduct our clinical trials may be insufficient, inadequate or delayed.

Any failure or delay in one of our clinical trials, including our Phase 2 development programs for ISIS 301012 and ISIS 113715, could reduce the commercial viability of our drugs, including ISIS 301012 and ISIS 113715.

**We have licensed the intellectual property, including commercialization rights, to our apoB-100, GCGR, and GCCR programs to Symphony GenIsis, Inc. and will not receive any future royalties or revenues with respect to the products in these programs, including ISIS 301012, ISIS 325568 and ISIS 377131 unless we exercise our option to acquire all of these drugs in the future. We may not have the financial resources to exercise this option or sufficient clinical data in order to determine whether we should exercise this option prior to its expiration.**

We have licensed to Symphony GenIsis our intellectual property rights, including commercialization rights, to our apoB-100, GCGR, and GCCR programs in exchange for Symphony GenIsis' investment of \$75 million to advance the clinical development of these programs. In exchange for this investment and for a five-year warrant to purchase shares of our common stock we issued to Symphony GenIsis, we received an exclusive purchase option to acquire all of the equity of Symphony GenIsis, thereby allowing us to reacquire our apoB-100, GCGR and GCCR programs, which include ISIS 301012, ISIS 325568 and ISIS 377131. The purchase option exercise price reflects a compounded annual rate of return that averages 32% and is 27% at the end of the anticipated four-year collaborative development period. We may pay the option exercise price in cash or a combination of cash and our common stock, at our sole discretion, provided that the common stock portion may not exceed 33% of the purchase option exercise price.

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

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

We have licensed to Symphony GenIsis our intellectual property rights, including commercialization rights, to our drugs in our apoB-100, GCGR, and GCCR programs in exchange for Symphony GenIsis' investment of \$75 million to advance the clinical development of these programs. We are responsible for developing these drugs in accordance with a specified development plan and related development budget. The Symphony GenIsis development committee supervises our development activities. The development committee is comprised of an equal number of representatives from Isis and Symphony GenIsis. If the development committee cannot resolve a particular development issue, the issue will be referred to the chief executive officers of Isis and Symphony GenIsis. Any disagreements between Symphony GenIsis and us regarding a development decision may cause significant delays in the development and commercialization of our drugs within our apoB-100, GCGR, and GCCR programs.

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

Our success will depend upon the medical community, patients and third-party payors accepting our products as medically useful, cost-effective and safe. We cannot guarantee that, if approved for commercialization, doctors will use our products to treat patients. We currently have one commercially available drug product, Vitravene, a treatment for cytomegalovirus, or CMV, retinitis in AIDS patients, which addresses a small market. Our partners and we may not successfully commercialize additional products.

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The degree of market acceptance for any of our products depends upon a number of factors, including:

- the receipt and scope of regulatory approvals;
- the establishment and demonstration in the medical and patient community of the efficacy and safety of our drugs and their potential advantages over competing products;
- the cost and effectiveness of our drugs compared to other available therapies;
- the patient convenience of the dosing regimen for our drugs; and
- reimbursement policies of government and third-party payors.

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

**If we cannot manufacture our drug products or contract with a third party to manufacture our drug products at costs that allow us to charge competitive prices to buyers, we will not be able to market products profitably.**

If we successfully commercialize any of our drugs, we may be required to establish large-scale commercial manufacturing capabilities. In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. We have limited experience manufacturing pharmaceutical products of the chemical class represented by our drugs, called oligonucleotides, on a commercial scale for the systemic administration of a drug. There are a small number of suppliers for certain capital equipment and raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our product costs. We may not be able to manufacture at a cost or in quantities necessary to make commercially successful products.

Also, manufacturers, including us, must adhere to the FDA's current Good Manufacturing Practices regulations which the FDA enforces through its facilities inspection program. We and our contract manufacturers may not be able to comply or maintain compliance with Good Manufacturing Practices regulations. Non-compliance could significantly delay or prevent our receipt of marketing approval for potential products or result in FDA enforcement action after approval that could limit the commercial success of our potential product.

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

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

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

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

Certain of our partners are pursuing other technologies or developing other drugs either on their own or in collaboration with others, including our competitors, to develop treatments for the same diseases targeted by our own collaborative programs. Competition may negatively impact a partner's focus on and commitment to our drugs and, as a result, could delay or otherwise negatively affect the commercialization of our drugs.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical

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testing and human clinical trials of new pharmaceutical products and in obtaining FDA and other regulatory approvals of products for use in health care. Accordingly, our competitors may succeed in obtaining regulatory approval for products earlier than we do. We will also compete with respect to marketing and sales capabilities, areas in which we have limited or no experience.

**We depend on third parties in the conduct of our clinical trials for our drugs and any failure of those parties to fulfill their obligations could adversely affect our development and commercialization plans.**

We depend on independent clinical investigators, contract research organizations and other third-party service providers in the conduct of our clinical trials for our drugs and expect to continue to do so in the future. For example, Medpace is the primary clinical research organization for clinical trials for ISIS 301012. We rely heavily on these parties for successful execution of our clinical trials, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Third parties may not complete activities on schedule, or may not conduct our clinical trials in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations or a termination of our relationship with these third parties could delay or prevent the development, approval and commercialization of our drugs, including ISIS 301012.

**We may not successfully develop or derive revenues from our business based on our Ibis T5000 Biosensor System.**

Our Ibis T5000 Biosensor System is subject to the risks inherent in developing tools based on innovative technologies. Our product is at an early stage of development and requires continued research and development to achieve our business objectives. For Ibis to be commercially successful, we must convince potential customers that our Ibis T5000 Biosensor System is an attractive alternative to existing methods of identifying pathogens. If our potential customers fail to purchase our Ibis T5000 Biosensor System due to competition or other factors, or if we fail to develop applications that lead to market acceptance, we may not recover our investment in this technology and our Ibis T5000 Biosensor System business could fail to meet our business and financial objectives.

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

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

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

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

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**If we fail to secure additional commercial or financial partners for our Ibis T5000 Biosensor System, our commercialization efforts for our Ibis T5000 Biosensor System may be harmed or delayed.**

In addition to Bruker Daltonics, we may depend on third parties to commercialize our Ibis T5000 Biosensor System, particularly in the areas of hospital-associated infection control and infectious disease diagnostics. Specifically, Ibis expects to depend on third parties to sell and distribute its assay kits to non-government customers in the healthcare-associated infection control and infectious disease diagnostic markets. We may not successfully establish a relationship in these markets or be able to make alternative arrangements. If we are unable to reach agreements with suitable commercial or financial partners, we may fail to meet our business objectives for the Ibis T5000 Biosensor System. Moreover, these relationships may not succeed, may require us to give up a part of our ownership interest, or may diminish our revenue targets on our Ibis instruments and related assay kits.

**We depend on government contracts for most of Ibis' revenues and the loss of government contracts or a decline in funding of existing or future government contracts could adversely affect our revenues and cash flows.**

Virtually all of Ibis' revenues are from the sale of services and products to the U.S. government. The U.S. government may cancel these contracts at any time without penalty or may change its requirements, programs or contract budget or decline to exercise option periods, even if we have fully performed our obligations. Since a large portion of Ibis' government contracts are milestone based, if Ibis fails to meet a specific milestone within the specified delivery date, our government partner may be more likely to reduce or cancel its contract with Ibis. Our revenues and cash flows from U.S. government contracts could also be reduced by declines in U.S. defense, homeland security and other federal agency budgets.

For the three months and year ended December 31, 2006, we derived approximately 13% and 37%, respectively, of our revenue from agencies of the U.S. government, including through our subcontract with SAIC. Because of the concentration of our contracts, we are vulnerable to adverse changes in our revenues and cash flows if a significant number of our U.S. government contracts and subcontracts are simultaneously delayed or canceled for budgetary, performance or other reasons.

If U.S. defense and other federal agencies choose to reduce their purchases under our contracts, exercise their right to terminate contracts, fail to exercise options to renew contracts or limit our ability to obtain new contract awards, our revenues and cash flows could be adversely affected.

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

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

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

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**If our Ibis T5000 Biosensor System's reliability does not meet market expectations, we may be unable to retain our existing customers and attract new customers.**

Complex instruments such as our Ibis T5000 Biosensor System typically require operating and reliability improvements following their initial introduction. As we continue to develop our Ibis T5000 Biosensor System and its related applications, we will need to make sure our customers are satisfied with the sensor's reliability. Our efforts to satisfy our customer's needs for instrument reliability could result in greater than anticipated service expenses or divert other resources. Additionally, if we fail to resolve reliability issues as they develop, we could materially damage our reputation, which could prevent us from retaining our existing customers and attracting new customers.

**If we had to replace a supplier of one of the major hardware components of our Ibis T5000 Biosensor System, it could delay our commercialization efforts and lengthen our sales cycle.**

We have a single supplier for each major hardware component of our Ibis T5000 Biosensor System. Although, we believe we would be able to find a replacement provider, if any of these suppliers stopped providing us with their respective components, identifying and securing a suitable replacement could delay our commercialization efforts and lengthen our sales cycle.

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

The market for products such as Ibis' is highly competitive. Currently, large reference laboratories, public health laboratories and hospitals perform the majority of diagnostic tests used by physicians and other health care providers. We expect that these laboratories will compete vigorously to maintain their dominance in the diagnostic testing market. To remain competitive, we will need to continually improve Ibis' products so that, when compared to alternatives, its products:

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

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

Many of our competitors have, and in the future these and other competitors may have, significantly greater financial, marketing, sales, manufacturing, distribution and technological resources than us. Moreover, these companies may have substantially greater expertise in conducting clinical trials and research and development, greater ability to obtain necessary intellectual property licenses and greater brand recognition than we do. In addition, our competitors may be in a better position to respond quickly to new or emerging technologies, may be able to undertake more extensive marketing campaigns, may adopt more aggressive pricing policies and may be more successful in attracting potential customers, employees and strategic partners than we are.

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

We expect to derive a significant portion of our Ibis revenues from the sale of assay kits necessary to use our Ibis T5000 Biosensor System. The need to quickly identify and contain major threats, such as the avian flu, could increase the demand for our assay kits. Conversely, improvements in containing or treating a threat, such as vaccines, would significantly reduce the need to identify and contain the threat. Any reduction in the need to identify or contain a threat could diminish the need for our assay kits, which could reduce our revenues.

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

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

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

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

Although our research staff seeks to discover particular nucleic acid sequences for targeted diseases, our ability to offer diagnostic tests for diseases may depend on the ability of third parties to discover particular sequences or markers and correlate them with disease, as well as the rate at which such discoveries are made. Our ability to design products that target these diseases may depend on our ability to obtain the necessary access to raw materials or intellectual property rights from third parties who make any of these discoveries. If we are unable to access new technologies or the rights to particular sequences or markers necessary for additional diagnostic products on commercially reasonable terms or at all, we may not be able to develop new diagnostic products or enter new markets.

**The sales cycles for our Ibis T5000 Biosensor Systems are lengthy, and we may expend substantial funds and management effort with no assurance of successfully selling our Ibis T5000 Biosensor Systems or services.**

The sales cycles for Ibis T5000 Biosensor Systems are typically lengthy. Our sales and licensing efforts, and those of our partners, will require the effective demonstration of the benefits, value, and differentiation and validation of our products and services, and significant training of multiple personnel and departments within a potential customer organization. We or our partners may be required to negotiate agreements containing terms unique to each prospective customer or licensee, which would lengthen the sales cycle. We may expend substantial funds and management effort with no assurance that we will sell our products. In addition, this lengthy sales cycle makes it more difficult for us to accurately forecast revenue in future periods and may cause revenues and operating results to vary significantly in future periods.

**If we or our partners are required to obtain regulatory approval for our Ibis T5000 Biosensor System, we may not successfully obtain approval.**

Ibis' business plan assumes a significant portion of its revenues will come from Ibis T5000 Biosensor Systems and assay kits for *in vitro* diagnostic purposes, whose uses are regulated by the FDA and comparable agencies of other countries. In addition, customers may wish to utilize the Ibis T5000 Biosensor System and assay kits in manners that require additional regulatory approval. To access these markets, Ibis' products may require either premarket approval or 510(k) clearance from the FDA and other regulatory agencies prior to marketing. The 510(k) clearance process usually takes from three to twelve months from submission, but can take longer. The premarket approval process is much more costly, lengthy, and uncertain and generally takes from six months to two years or longer from submission. In addition, commercialization of any diagnostic or other product that our licensees or collaborators or we develop would depend upon successful completion of preclinical testing and clinical trials. Preclinical testing and clinical trials are long, expensive and uncertain processes, and we do not know whether we, our licensees or any of our collaborators, would be permitted or able to undertake clinical trials of any potential products. It may take us or our licensees or collaborators many years to complete any such testing, and failure could occur at any stage.

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Preliminary results of clinical trials do not necessarily predict final results, and acceptable results in early clinical trials may not be repeated in later clinical trials. We or our collaborators may encounter delays or rejections of potential products based on changes in regulatory policy for product approval during the period of product development and regulatory agency review. If our Ibis T5000 Biosensor System is considered a medical device, after gaining market approval from the FDA, our Ibis T5000 Biosensor System may be subject to ongoing FDA requirements governing the labeling, packaging, storage, advertising, promotion, recordkeeping and reporting of safety and other post-market information.

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

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

**RISKS RELATED TO THE CONVERTIBLE NOTES**

**The Notes are unsecured and subordinated to our existing and future senior indebtedness and to our existing and future secured debt. The Notes are also effectively subordinated to the liabilities of our subsidiaries.**

The Notes are unsecured and subordinated in right of payment to our existing and future senior indebtedness. In the event of bankruptcy, liquidation or reorganization or upon acceleration of the Notes due to an event of default under the indenture relating to the Notes and in certain other events, our assets will be available to pay obligations on the Notes only after all senior indebtedness, including secured debt, has been paid in full in cash. The Notes are also effectively subordinated to the liabilities of our subsidiaries. There may not be sufficient assets remaining to pay amounts due on any or all of the Notes then outstanding. As a result, the holders of our senior indebtedness or secured debt may recover more, ratably, than the holders of the Notes or our other subordinated indebtedness. The indenture does not limit our ability to incur additional senior indebtedness, secured debt or any other indebtedness. Any significant additional senior indebtedness or secured debt incurred may also materially adversely impact our ability to service our debt, including the Notes. In addition, the holders of our senior indebtedness may, under specific circumstances, restrict or prohibit us from making payments on the Notes. As of December 31, 2006, we had approximately \$15.0 million of senior indebtedness outstanding, all of which was secured debt. We anticipate that from time to time we may incur additional indebtedness, including senior indebtedness.

**The Notes do not contain restrictive covenants and provide only limited protection in the event of a change of control.**

The indenture under which the Notes were issued does not contain restrictive covenants that would protect you from several kinds of transactions that may adversely affect you. In particular, the indenture does not contain covenants that limit our ability to pay dividends or make distributions on or redeem our capital stock or limit our ability to incur additional indebtedness and, therefore, may not protect you in the event of a highly leveraged transaction or other similar transaction. The requirement that we offer to repurchase the Notes upon a change of control is limited to the transactions specified in the definition of a "fundamental change" under "Description of Notes — Repurchase at the Option of the Holder — Fundamental Change Put." Similarly, the circumstances under which we are required to adjust the conversion rate upon the occurrence of a "non-stock change of control" are limited to circumstances where the

Accordingly, subject to restrictions contained in our other debt agreements, we could enter into certain transactions, such as acquisitions, refinancings or recapitalizations, that could affect our capital structure and the value of the Notes and common stock but would not constitute a fundamental change under the Notes.

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**We may be unable to repurchase the Notes for cash when required by the holders, including following a fundamental change.**

Holder of the Notes has the right to require us to repurchase the Notes on specified dates or upon the occurrence of a fundamental change prior to maturity as described under “Description of Notes — Repurchase at the Option of the Holder — Optional Put” and “— Fundamental Change Put.” Any of our future debt agreements may contain a similar provision. We may not have sufficient funds to make the required repurchase in cash at such time or the ability to arrange necessary financing on acceptable terms. In addition, our ability to repurchase the Notes in cash may be limited by law or the terms of other agreements relating to our debt outstanding at the time, including our loan agreement with Silicon Valley Bank, which will limit our ability to purchase the Notes for cash in specific circumstances. If we fail to repurchase the Notes in cash as required by the indenture, it would constitute an event of default under the indenture governing the Notes, which, in turn, would constitute an event of default under our loan agreement with Silicon Valley Bank.

**Some significant restructuring transactions may not constitute a fundamental change, in which case we would not be obligated to offer to repurchase the Notes.**

Upon the occurrence of a fundamental change, you have the right to require us to offer to repurchase the Notes. However, the fundamental change provisions will not afford protection to holders of the Notes in the event of specific transactions. For example, transactions such as leveraged recapitalizations, refinancings, restructurings or acquisitions initiated by us would not constitute a fundamental change requiring us to repurchase the Notes. In the event of any such transaction, the holders would not have the right to require us to repurchase the Notes, even though each of these transactions could increase the amount of our indebtedness, or otherwise adversely affect our capital structure, thereby adversely affecting the holders of the Notes.

**The adjustment to the conversion rate upon the occurrence of certain types of fundamental changes may not adequately compensate you for the lost option time value of your Notes as a result of such fundamental change.**

If certain types of fundamental changes occur on or prior to the date when the Notes may be redeemed, we may adjust the conversion rate of the Notes to increase the number of shares issuable upon conversion. The number of additional shares to be issued will be determined based on the date on which the fundamental change becomes effective and the price paid per share of our common stock in the fundamental change as described under “Description of Notes — Conversion Procedures — Adjustment to Conversion Price Upon a Non-Stock Change of Control.” Although this adjustment is designed to compensate you for the lost option value of your Notes as a result of certain types of fundamental changes, the adjustment is only an approximation of such lost value based upon assumptions made on the date of this prospectus and may not adequately compensate you for such loss. In addition, if the price paid per share of our common stock in the fundamental change is less than \$11.25 or more than \$35.00, subject to adjustment, there will be no such adjustment.

**The failure of a market to develop for the Notes could adversely affect the liquidity and value of your Notes.**

We do not intend to apply for listing of the Notes on any securities exchange or for quotation of the Notes on any automated dealer quotation system. A market may not develop for the Notes, and there can be no assurance as to the liquidity of any market that may develop for the Notes. If an active, liquid market does not develop for the Notes, the market price and liquidity of the Notes may be adversely affected. If any of the Notes are traded after their initial issuance, they may trade at a discount from their initial offering price.

The liquidity of the trading market, if any, and future trading prices of the Notes will depend on many factors, including, among other things, the market price of our common stock, our ability to register the resale of the Notes and the shares of common stock issuable upon conversion of the Notes, prevailing interest rates, our operating results, financial performance and prospects, the market for similar securities and the overall securities market, and may be adversely affected by unfavorable changes in these factors. Historically, the market for convertible debt and for the securities of biotechnology companies has been subject to disruptions that have caused volatility in prices. It is possible that the market for the Notes will be subject to disruptions which may have a negative effect on the holders of the Notes, regardless of our operating results, financial performance or prospects.

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**The conditional conversion feature of the Notes could result in your receiving less than the value of the common stock into which the Notes are convertible.**

The Notes are convertible into shares of our common stock only if specified conditions are met. If these conditions are not met, you will not be able to convert your Notes, and you may not be able to receive the value of the common stock into which the Notes would otherwise be convertible.

**Upon conversion of the Notes, we may pay cash in lieu of issuing shares of our common stock or a combination of cash and shares of our common stock. Therefore, holders of the Notes may receive no shares of our common stock or fewer shares than the number into which their Notes are convertible.**

We have the right to satisfy our conversion obligation to holders by issuing shares of common stock into which the Notes are convertible, the cash value of the common stock into which the Notes are convertible, or a combination thereof. In addition, we have the right to irrevocably elect to satisfy our conversion obligation in cash with respect to the principal amount of the Notes to be converted after the date of such election. Accordingly, upon conversion of the Notes, holders may not receive any shares of our common stock, or they might receive fewer shares of common stock relative to the conversion value of the

Notes. Further, our liquidity may be reduced to the extent that we choose to deliver cash rather than shares of common stock upon conversion of the Notes. In addition, in the event of our bankruptcy, insolvency or certain similar proceedings during the cash settlement averaging period (as defined under “Description of Notes — Conversion Procedures — Settlement Upon Conversion”), there is a risk that a bankruptcy court may decide a holder’s claim to receive such cash and/or shares could be subordinated to the claims of our creditors as a result of such holder’s claim being treated as an equity claim in bankruptcy.

**The conversion rate of the Notes may not be adjusted for all dilutive events that may adversely affect the trading price of the Notes or the common stock issuable upon conversion of the Notes.**

The conversion rate of the Notes is subject to adjustment upon certain events, including the issuance of stock dividends on our common stock, the issuance of rights or warrants, subdivisions, combinations, distributions of capital stock, indebtedness or assets, cash dividends and issuer tender or exchange offers as described under “Description of Notes — Conversion Procedures — Conversion Rate Adjustments.” The conversion rate will not be adjusted for certain other events that may adversely affect the trading price of the Notes or the common stock issuable upon conversion of the Notes, including the issuance of additional shares of our common stock or securities convertible into our common stock.

**If we pay a cash dividend on our common stock, you may be deemed to have received a taxable dividend without the receipt of any cash.**

If we pay a cash dividend on our common stock, an adjustment to the conversion rate will result, and you may be deemed to have received a taxable dividend subject to United States federal income tax without the receipt of any cash. If you are a non-U.S. holder (as defined in “Certain U.S. Federal Tax Considerations”), such deemed dividend may be subject to United States federal withholding tax at a 30% rate or such lower rate as may be specified by an applicable treaty. See “Certain U.S. Federal Tax Considerations.”

**SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS**

This prospectus and the documents incorporated by reference contain forward-looking statements regarding Isis Pharmaceuticals’ business, the financial position and outlook for Isis and Ibis Biosciences, and the therapeutic and commercial potential of Isis’ technologies and products in development. Any statement describing Isis’ goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis’ goals or projections. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, in developing and commercializing systems to identify infectious organisms that are effective and commercially attractive, and in the endeavor of building a business around such products. Isis’ forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis’ forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in the section entitled “Risk Factors” in this prospectus. As a result, you are cautioned not to rely on these forward-looking statements.

**RATIO OF EARNINGS TO FIXED CHARGES**

The following table sets forth our ratio of earnings to fixed charges for each of the periods indicated. As earnings are inadequate to cover the combined fixed charges, we have provided the deficiency amounts. For purposes of calculating this deficiency, earnings consist of income (loss) from continuing operations before (i) income taxes, (ii) income (loss) from equity investees and (iii) fixed charges. Fixed charges consist of interest expense, including amortization of debt issuance costs, and the portion of rent expense which we believe is representative of the interest component of rental expense. For the periods indicated below, we had no outstanding shares of preferred stock with required dividend payments.

	Fiscal Year Ended December 31,				
	2002	2003	2004	2005	2006
Deficiency of earnings available to cover fixed charges	\$ (72,242)	\$ (94,996)	\$ (142,503)	\$ (72,401)	\$ (68,924)

**PRICE RANGE OF COMMON STOCK**

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

	HIGH	LOW
<b>2007</b>		
First Quarter (through March 12, 2007)	\$ 12.59	\$ 8.30
<b>2006</b>		
First Quarter	\$ 9.34	\$ 5.09
Second Quarter	\$ 9.50	\$ 5.76
Third Quarter	\$ 7.89	\$ 5.57
Fourth Quarter	\$ 14.0	\$ 7.06
<b>2005</b>		



First Quarter	\$ 6.09	\$ 3.76
Second Quarter	\$ 4.29	\$ 2.76
Third Quarter	\$ 5.80	\$ 3.75
Fourth Quarter	\$ 5.41	\$ 4.20

As of March 12, 2007, there were approximately 960 stockholders of record of our common stock. On March 12, 2007, the closing price of our common stock on the Nasdaq Global Market was \$9.38.

## DIVIDEND POLICY

We have never declared or paid any cash dividends on our capital stock. We intend to retain any future earnings to support operations and to finance the growth and development of our business and we do not anticipate paying cash dividends for the foreseeable future.

## USE OF PROCEEDS

We will receive no proceeds from the resale by the selling security holders of the notes or the common stock issuable upon conversion of the notes. The selling security holders will receive all of the net proceeds from the resales.

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## SELLING SECURITY HOLDERS

We initially issued the notes to the initial purchasers of the notes who then resold the notes in transactions exempt from the registration requirements of the Securities Act to persons reasonably believed to be “qualified institutional buyers” (as defined in Rule 144A under the Securities Act). The selling security holders (which term includes their transferees, pledgees, donees or their successors) may from time to time offer and sell pursuant to this prospectus or any applicable prospectus supplement any or all of the notes and common stock issuable upon conversion of the notes.

No offer or sale under this prospectus may be made by a selling security holder unless that holder is listed in the table in this prospectus or until that holder has notified us and a supplement to this prospectus has been filed or an amendment to the registration statement of which this prospectus is a part has become effective. We will supplement or amend this prospectus to include additional selling security holders upon request and upon provision of all required information to us. Information concerning the selling security holders may change from time to time and any changed information will be set forth in supplements to this prospectus if and when necessary.

The following table sets forth information about each selling security holder, including the name, the number and percentage of the notes beneficially owned and being offered by the selling security holder and the number and percentage of common stock beneficially owned and being offered by the selling security holder. The percentages of common stock beneficially owned and being offered are based on the number of shares of our common stock that were outstanding as of March 12, 2007. Unless otherwise indicated below, none of the selling security holders nor any of their affiliates, officers, directors or principal equity holders has held any position or office or has had any material relationship with us within the past three years.

Name	Principal Amount of Notes Beneficially Owned and Offered Hereby	Percentage of Notes Outstanding	Shares of Common Stock Beneficially Owned and Offered Hereby	Percentage of Common Stock Outstanding
Absolute Strategies Fund, Forum Funds Trust	400,000	*	27,350	—
ADI Alternative Investments	1,000,000	*	68,376	—
ADI Alternative Investments c/o Casam ADI CB Arbitrage	1,000,000	*	68,376	—
ADI Alternative Investments c/o Kallista Master Fund Ltd.	2,000,000	1.2%	136,752	—
Admiral Flagship Master Fund, Ltd.	500,000	*	34,188	—
Advent Convertible ARB Master	4,628,000	2.8%	316,444	—
Advent Enhanced Phoenix Fund	2,000,000	1.2%	136,752	—
AHFP Context	410,000	*	28,034	—
Alcon Laboratories	377,000	*	25,777	—
Altma Fund SICAV PLC in respect of the Grafton Sub Fund	1,020,000	*	69,743	—
Argent Classic Convertible Arbitrage Fund L.P.	850,000	*	58,119	—
Argent Classic Convertible Arbitrage Fund Ltd.	5,280,000	3.2%	361,025	—
Argent Classic Convertible Arbitrage Fund II, L.P.	200,000	*	13,675	—
Argentum Multi-Strategy Fund Ltd. — Classic	80,000	*	5,470	—
Arlington County Employees Retirement System	542,000	*	37,059	—
Barclays Capital Securities Ltd.	5,500,000	3.4%	376,068	—
B.C. McCabe Foundation	80,000	*	5,470	—
BNP Paribas Arbitrage(1)**	500,000	*	34,188	—
British Virgin Island Social Security Board	125,000	*	8,547	—
Calamos Market Neutral Income Fund — Calamos Investment Trust	5,000,000	3.1%	341,880	—
CASAM Argent Classic Convertible Arbitrage Fund Limited	160,000	*	10,940	—
CASAM Context Offshore Advantage Fund Limited	380,000	*	25,982	—
Citadel Equity Fund, Ltd.(2)**	5,000,000	3.1%	341,880	*
City of Shreveport (LA) Employees Retirement System	80,000	*	5,470	—
City University of New York (CUNY)	108,000	*	7,384	—
ClearBridge Asset Management Inc.(3)**	7,050,000	4.3%	482,051	—
CNH CA Master Account, L.P.(4)	500,000	*	34,188	—

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Columbia Convertible Securities Fund(5)	1,960,000	1.2%	134,017	*
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Commissioners of the Land Office	850,000	*	58,119	—
Constans Healthcare Convertible Arbitrage Fund	250,000	*	17,094	—
Context Advantage Master Fund, LP	3,820,000	2.4%	261,196	—
Daimler Chrysler Corp Emp #1 Pension Plan, DTD 4/1/89(6)	787,000	*	53,811	—
Elite Classic Convertible Arbitrage Ltd.	160,000	*	10,940	—
Federated Kaufman Fund, a portfolio of Federated Equity Funds(7)	19,800,000	12.2%	1,353,846	12.7%
Finch Tactical Plus Class B	170,000	*	11,623	—
Florida Power and Light Group Employee Pension Plan(6)	304,000	*	20,786	—
Franklin and Marshall College(6)	19,000	*	1,299	—
Froley Revy Alternative Strategies	600,000	*	41,025	—
GLG Market Neutral Fund(8)	6,000,000	3.7%	410,256	—
GMIMCO Trust	990,000	*	67,692	—
Grady Hospital Foundation	104,000	*	7,111	—
HFRCA Opportunity Master Trust	205,000	*	14,017	—
Institutional Benchmarks Series (Master Feeder) Limited in respect of Alcor series	200,000	*	13,675	—
Intl. Truck & Engine Corp Non Contributory Retirement Plan Trust	635,000	*	43,418	—
Intl. Truck & Engine Corp Retirement Plan for Salaried Employee's Trust	280,000	*	19,145	—
KeySpan Foundation	40,000	*	2,735	—
KeySpan Insurance Company	140,000	*	9,572	—
LDG, Limited(9)	222,000	*	15,179	—
Lord Abbett Investment Trust — LA Convertible Fund	3,080,000	1.9%	210,598	—
Lyxor/Context Fund LTD	790,000	*	54,017	—
Lyxor Master Trust Fund	167,000	*	11,418	—
Mohican VCA Master Fund Ltd	3,100,000	1.9%	211,965	—
National Fuel & Gas Company Retirement Plan	445,000	*	30,427	—
NFS — SCI Funeral and Merchandise Fixed Common Trust	30,000	*	2,051	—
Occidental Petroleum Corporation	250,000	*	17,094	—
The Northwestern Mutual Life Insurance Company — General Account(10)**	2,250,000	1.4%	153,846	—
The Northwestern Mutual Life Insurance Company — Group Annuity Separate Account(10)**	250,000	*	17,094	—
NYC Teachers' Variable Annuity Fund	1,400,000	*	95,726	—
Philadelphia Board of Pensions	550,000	*	37,606	—
Police & Fire Retirement System of the City of Detroit	416,000	*	28,444	—
Polygon Global Opportunities Master Fund(11)	1,000,000	*	68,376	—
ProMutual	685,000	*	46,837	—
Rampart Enhanced Convertible Investors, LLC(6)	140,000	*	9,572	—
San Francisco City and County ERS	1,071,000	*	73,230	—
SCI Cemetary Merchandise Common Trust	20,000	*	1,367	—
SCI Pre-Need Common Trust Fund	20,000	*	1,367	—
Stark Master Fund Ltd.(12)**	6,500,000	4.0%	444,444	—
Sterling Invest Co.	1,675,000	1.0%	114,529	—
Total Fina Elf Finance USA, Inc.	245,000	*	16,752	—
TQA Master Fund Ltd.(9)	1,425,000	*	97,435	—
TQA Master Plus Fund, Ltd.(9)(13)	885,000	*	60,512	*
Trustmark Insurance Company	267,000	*	18,256	—
Vermont Mutual Insurance Company	140,000	*	9,572	—
Vicis Capital Master Fund	9,000,000	5.5%	615,384	—
Wachovia Securities International Ltd(14)**	500,000	*	34,188	—
Worldwide Transactions Limited	210,000	*	14,358	—
Xavex Convertible Arbitrage 10 Fund	270,000	*	18,461	—
Zurich Institutional Benchmarks Master Fund Ltd. c/o TQA Investors, LLC(9)	468,000	*	32,000	—

\* Less than 1%

\*\* The selling security holder has represented to us that the notes held by them were purchased in the ordinary course of business and that at the time of purchase of the notes held by them, they did not have any agreements or understandings, directly or indirectly, with any person to distribute the notes held by them or the common stock issuable upon conversion of the notes held by them.

- (1) BNP Paribas Security Corp. is an affiliate of BNP Paribus Arbitrage, a registered broker-dealer.
- (2) Citadel Equity Fund, Ltd. also beneficially owns 630 shares of our common stock, which are not included for sale under this prospectus. The broker-dealers are under common control with Citadel Equity Fund Ltd. and is directly owned by Citadel Equity Fund. The broker dealers are: Aragon Investments Ltd., Palofax Trading LLC, Citadel Trading Group, LLC and Citadel Derivatives Group, LLC. Citadel Limited Partnership ("CLP") is the trading manager of Citadel Equity Fund Ltd. and consequently has investment discretion over securities held by Citadel Equity Fund Ltd. Citadel Investment Group, LLC ("CIG") controls CLP. Kenneth C. Griffin controls CIG and therefore has ultimate investment discretion over securities held by Citadel Equity Fund Ltd. CLP, CIG, and Mr. Griffin each disclaim beneficial ownership of the shares held by Citadel Equity Fund Ltd.
- (3) Selling Security Holder is under common control with Legg Mason Investors Services, LLC ("LMIS"), a limited purpose broker-dealer affiliate. LMIS serves as a principal underwriter for certain mutual funds managed by investment advisory affiliates of Legg Mason Inc.

- (4) CNH Partners, LLC is Investment Advisor of the Selling Securityholder and has sole voting and dispositive power over the securities. Investment principals for the Advisor are Robert Krail, Mark Mitchell and Todd Pulvino.
- (5) Columbia Convertible Securities Fund also beneficially owns \$1,960,000 principal amount of our 5.5% convertible subordinated notes due 2009, which are convertible into approximately 117,894 shares of our common stock. Neither of these securities are included for sale under this prospectus.
- (6) Palisade Capital Management, LLC acts as an Investment Advisor.
- (7) Federated Kaufman Fund also beneficially owns 9,274,660 shares of our common stock and 1,176,470 shares of our common stock issuable upon exercise of warrants. Neither of these securities are included for sale under this prospectus.

- (8) GLG Market Neutral Fund is a publicly owned company listed on the Irish Stock Exchange. GLG Partners LP, and English limited partnership, acts as the investment manager of the fund and has voting and dispositive power over the securities held by the fund. The general partner of GLG Partners LP is GLG Partners Limited, an English limited company. The shareholders of GLG Partners Limited are Noam Gottesman, Pierre Lagrange, Jonathan Green, Philippe Jabre and Lehman Brothers (Cayman) Limited, a subsidiary of Lehman Brothers Holdings, Inc., a publicly-held entity. The managing directors of GLG Partners Limited are Noam Gottesman, Pierre Lagrange and Emmanuel Roman and, as a result, each has voting and dispositive power over the securities held by the fund. GLG Partners LP, GLG Partners Limited, Noam Gottesman, Pierre Lagrange and Emmanuel Roman disclaim beneficial ownership of the securities held by the Fund, except for their pecuniary interest therein.
- (9) TQA Investors LLC has sole investment power and shared voting power. Its members are: John Idone, Paul Bucci and Darren Langis and Andrew Anderson.
- (10) The following NASD members are affiliated with Northwestern Mutual: Northwestern Mutual Investment Services, LLC, Russell Institutional Services, Russell Implementation Services, Inc., Russell Fund Distributors, Inc., and Todd Securities, LLC
- (11) Polygon Investment Partner LLP and Polygon Investment Partners LP (the "Investment Manager"), Polygon Investments Ltd. (the "Manager"), Alexander E. Jackson, Reade E. Griffith, and Patrick G. G. Dear share voting and dispositive power of the securities held by Polygon Global Opportunities Master Fund. The Investment Mangers, the Manger, Alexander E. Jackson, Reade E. Griffith, and Patrick G. G. Dear disclaim beneficial ownership of the securities held by Polygon Global Opportunities Master Fund.
- (12) Stark Master Fund Ltd. is an affiliate of Reliant Trading, a registered broker-dealer.
- (13) TQA Master Plus Fund, Ltd also beneficially owns 10,000 shares of our common stock, which are not included for sale under this prospectus.
- (14) Wachovia Securities Intl. Ltd and Wachovia Capital Markets LLC are subsidiaries of Wachovia Corporation.

We prepared this table based on the information supplied to us by the selling security holders named in the table and we have not sought to verify such information.

The selling security holders listed in the above table may have sold or transferred, in transactions exempt from the registration requirements of the Securities Act, some or all of their notes since the date on which the information in the above table was provided to us. Information about the selling security holders may change over time.

Because the selling security holders may offer all or some of the notes or the shares of common stock issuable upon conversion of the notes from time to time, we cannot estimate the amount of the notes or shares of common stock that will be held by the selling security holders upon the termination of any particular offering by a selling security holder. See "Plan of Distribution."

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## PLAN OF DISTRIBUTION

The selling securityholders, which term includes all transferees, pledgees, donees or their successors, may from time to time sell the notes and the common stock into which the notes are convertible covered by this prospectus, which we refer to in this section as the "securities," directly to purchasers or offer the securities through underwriters, broker-dealers or agents, who may receive compensation in the form of underwriting discounts, concessions or commissions from the selling securityholders and/or the purchasers of securities for whom they may act as agent, which discounts, concessions or commissions as to any particular underwriter, broker-dealer or agent may be in excess of those customary in the types of transactions involved.

The securities may be sold in one or more transactions:

- at fixed prices;
- at prevailing market prices at the time of sale;
- at varying prices determined at the time of sale; or
- at negotiated prices.

These sales may be effected in transactions, which may involve crosses or block transactions, in the following manner:

- on any national securities exchange or quotation service on which the securities may be listed or quoted at the time of sale;
- in the over-the-counter-market;
- in transactions otherwise than on these exchanges or services or in the over-the-counter market; or
- through the writing and exercise of options, whether these options are listed on any options exchange or otherwise.

In connection with the sale of the securities, the selling securityholders may enter into hedging transactions with broker-dealers or other financial institutions, which may in turn engage in short sales of the securities in the course of hedging positions they assume. The selling securityholders may sell the securities short and deliver securities to close out short positions, or loan or pledge the securities or broker-dealers that in turn may sell these securities. The selling securityholders may also pledge or grant security interests in some or all of their securities, and, if the selling securityholders default in the performance of their obligations, the pledgees or secured parties may offer and sell the securities from time to time pursuant to this prospectus.

Our outstanding common stock is listed for trading on the Nasdaq Global Market under the symbol "ISIS." We do not intend to list the notes on any securities exchange. We cannot assure you as to the liquidity of any trading market for the notes that may develop.

In order to comply with the securities laws of some jurisdictions, if applicable, the holders of securities may offer and sell those securities in such jurisdictions only through registered or licensed brokers or dealers. In addition, under certain circumstances, in some jurisdictions the securities may not be offered or sold unless they have been registered or qualified for sale in the applicable jurisdiction or an exemption from registration or qualification requirements is available and is complied with.

The selling securityholders, and any underwriters, broker-dealers or agents that participate in the sale of the securities, may be "underwriters" within the meaning of Section 2(11) of the Securities Act. Any discounts, commissions, concessions or profit they earn on any sale of the securities may be underwriting compensation under the Securities Act. The selling securityholders have acknowledged that they understand their obligations to comply

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with the provisions of the Exchange Act and the rules thereunder relating to stock manipulation, particularly Regulation M, and have agreed that they will not engage in any transaction in violation of such provisions.

If required, at the time of a particular offering of securities by a selling securityholder, a supplement to this prospectus will be circulated setting forth the name or names of any underwriters, broker-dealers or agents, any discounts, commissions or other terms constituting compensation for underwriters and any discounts, commissions or concessions allowed or reallocated or paid to agents or broker-dealers.

We entered into a registration rights agreement for the benefit of holders of the securities to register their securities under applicable federal and state securities laws under specific circumstances and at specific times. The registration rights agreements provided for cross indemnification of the selling securityholders and us and their and our respective directors, officers and controlling persons against specific liabilities in connection with the offer and sale of the securities, including liabilities under the Securities Act. In the event the selling securityholders sell their securities through any underwriter, dealer or agent the registration rights agreement provides for indemnification by us of those underwriters, dealers or agents and their respective directors, officers and controlling persons against specified liabilities in connection with the offer and sale of those securities. Pursuant to the registration rights agreement, we will bear all fees and expenses incurred in connection with the registration of the securities, except that selling securityholders will pay all underwriting discounts and commissions and transfer taxes.

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## DESCRIPTION OF NOTES

On January 23, 2007, we issued and sold the notes in a private placement transaction. The initial purchasers of the notes in that offering resold the notes to persons reasonably believed to be qualified institutional buyers (as defined in Rule 144A under the Securities Act). The convertible notes were issued under the indenture dated January 23, 2007 between us and Wells Fargo Bank, N.A., as trustee. The following statements are subject to the detailed provisions of the indenture and are qualified in their entirety by reference to the indenture. The indenture has been filed as an exhibit to the registration statement of which this prospectus is a part. Particular provisions of the indenture which are referred to in this prospectus are incorporated by reference as a part of the statements made, and the statements are qualified in their entirety by the reference. For purposes of this summary, the terms "Isis," "we," "us" and "our" refer only to Isis Pharmaceuticals, Inc. and not to any of our subsidiaries.

### Brief Description of the Notes

The Notes bear interest at a rate of 2<sup>5</sup>/<sub>8</sub> % per year, payable semi-annually in arrears, on February 15 and August 15 of each year, commencing on August 15, 2007 and are:

- initially limited to \$162.5 million aggregate principal amount;
- our unsecured subordinated obligations and are to be subordinated in right of payment to all of our existing and future senior indebtedness, including our secured indebtedness; structurally subordinated to the indebtedness of our subsidiaries; and equal in right of payment with our 5<sup>1</sup>/<sub>2</sub> % convertible subordinated notes due 2009;
- convertible by you at any time on or prior to the business day preceding the maturity date, only upon satisfaction of at least one of the conditions for conversion, as described under "—Conversion Rights," into shares of our common stock initially based on a conversion rate of 68.3761 shares of our common stock per \$1,000 principal amount of Notes, which represents an initial conversion price of approximately \$14.63 per share. As described under "— Conversion Procedures — Settlement Upon Conversion," upon conversion we may choose to deliver either shares of our common stock, cash or a combination of cash and shares of our common stock in satisfaction of our obligations upon conversion of the Notes. In the event of specific types of fundamental changes, we will increase the conversion rate or, in lieu thereof, we may elect to adjust the conversion obligation and conversion rate so that the Notes are convertible into shares of the acquiring or surviving company, in each case as described herein;
- subject to redemption for cash by us at any time on or after February 15, 2012, in whole or in part, at the redemption prices described below under "Optional Redemption," plus accrued and unpaid interest (including additional interest, if any) to, but not including, the redemption date;
- subject to repurchase by us, at your option, on February 15, 2014, February 15, 2017 and February 15, 2022, at a cash repurchase price equal to 100% of the principal amount of the Notes, plus accrued and unpaid interest (including additional interest, if any) to, but not including, the repurchase date, as set forth under "— Repurchase at the Option of the Holder — Optional Put";

- subject to repurchase by us at your option if a fundamental change occurs, at a cash repurchase price equal to 100% of the principal amount of the Notes, plus accrued and unpaid interest (including additional interest, if any) to, but not including, the repurchase date, as set forth under “— Repurchase at the Option of the Holder — Fundamental Change Put”; and
- due on February 15, 2027, unless earlier converted, redeemed by us at our option or repurchased by us at your option.

Neither we nor any of our subsidiaries will be subject to any financial covenants under the indenture. In addition, neither we nor any of our subsidiaries will be restricted under the indenture from paying dividends, incurring debt or issuing or repurchasing our securities. You are not afforded protection under the indenture in the event of a highly leveraged transaction or a change in control of us, except to the extent described below under “— Conversion Rights” and “— Repurchase at the Option of the Holder — Fundamental Change Put.”

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No sinking fund is provided for the Notes, and the Notes will not be subject to defeasance.

The Notes were initially issued in book-entry form only in denominations of \$1,000 principal amount and whole multiples thereof. Beneficial interests in the Notes are shown on, and transfers of beneficial interests in the Notes are effected only through, records maintained by The Depository Trust Company, or DTC, or its nominee, and any such interests may not be exchanged for certificated Notes except in limited circumstances. For information regarding conversion, registration of transfer and exchange of global Notes held in DTC, see “— Form, Denomination and Registration — Global Notes Book-Entry Form.”

If certificated Notes are issued, you may present them for conversion, registration of transfer and exchange, without service charge, at our office or agency, which will initially be the office or agency of the trustee.

#### **Additional Notes**

We may, without the consent of the holders of the Notes, increase the principal amount of the Notes by issuing additional Notes in the future on the same terms and conditions, except for any differences in the issue price and interest accrued prior to the issue date of the additional Notes; provided that such differences do not cause the additional Notes to constitute a different class of securities than the Notes for U.S. federal income tax purposes; and provided further, that the additional Notes have the same CUSIP number as the Notes offered hereby. The Notes offered by this prospectus and any additional Notes would rank equally and ratably and would be treated as a single class for all purposes under the Indenture. No additional Notes may be issued if any event of default has occurred with respect to the Notes.

#### **Payment at Maturity**

On the maturity date, each holder will be entitled to receive on such date \$1,000 in cash for each \$1,000 in principal amount of Notes, together with premium, if any, accrued and unpaid interest, including additional interest, if any, to, but not including, the maturity date. With respect to global Notes, principal, premium, if any, and interest, including additional interest, if any, will be paid to DTC in immediately available funds. With respect to any certificated Notes, principal and interest, including additional interest, if any, will be payable at our office or agency, which initially will be the office or agency of the trustee.

#### **Interest**

The Notes will bear interest at a rate of 2<sup>5</sup>/<sub>8</sub> % per year. Interest will accrue from January 23, 2007, or from the most recent date to which interest has been paid or duly provided for. We will pay interest (including additional interest, if any) semi-annually, in arrears on February 15 and August 15 of each year, commencing on August 15, 2007, to holders of record at 5:00 p.m., New York City time, on the preceding February 1 and August 1, respectively. However, there are two exceptions to the preceding sentence:

- we will not pay in cash accrued interest (excluding any additional interest) on any Notes when they are converted, except as described under “— Conversion Rights”; and
- we will pay accrued and unpaid interest (including additional interest, if any) to a person other than the holder of record on the record date on the maturity date. On such date, we will pay accrued and unpaid interest only to the person to whom we pay the principal amount.

Similarly, the interest payable upon redemption or repurchase following a fundamental change will be payable to the person to whom principal is payable upon maturity or pursuant to such redemption or repurchase following a fundamental change (unless the redemption date or the fundamental change repurchase date, as the case may be, is after a record date and on or prior to the corresponding interest payment date, in which case the semi-annual payment of interest becoming due on such interest payment date will be payable to the holder of such Notes registered as such on the applicable record date).

We will pay interest on:

- global Notes to DTC in immediately available funds;

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- any certificated Notes having a principal amount of less than \$2,000,000, by check mailed to the holders of those Notes; provided, however, at maturity, interest will be payable as described under “— Payment at Maturity”; and

any certificated Notes having a principal amount of \$2,000,000 or more, by wire transfer in immediately available funds at the election of the holders of these Notes duly delivered to the trustee at least five business days prior to the relevant interest payment date; provided, however, at maturity, interest will be payable as described under “— Payment at Maturity.”

Interest is calculated on the basis of a 360-day year consisting of twelve 30-day months. If a payment date is not a business day, payment will be made on the next succeeding business day, and no additional interest will accrue thereon.

To the extent lawful, payments of principal or interest (including additional interest, if any) on the Notes that are not made when due will accrue interest at the annual rate of 1% above the then applicable interest rate from the required payment date.

## Ranking and Subordination

The indebtedness evidenced by the Notes will be unsecured and subordinated to the extent provided in the indenture to the prior payment in full of all our senior indebtedness, including all of our secured indebtedness which includes approximately \$14.0 million outstanding under our Silicon Valley Bank term loan and approximately \$1.0 million under our capital leases as of December 31, 2006. The Notes are structurally subordinated to all indebtedness and other liabilities, including trade payables and lease obligations, if any, of our subsidiaries. Upon any distribution of our assets upon any dissolution, winding up, liquidation or reorganization, the payment of the principal of, or premium, if any, and interest on the Notes will be subordinated to the extent provided in the indenture in right of payment to the prior payment in full in cash or other payment satisfactory to the holders of senior indebtedness of all senior indebtedness. In the event of any acceleration of the Notes because of an event of default, the holders of any senior indebtedness then outstanding will be entitled to payment in full in cash or other payment satisfactory to the holders of senior indebtedness of all obligations in respect of such senior indebtedness before the holders of the Notes are entitled to receive any payment or distribution in respect thereof. The indenture requires that we promptly notify holders of senior indebtedness if payment of the Notes is accelerated because of an event of default. The Notes rank equal in right of payment with our 5 ½% convertible subordinated notes due 2009.

We also may not make any payment upon or in respect of the Notes (including upon redemption) if (i) a payment default occurs and is continuing beyond any applicable period of grace or (ii) any other default occurs and is continuing with respect to designated senior indebtedness (as defined below) that permits holders of such designated senior indebtedness to accelerate its maturity, and the trustee receives a notice of such default (a “payment blockage notice”) from us or another person permitted to give such notice under the indenture (a “non-payment default”). Payments on the Notes may and will be resumed (a) in case of a payment default, upon the date on which such default is cured or waived or ceases to exist and (b) in case of a non-payment default, the earlier of the date on which such non-payment default is cured or waived or ceases to exist or 179 days after the date on which the applicable payment blockage notice is received. No new period of payment blockage may be commenced pursuant to clause (ii) above unless and until (i) 365 days have elapsed since the initial effectiveness of the immediately prior payment blockage notice and (ii) all scheduled payments of principal, premium, if any, and interest on the Notes that have come due have been paid in full in cash. No non-payment default that existed or was continuing on the date of delivery of any payment blockage notice to the trustee will be, or will be made, the basis for a subsequent payment blockage notice.

However, if the trustee, any paying agent on behalf of us or any holder of the Notes receives any payment or distribution of our assets of any kind in contravention of any of the subordination provisions of the indenture, whether in cash, property or securities, including, without limitation, by way of set-off or otherwise, in respect of the Notes before all senior indebtedness is paid in full in cash or other payment satisfactory to holders of senior indebtedness, then such payment or distribution will be held by the recipient in trust for the benefit of holders of senior indebtedness or their representatives to the extent necessary to make payment in full in cash or payment satisfactory to the holders of senior indebtedness of all senior indebtedness remaining unpaid, after giving effect to any concurrent payment or distribution, or provision therefor, to or for the holders of senior indebtedness.

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By reason of the subordination provisions described above, in the event of our bankruptcy, dissolution or reorganization, holders of senior indebtedness may receive more, ratably, and holders of the Notes may receive less, ratably, than our other creditors. Such subordination will not prevent the occurrence of any event of default under the indenture.

The term “senior indebtedness” means the principal of, premium, if any, accrued and unpaid interest (including all interest accruing subsequent to the commencement of any bankruptcy or similar proceeding, whether or not a claim for post-petition interest is allowable as a claim in any such proceeding) and rent payable on or in connection with, and all fees, costs, expenses and other amounts accrued or due on or in connection with, our indebtedness (as defined below), whether outstanding on the date of the indenture or thereafter created, incurred, assumed, guaranteed or in effect guaranteed by us (including all deferrals, renewals, extensions or refundings of, or amendments, modifications or supplements to, the foregoing), unless in the case of any particular indebtedness the instrument creating or evidencing the same or the assumption or guarantee thereof expressly provides that such indebtedness will not be senior in right of payment to the Notes or expressly provides that such indebtedness is *pari passu* or junior to the Notes. However, the term senior indebtedness will not include our 5 ½% convertible subordinated notes due 2009, or indebtedness of ours to any subsidiary of ours, a majority of the voting stock of which is owned, directly or indirectly, by us.

The term “indebtedness” means, with respect to any person (as defined in the indenture), and without duplication: (a) all indebtedness, obligations and other liabilities (contingent or otherwise) of such person for borrowed money (including our obligations in respect of overdrafts, foreign exchange contracts, currency exchange agreements, interest rate protection agreements, and any loans or advances from banks, whether or not evidenced by notes or similar instruments) or evidenced by bonds, debentures, notes or similar instruments (whether or not the recourse of the lender is to the whole of the assets of such person or to only a portion thereof), other than any account payable or other accrued current liability or obligation incurred in the ordinary course of business in connection with the obtaining of materials or services; (b) all reimbursement obligations and other liabilities (contingent or otherwise) of such person with respect to letters of credit, bank guarantees or bankers’ acceptances; (c) all obligations and liabilities (contingent or otherwise) in respect of leases of such person required, in conformity with generally accepted accounting principles, to be accounted for as capitalized lease obligations on the balance sheet of such person and all obligations and other liabilities (contingent or otherwise) under any lease or related document (including a purchase agreement) in connection with the lease of real property which provides that such person is contractually obligated to purchase or cause a third party to purchase the leased property and thereby guarantee a minimum residual value of the leased property to the lessor and the obligations of such person under such lease or related document to purchase or to cause a third party to purchase such leased property; (d) all obligations of such person (contingent or otherwise) with respect to an interest rate or other swap, cap or collar agreement or other similar instrument or agreement or foreign currency hedge, exchange, purchase or similar instrument or agreement; (e) all direct or indirect guaranties or similar agreements by such person in respect of, and obligations or liabilities (contingent or otherwise) of such person to purchase or otherwise acquire or otherwise assure a creditor against loss in respect of, indebtedness, obligations or liabilities of another person

of the kind described in clauses (a) through (d); (f) any indebtedness or other obligations described in clauses (a) through (e) secured by any mortgage, pledge, lien or other encumbrance existing on property which is owned or held by such person, regardless of whether the indebtedness or other obligation secured thereby will have been assumed by such person; and (g) any and all deferrals, renewals, extensions and refundings of, or amendments, modifications or supplements to, any indebtedness, obligation or liability of the kind described in clauses (a) through (f).

The term “designated senior indebtedness” means our obligations under any particular senior indebtedness with respect to which the instrument creating or evidencing the same or the assumption or guarantee thereof (or related agreements or documents to which we are a party) expressly provides that such senior indebtedness will be “designated senior indebtedness” for purposes of the indenture (provided that such instrument, agreement or other document may place limitations and conditions on the right of such senior indebtedness to exercise the rights of designated senior indebtedness).

As of December 31, 2006, we had approximately \$15.0 million of indebtedness outstanding that would have constituted senior indebtedness, including our secured indebtedness, which includes approximately \$14.0 million outstanding under our Silicon Valley Bank term loan and approximately \$1.0 million under our capital leases. The indenture does not limit the amount of additional indebtedness, including senior indebtedness, which we can create, incur, assume or guarantee, nor does the indenture limit the amount of indebtedness or other liabilities that any subsidiary of ours can create, incur, assume or guarantee.

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We are obligated to pay reasonable compensation to the trustee and to indemnify the trustee against specific losses, liabilities or expenses incurred by it in connection with its duties relating to the Notes. The trustee’s claims for such payments will generally be senior to those of the holders of the Notes in respect of all funds collected or held by the trustee.

### Conversion Rights

Holders may convert their Notes prior to the close of business on the business day preceding the maturity date based on an initial conversion rate of 68.3761 shares of common stock per \$1,000 principal amount of Notes (equivalent to an initial conversion price of approximately \$14.63 per share), only if the conditions for conversion described below are satisfied. The conversion rate will be subject to adjustment as described below. As described under “— Conversion Procedures — Settlement Upon Conversion,” upon conversion, we may choose to deliver, in lieu of shares of our common stock, cash or a combination of cash and shares of our common stock. At any time on or prior to the 26<sup>th</sup> trading day preceding the maturity date, we may irrevocably elect to satisfy our conversion obligation with respect to the principal amount of the Notes to be converted in cash, with any remaining amount to be satisfied in shares of our common stock or cash as we may subsequently elect, as described under “— Conversion Procedures — Settlement Upon Conversion — Our Right to Irrevocably Elect Cash Payment of Principal Upon Conversion.” Unless we have previously redeemed or purchased the Notes, you will have the right to convert any portion of the principal amount of any Notes that is an integral multiple of \$1,000 at any time on or prior to the close of business on the business day immediately preceding the maturity date only under the following circumstances:

- (1) prior to February 15, 2025, on any date during any fiscal quarter beginning after March 31, 2007 (and only during such fiscal quarter) if the closing sale price of our common stock was more than 120% of the then current conversion price for at least 20 trading days in the period of the 30 consecutive trading days ending on the last trading day of the previous fiscal quarter, as described below in more detail under “— Conversion Upon Satisfaction of Market Price Condition”;
- (2) at any time on or after February 15, 2025, as described below in more detail under “—Conversion 2 Years Prior to Maturity”;
- (3) with respect to any Notes called for redemption, until the close of business on the business day prior to the redemption date, as described below in more detail under “— Conversion Upon Notice of Redemption”;
- (4) if we distribute to all or substantially all holders of our common stock rights or warrants entitling them to purchase, for a period of 45 calendar days or less, shares of our common stock at a price less than the average closing sale price for the ten trading days preceding the declaration date for such distribution, as described below in more detail under “— Conversion Upon Specified Corporate Transactions”;
- (5) if we distribute to all or substantially all holders of our common stock, cash or other assets, debt securities or rights to purchase our securities, which distribution has a per share value exceeding 5% of the closing sale price of our common stock on the trading day preceding the declaration date for such distribution, as described below in more detail under “— Conversion Upon Specified Corporate Transactions”;
- (6) during a specified period if a fundamental change occurs, as described in more detail below under “— Conversion Upon a Fundamental Change”; or
- (7) during the five consecutive business-day period following any five consecutive trading-day period in which the trading price for the Notes for each day during such five trading-day period was less than 98% of the closing sale price of our common stock during such five trading-day period multiplied by the then current conversion rate, as described in more detail below under “— Conversion Upon Satisfaction of Trading Price Condition”; we refer to this condition as the “trading price condition.”

In the case of clauses (4) and (5) immediately above, we will notify you at least 20 calendar days prior to the ex-dividend date for such distribution; once we have given such notice, you may surrender your Notes for conversion at any time until the earlier of 5:00 p.m., New York City time, on the business day preceding the ex-dividend

date and any announcement by us that such distribution will not take place; in the case of a distribution identified in clauses (4) and (5) immediately above, you may not convert your Notes if you will otherwise participate in the distribution without conversion as a result of holding the Notes.

The “closing sale price” of any share of our common stock on any trading date means the closing sale price of such security (or if no closing sale price is reported, the average of the closing bid and closing ask prices or, if more than one in either case, the average of the average closing bid and the average closing ask prices) on such date as reported in composite transactions for the principal U.S. securities exchange on which our common stock is traded or, if our common stock is not listed on a U.S. national or regional securities exchange, as reported by the Nasdaq Stock Market or by Pink Sheets LLC. In the absence of such a quotation, the closing sale price will be determined by a nationally recognized securities dealer retained by us for that purpose. The closing sale price will be determined without reference to extended or after hours trading. The “conversion price” on any day will equal \$1,000 divided by the conversion rate in effect on that day.

Except as provided in the next paragraph, upon conversion, you will not receive any separate cash payment of accrued and unpaid interest (excluding any additional interest) on the Notes. Accrued and unpaid interest (excluding any additional interest) and accrued tax original issue discount, if any, to the conversion date is deemed to be paid in full with the shares of our common stock issued or cash paid upon conversion rather than cancelled, extinguished or forfeited.

If you convert after the record date for an interest payment but prior to the corresponding interest payment date, you will receive on the corresponding interest payment date the interest (including additional interest, if any) accrued and unpaid on your Notes, notwithstanding your conversion of those Notes prior to the interest payment date, assuming you were the holder of record on the corresponding record date. However, except as provided in the next sentence, at the time you surrender your Notes for conversion, you must pay us an amount equal to the interest (excluding any additional interest) that has accrued and will be paid on the Notes being converted on the corresponding interest payment date. You are not required to make such payment:

- if you convert your Notes in connection with a redemption and we have specified a redemption date that is after a record date and on or prior to the corresponding interest payment date;
- if you convert your Notes in connection with a fundamental change and we have specified a fundamental change repurchase date that is after a record date and on or prior to the corresponding interest payment date; or
- to the extent of any overdue interest (including overdue additional interest, if any), if overdue interest (or overdue additional interest) exists at the time of conversion with respect to your Notes.

Except as described under “— Conversion Procedures — Conversion Rate Adjustments,” we will not make any payment or other adjustment for dividends on any common stock issued upon conversion of the Notes.

We will not issue fractional shares of our common stock upon conversion of the Notes. Instead, we will pay cash in lieu of fractional shares based on the closing sale price of our common stock on the trading day immediately preceding the conversion date.

#### ***Conversion Upon Satisfaction of Market Price Condition***

Prior to February 15, 2025, you will have the right to convert your Notes at any time on any date during any fiscal quarter beginning after March 31, 2007 (and only during such fiscal quarter) if the closing sale price of our common stock was more than 120% of the then current conversion price for at least 20 trading days in the period of the 30 consecutive trading days ending on the last trading day of the previous fiscal quarter.

#### ***Conversion 2 Years Prior to Maturity***

You will have the right to convert your Notes at any time on or after February 15, 2025.

#### ***Conversion Upon Notice of Redemption***

You will have the right to convert your Notes called for redemption at any time prior to the close of business on the business day prior to the redemption date, even if it is not otherwise convertible at such time, after which time your right to convert will expire unless we default in the payment of the redemption price.

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#### ***Conversion Upon Specified Corporate Transactions***

You will have the right to convert your Notes if we:

- distribute to all or substantially all holders of our common stock rights or warrants (other than pursuant to a rights plan) entitling them to purchase, for a period of 45 calendar days or less, shares of our common stock at a price less than the average closing sale price for the ten trading days preceding the declaration date for such distribution; or
- distribute to all or substantially all holders of our common stock, cash or other assets, debt securities or rights to purchase our securities (other than pursuant to a rights plan), which distribution has a per share value exceeding 5% of the closing sale price of our common stock on the trading day preceding the declaration date for such distribution.

We will notify you at least 20 calendar days prior to the ex-dividend date for such distribution. Once we have given such notice, you may surrender your Notes for conversion at any time until the earlier of 5:00 p.m., New York City time, on the business day preceding the ex-dividend date or any announcement by us that such distribution will not take place. You may not convert any of your Notes based on this conversion contingency if you will otherwise participate in the distribution without conversion as a result of holding the Notes.



In addition, if we are a party to a consolidation, merger, binding share exchange, or sale or conveyance of all or substantially all of our property and assets, in each case pursuant to which our common stock would be converted into cash, securities and/or other property, a Note may be surrendered for conversion at any time from and after the date that is 15 days prior to the anticipated effective date of the transaction until, but excluding, the date that is 15 days after the actual effective date of such transaction, unless the transaction also constitutes a fundamental change, as defined below under “— Repurchase at the Option of the Holder — Fundamental Change Put,” in which case the Notes will be convertible as described below under “— Conversion Upon a Fundamental Change.” If we are party to a consolidation, merger or binding share exchange, or sale or conveyance of all or substantially all of our property and assets, pursuant to which our common stock is converted into cash, securities and/or other property (regardless of whether the transaction constitutes a fundamental change), from and after the effective date of the consolidation, merger or binding share exchange, or sale or conveyance of all or substantially all of our property and assets, the amount of cash, securities and/or other property issuable upon conversion of a Note will be as described under “—Conversion Procedures.” If such transaction also constitutes a fundamental change, the holder will be able to require us to purchase all or a portion of such holder’s Notes as described under “— Repurchase at the Option of the Holder — Fundamental Change Put.”

### ***Conversion Upon a Fundamental Change***

If a fundamental change (as defined under “— Repurchase at the Option of the Holder — Fundamental Change Put”) occurs, you will have the right to convert your Notes at any time beginning on the effective date of the fundamental change until 5:00 p.m., New York City time, on the date that is 15 calendar days after the actual effective date, or, if applicable, the business day preceding the repurchase date relating to such fundamental change repurchase date. We will notify you of the anticipated effective date of any fundamental change at least 20 calendar days prior to such date. If you convert your Notes during the time period described above in connection with a fundamental change, you will receive:

- the number of shares of our common stock into which your Notes are convertible (if the Notes are surrendered for conversion prior to the earlier of the actual effective date of the fundamental change and the record date for receiving distributions in connection with a fundamental change) or the kind and amount of cash, securities and other assets or property which you would have received if you had held the number of shares of common stock into which your Notes were convertible immediately prior to the transaction (if Notes are surrendered for conversion after such date; provided that, if such date is the record date, you will receive the cash, securities and other assets or property on the actual effective date and provided, further, that, in the event that we have made an election to make a cash payment of principal upon conversion as described above, such election will remain binding notwithstanding the form of consideration received by holders of our common stock); and
- under specific circumstances, additional shares of common stock, which will be in an amount determined as set forth under “— Conversion Procedures — Adjustment in Conversion Rate Upon a Non-Stock Change of Control” and which will be payable following specific types of fundamental change.

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If you have submitted any or all of your Notes for repurchase, unless you have withdrawn such Notes in a timely fashion, your conversion rights on the Notes so subject to repurchase will expire at 5:00 p.m., New York City time, on the business day preceding the repurchase date, unless we default in the payment of the repurchase price. If you have submitted any Notes for repurchase, such Notes may be converted only if you submit a withdrawal notice, and if the Notes are evidenced by a global Notes, you comply with appropriate DTC procedures.

### ***Conversion Upon Satisfaction of Trading Price Condition***

You may surrender your Notes for conversion prior to maturity during the five business-day period following any five consecutive trading-day period in which the “trading price” per \$1,000 principal amount of Notes, as determined following a request by a holder of Notes in accordance with the procedures described below, for each trading day of such five trading-day period was less than 98% of the product of the closing sale price of our common stock for each day during such five-day trading period and the then current conversion rate.

The “trading price” of the Notes on any date of determination means the average of the secondary market bid quotations per \$1,000 principal amount of Notes obtained by the trustee for \$5,000,000 principal amount of the Notes at approximately 3:30 p.m., New York City time, on such determination date from two independent nationally recognized securities dealers we select, which may include one or more of the initial purchasers, provided that if at least two such bids cannot reasonably be obtained by the trustee, but one such bid can reasonably be obtained by the trustee, this one bid will be used. If the trustee cannot reasonably obtain at least one bid for \$5,000,000 principal amount of the Notes from a nationally recognized securities dealer or, in our reasonable judgment, the bid quotations are not indicative of the secondary market value of the Notes, then, for purposes of the trading price condition only, the trading price of the Notes will be deemed to be less than 98% of the applicable conversion rate of the Notes multiplied by the closing sale price of our common stock on such determination date.

The trustee will determine the trading price of the Notes upon our request. We will have no obligation to make that request unless a holder of Notes requests that we do so. If a holder provides such request, we will instruct the trustee to determine the trading price of the Notes for each trading day until the minimum trading price threshold is exceeded.

## **Conversion Procedures**

### ***Procedures to be Followed by a Holder***

If you hold a beneficial interest in a global Note, to convert you must deliver to DTC the appropriate instruction form for conversion pursuant to DTC’s conversion program and, if required, pay funds equal to interest (excluding any additional interest) payable on the next interest payment date to which you are not entitled and, if required, pay all taxes or duties, if any.

If you hold a certificated Notes, to convert you must:

- complete and manually sign the conversion notice on the back of the Notes or a facsimile of the conversion notice;
- deliver the completed conversion notice and the Notes to be converted to the conversion agent;

- if required, furnish appropriate endorsements and transfer documents;
- if required, pay funds equal to interest (but excluding any additional interest) payable on the next interest payment date to which you are not entitled; and
- if required, pay all transfer or similar taxes, if any.

The conversion date will be the date on which you have satisfied all of the foregoing requirements. The Notes will be deemed to have been converted immediately prior to 5:00 p.m., New York City time, on the conversion date.

You will not be required to pay any taxes or duties relating to the issuance or delivery of our common stock if you exercise your conversion rights, but you will be required to pay any tax or duty that may be payable relating to

any transfer involved in the issuance or delivery of the common stock in a name other than your own. Certificates representing common stock will be issued and delivered only after all applicable taxes and duties, if any, payable by you have been paid in full.

### ***Settlement Upon Conversion***

Except to the extent we have irrevocably elected to make a cash payment of principal upon conversion as described below, we may elect to deliver either shares of our common stock, cash or a combination of cash and shares of our common stock in satisfaction of our obligations upon conversion of the Notes (including with respect to any additional shares described under “— Adjustment to Conversion Rate Upon a Non-Stock Change of Control” below).

Except to the extent we have irrevocably elected to make a cash payment of principal upon conversion, we will inform the holders through the trustee of the method we choose to satisfy our obligation upon conversion:

- if we have called the Notes for redemption, in our notice of redemption;
- if a fundamental change has occurred, in the notice of fundamental change described under “— Repurchase at the Option of the Holder — Fundamental Change Put”;
- in respect of the Notes to be converted during the period beginning 25 trading days preceding the maturity date and ending one trading day preceding the maturity date, 26 trading days preceding the maturity date; and
- in all other cases, no later than two trading days following the conversion date.

However, if we have not irrevocably elected to make a cash payment of principal upon conversion or otherwise given notice of our intention to deliver cash or a combination of cash and shares of our common stock upon settlement, we will deliver only common stock in satisfaction of our obligations upon conversion of the Notes.

If we choose to satisfy any portion of our conversion obligation by delivering cash, we will specify the portion to be satisfied by the delivery of cash either as a percentage of the conversion obligation or as the lesser of (a) a fixed dollar amount and (b) the conversion value (as defined below). We will treat all holders converting on the same trading day in the same manner. We will not, however, have any obligation to satisfy our conversion obligations arising on different trading days in the same manner except to the extent that we have made an irrevocable settlement election. That is, we may choose on one trading day to satisfy our conversion obligation by delivering shares of our common stock only and choose on another trading day to satisfy our conversion obligation by delivering cash or a combination of cash and shares of our common stock except to the extent that we have made an irrevocable settlement election. We may also choose to satisfy our conversion obligation for different combinations of cash and shares of our common stock on different trading days except to the extent that we have made an irrevocable settlement election.

If we elect to satisfy any portion of our conversion obligation in cash (other than cash in lieu of fractional shares if applicable), you may retract your conversion notice at any time during the two trading-day period beginning on the trading day after we have notified the trustee of our method of settlement. We refer to this period as the “conversion retraction period.” However, you cannot retract your conversion notice if: (a) we irrevocably elected to make a cash payment of principal upon conversion before you delivered your conversion notice, (b) you are converting your Notes in connection with a redemption or a fundamental change, (c) you are converting your Notes during the period beginning 25 trading days preceding the maturity date and ending one trading day preceding the maturity date or (d) we do not elect to satisfy any portion of our conversion obligation in cash.

Settlement in shares of our common stock only will occur as soon as practicable after we notify you that we have chosen this method of settlement. Settlement in cash and/or shares of our common stock will occur on the second trading day following the final trading day of the conversion period (as defined below).

The settlement amount will be computed as follows:

- (1) if we elect to satisfy the entire conversion obligation in common stock, we will deliver to the holder for each \$1,000 principal amount of the Notes converted a number of shares of our

- (2) if we elect to satisfy the entire conversion obligation in cash, we will deliver to the holder, for each \$1,000 principal amount of the Notes converted, cash in an amount equal to the conversion value;
- (3) if we elect to satisfy the conversion obligation in a combination of cash and common stock, we will deliver to the holder for each \$1,000 principal amount of the Notes converted:
  - (i) the fixed dollar amount per \$1,000 principal amount of the Notes of the conversion obligation to be satisfied in cash specified in the notice regarding our chosen method of settlement or, if lower, the conversion value in cash, or (ii) the percentage of the conversion obligation to be satisfied in cash specified in the notice regarding our chosen method of settlement multiplied by the conversion value, as the case may be (the “cash amount”); and
  - a number of shares for each of the 20 trading days in the conversion period equal to 1/20th of (i) the conversion rate then in effect minus (ii) the quotient of (x) the cash amount divided by (y) the closing sale price of our common stock for that trading day (plus cash in lieu of fractional shares if applicable).

“Trading day” means a day during which (i) trading in our common stock generally occurs, (ii) there is no market disruption event and (iii) a closing sale price of our common stock is provided on the Nasdaq Global Market or, if our common stock is not listed on the Nasdaq Global Market, on the principal other U.S. national or regional securities exchange on which our common stock is then listed or, if our common stock is not listed on a U.S. national or regional securities exchange, on the principal or other market on which our common stock is then traded.

“Market disruption event” means the occurrence or existence during the one-half hour period ending on the scheduled close of trading on any trading day for our common stock of any material suspension or limitation imposed on trading (by reason of movements in price exceeding limits permitted by the stock exchange or otherwise) in our common stock or in any options, contracts or future contracts relating to our common stock.

The “conversion period” means the 20-trading day period:

- if we have called the Notes delivered for conversion for redemption, ending on the third trading day immediately preceding the redemption date;
- with respect to conversions in connection with a fundamental change, ending on the third trading day prior to the repurchase date relating to such fundamental change;
- with respect to conversion notices received during the period beginning 25 trading days preceding the maturity date and ending one trading day preceding the maturity date, ending on the third trading day immediately preceding the maturity date;
- if we have irrevocably elected to make a cash payment of principal upon conversion, beginning on the third trading day following our receipt of your conversion notice; and
- in all other cases, beginning on the trading day following the final trading day of the conversion retraction period.

The “conversion value,” for every \$1,000 principal amount of the Notes being converted, means an amount equal to the sum of the daily conversion values for each of the 20 trading days in the conversion period, where the “daily conversion value” for any trading day equals 1/20th of:

- the conversion rate in effect on that day multiplied by
- the closing sale price of our common stock on that day.

We will deliver cash in lieu of any fractional shares of common stock issuable in connection with payment of the settlement amount.

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### ***Our Right to Irrevocably Elect Cash Payment Upon Conversion***

At any time on or prior to the 26th trading day preceding the maturity date, we may irrevocably elect to satisfy in cash our conversion obligation with respect to the lower of the conversion value or the principal amount of the Notes to be converted after the date of such election, with any remaining amount to be satisfied in shares of our common stock or cash as we may subsequently elect. Such irrevocable election with respect to the principal amount of the Notes would be in our sole discretion without the consent of the holders of the Notes. If we make such election, we will notify the trustee and the holders of the Notes at their addresses shown in the register of the registrar.

The settlement amount with respect to the principal amount of the Notes will be computed as described under clause (3) above, using at least \$1,000 as the fixed dollar amount per \$1,000 principal amount of Notes of the conversion obligation to be satisfied in cash; provided that in no event will we be required to deliver an amount of cash in excess of the conversion value.

### ***Conversion Rate Adjustments***

We will adjust the conversion rate for specific events, including:

- (1) issuances of our common stock as a dividend or distribution on our common stock;
- (2) certain subdivisions, combinations or reclassifications of our common stock;
- (3) issuances to all holders of our common stock of certain rights or warrants to purchase, for a period of up to 45 days, our common stock at less than the then-current market price of our common stock, provided that the conversion rate will be readjusted to the extent that any of the rights or warrants are not exercised prior to their expiration;

- (4) distributions to all holders of our common stock, shares of our capital stock (other than our common stock), evidences of our indebtedness or assets, including securities, but excluding:
- the rights and warrants referred to in clause (3) above;
  - any dividends and distributions in connection with a reclassification, change, consolidation, merger, combination, sale or conveyance resulting in a change in the conversion consideration pursuant to the sixth succeeding paragraph below;
  - any dividends or distributions paid exclusively in cash; or
  - any dividends or distributions referred to in the clause (1) above;
- (5) dividends or other distributions consisting exclusively of cash to all holders of our common stock (other than dividends or distributions made in connection with our liquidation, dissolution or winding-up or upon a merger or consolidation), in which event the conversion rate will be adjusted by multiplying:
- the conversion rate by, a fraction,
  - the numerator of which will be the current market price of our common stock and the denominator of which will be the current market price of our common stock minus the amount per share of such dividend or distribution; or
- (6) purchases of our common stock pursuant to a tender offer or exchange offer made by us or any of our subsidiaries to the extent that the cash and value of any other consideration included in the payment per share of common stock exceeds the closing sale price per share of our common stock on the trading day next succeeding the last date on which tenders or exchanges may be made pursuant to such tender or exchange offer.

For purposes of clause (3) and (5) above, “current market price” means the average closing sale price of our

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common stock for the 10 consecutive trading days immediately prior to the ex-dividend date for the distribution requiring such computation.

To the extent that any future rights plan adopted by us is in effect upon conversion of the Notes into common stock only or a combination of cash and common stock, you will receive, in addition to the common stock, the rights under the applicable rights agreement unless the rights have separated from our common stock at the time of conversion of the Notes, in which case, the conversion rate will be adjusted as if we distributed to all holders of our common stock shares of our capital stock, evidences of indebtedness or assets as described above in clause (4), subject to readjustment in the event of the expiration, termination or redemption of such rights.

We will not make any adjustment if holders may participate in the transaction or in certain other cases. In cases where the fair market value of assets, debt securities or certain rights, warrants or options to purchase our securities, applicable to one share of common stock, distributed to stockholders:

- equals or exceeds the average closing price of the common stock over the ten consecutive trading day period ending on the record date for such distribution, or
- such average closing price exceeds the fair market value of such assets, debt securities or rights, warrants or options so distributed by less than \$1.00,

rather than being entitled to an adjustment in the conversion price, the holder of the Notes will be entitled to receive upon conversion, in addition to the shares of common stock, the kind and amount of assets, debt securities or rights, warrants or options comprising the distribution that such holder would have received if such holder had converted such Notes into common stock immediately prior to the record date for determining the stockholders entitled to receive the distribution.

Except as stated above, we will not adjust the conversion rate for the issuance of our common stock or any securities convertible into or exchangeable for our common stock or carrying the right to purchase any of the foregoing.

In the event that we distribute shares of capital stock of a subsidiary of ours pursuant to clause (4) above, the conversion rate will be adjusted, if at all, based on the market value of the subsidiary stock so distributed relative to the market value of our common stock, in each case over a measurement period following the distribution.

If we:

- reclassify or change our common stock (other than changes resulting from a subdivision or combination), or
- consolidate or merge with or into any person or sell, lease, transfer, convey or otherwise dispose of all or substantially all of our assets and those of our subsidiaries taken as a whole to another person,

and the holders of our common stock receive stock, other securities or other property or assets (including cash or any combination thereof) with respect to or in exchange for their common stock, each outstanding Note will, without the consent of any holders of the Notes, become convertible only into the consideration the holders of the Notes would have received if they had converted their Notes immediately prior to such reclassification, change, consolidation, merger, sale, lease, transfer, conveyance or other disposition, except in the limited case of a public acquirer change of control where we elect to have the Notes convertible into public acquirer common stock as described below under “— Conversion After a Public Acquirer Change of Control” and except that, in the event that we have made an irrevocable election to make a cash payment upon conversion as described above, such election will remain binding notwithstanding the form of consideration received by holders of our common stock. In the event holders of our common stock have the opportunity to elect the form of consideration to be received in such transaction, then from and after the effective date of such transaction, the Notes will be convertible

into the consideration that a majority of the holders of our common stock who made such an election received in such transaction. We may not become a party to any such transaction unless its terms are consistent with the foregoing.

If a taxable distribution to holders of our common stock or other transaction occurs that results in any adjustment of the conversion rate (including an adjustment at our option), you may, in specific circumstances, be deemed to have received a distribution subject to U.S. income tax as a dividend. In specific other circumstances, the

absence of an adjustment may result in a taxable dividend to the holders of our common stock. See “Certain U.S. Federal Tax Considerations.”

We may from time to time, to the extent permitted by law, increase the conversion rate of the Notes by any amount for any period of at least 20 business days. In that case, we will give at least 15 days prior notice of such increase. We may make such increases in the conversion rate, in addition to those set forth above, as our board of directors deems advisable to avoid or diminish any income tax to holders of our common stock resulting from any dividend or distribution of stock (or rights to acquire stock) or from any event treated as such for income tax purposes.

We will not be required to make an adjustment in the conversion rate unless the adjustment would require a change of at least 1% in the conversion rate. However, we will carry forward any adjustment that is less than 1% of the conversion rate, take such carried-forward adjustments into account in any subsequent adjustment, and make such carried forward adjustments, regardless of whether the aggregate adjustment is less than 1%, (a) annually on the anniversary of the first date of issue of the Notes and otherwise (b)(1) five business days prior to the maturity of the Notes (whether at stated maturity or otherwise) or (2) prior to the redemption date or repurchase date, unless such adjustment has already been made.

If we adjust the conversion rate pursuant to the above provisions, we will (1) provide written notification to the conversion agent and (2) either issue a press release through Business Wire containing the relevant information, file an 8-K with the relevant information or make this information available on our website or through another public medium as we may use at that time.

#### ***Adjustment to Conversion Rate Upon a Non-Stock Change of Control***

If and only to the extent you elect to convert your Notes in connection with a transaction described under clause (1) or clause (4) under the definition of a fundamental change described below under “— Repurchase at the Option of the Holder — Fundamental Change Put” pursuant to which 10% or more of the consideration for our common stock (other than cash payments for fractional shares and cash payments made in respect of dissenters’ appraisal rights) in such fundamental change transaction consists of cash or securities (or other property) that are not shares of common stock, depositary receipts or other certificates representing common equity interests traded or scheduled to be traded immediately following such transaction on a U.S. national securities exchange, the Nasdaq Global Select Market or the Nasdaq Global Market, which we refer to as a “non-stock change of control,” we will increase the conversion rate as described below, subject to our rights described below under “— Conversion After a Public Acquirer Change of Control.” The number of additional shares by which the conversion is increased (the “additional shares”) will be determined by reference to the table below, based on the date on which the non-stock change of control becomes effective (the “effective date”) and the price (the “stock price”) paid per share for our common stock in such non-stock change of control. If holders of our common stock receive only cash in such transaction, the price paid per share will be the cash amount paid per share. Otherwise, the price paid per share will be the average of the last reported sale prices of our common stock on the five trading days prior to but not including the effective date of such non-stock change of control. We will notify you of the anticipated effective date of any fundamental change at least 20 calendar days prior to such date.

A conversion of the Notes by a holder will be deemed for these purposes to be “in connection with” a non-stock change of control if the conversion notice is received by the conversion agent following the effective date of the non-stock change of control but before the close of business on the business day immediately preceding the related repurchase date (as specified in the repurchase notice described under “— Repurchase at the Option of the Holder — Fundamental Change Put”).

The number of additional shares will be adjusted in the same manner as and as of any date on which the conversion rate of the Notes is adjusted as described above under “— Conversion Rate Adjustments.” The stock prices set forth in the first row of the table below (i.e., the column headers) will be simultaneously adjusted to equal the stock prices immediately prior to such adjustment, multiplied by a fraction, the numerator of which is the conversion rate immediately prior to the adjustment and the denominator of which is the conversion rate as so adjusted.

The following table sets forth an indicative number of additional shares by which the conversion rate will be increased:

Effective Date	Stock Price									
	\$11.25	\$14.63	\$17.50	\$20.00	\$22.50	\$25.00	\$27.50	\$30.00	\$32.50	\$35.00
January 24, 2007	20.5127	13.0547	9.5132	7.4761	6.0233	4.9498	4.1326	3.4953	2.9936	2.5831
February 15, 2008	20.1768	12.3913	8.7956	6.7783	5.3703	4.3510	3.5894	3.0049	2.5500	2.1854
February 15, 2009	19.4806	11.3692	7.7668	5.8165	4.4981	3.5720	2.8992	2.3952	2.0081	1.7084
February 15, 2010	18.3509	9.8224	6.2720	4.4661	3.3134	2.5468	2.0169	1.6369	1.3549	1.1417
February 15, 2011	16.5402	7.3061	3.9699	2.5152	1.7108	1.2417	0.9527	0.7627	0.6300	0.5322
February 15, 2012	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

The exact stock price and effective dates may not be set forth on the table, in which case, if the stock price is:

- between two stock price amounts on the table or the effective date is between two dates on the table, the number of additional shares will be determined by straight-line interpolation between the number of additional shares set forth for the higher and lower stock price amounts and the two dates, as applicable, based on a 360-day year;
- in excess of \$35.00 per share (subject to adjustment), no additional shares will be issued upon conversion;
- less than \$11.25 per share (subject to adjustment), no additional shares will be issued upon conversion.

However, in no event will the total number of shares of common stock issuable upon conversion exceed 88.8888 per \$1,000 principal amount of the Notes, subject to adjustments in the same manner as the conversion rate.

Additional shares deliverable as described in this section “— Adjustment to Conversion Rate Upon a Non-Stock Change of Control,” or cash in lieu thereof, will be delivered on the settlement date applicable to the relevant conversion.

### ***Conversion After a Public Acquirer Change of Control***

However, in the case of a non-stock change of control constituting a public acquirer change of control (as defined below), we may, in lieu of issuing additional shares upon conversion as described in

“— Adjustment to Conversion Rate Upon a Non-Stock Change of Control” above, elect to adjust our conversion obligation and the conversion rate such that from and after the effective date of such public acquirer change of control, holders of the Notes will be entitled to convert their Notes (subject to the satisfaction of specific conditions) into shares of public acquirer common stock (as defined below), and the conversion rate in effect immediately before the public acquirer change of control will be adjusted by multiplying it by a fraction:

- the numerator of which will be (i) in the case of a public acquirer change of control pursuant to which our common stock is converted solely into cash, the value of such cash paid or payable per share of common stock or (ii) in the case of any other public acquirer change of control, the average of the closing sale prices of our common stock for the five consecutive trading days prior to but excluding the effective date of such public acquirer change of control, and
- the denominator of which will be the average of the last reported sale prices of the public acquirer common stock for the five consecutive trading days commencing on the trading day next succeeding the effective date of such public acquirer change of control.

A “public acquirer change of control” means a non-stock change of control in which the acquirer has a class of common stock traded on a U.S. national securities exchange or listed on the Nasdaq Global Select Market or the Nasdaq Global Market or that will be so traded or quoted when issued or exchanged in connection with such non-stock change of control (the “public acquirer common stock”). If an acquirer does not itself have a class of common stock satisfying the foregoing requirement, it will be deemed to have “public acquirer common stock” if a corporation that directly or indirectly owns at least a majority of the acquirer has a class of common stock satisfying the foregoing requirement, provided that such corporation fully and unconditionally guarantees the Notes, in which case all references to public acquirer common stock will refer to such class of common stock. Majority owned for these purposes means having “beneficial ownership” (as defined in Rule 13d-3 under the Exchange Act) of more than 50% of the total voting power of all shares of the respective entity’s capital stock that are entitled to vote generally in the election of directors.

Upon a public acquirer change of control, if we so elect, holders may convert their Notes (subject to the satisfaction of the conditions to conversion described under “— Conversion Procedures — Procedures to be Followed by a Holder” above) for public acquirer common stock at the adjusted conversion rate described in the second preceding paragraph but will not be entitled to receive additional shares upon conversion as described under “— Adjustment to Conversion Rate Upon a Non-Stock Change of Control.” We are required to notify holders of our election in our notice to holders of such transaction. Following any such election, the provisions set forth herein, including those set forth under “— Settlement Upon Conversion” will continue to apply except that reference to our common stock will be deemed to refer to the public acquirer common stock. In addition, upon a public acquirer change of control, in lieu of converting the Notes, the holder can, subject to specific conditions, require us to repurchase all or a portion of the Notes owned by the holder as described below under “— Repurchase at the Option of the Holders — Fundamental Change Put.”

### **Optional Redemption**

At any time on or after February 15, 2012, we may redeem all or a part of the Notes at cash redemption prices set forth below, plus accrued and unpaid interest (including additional interest, if any) to, but excluding, the redemption date. However, if the redemption date is after a record date and on or prior to the corresponding interest payment date, the interest (including additional interest, if any) will be paid on the redemption date to the holder of record on the record date.

The redemption price for the Notes, expressed as a percentage of principal amount, is as follows for the periods set forth below:

<b>Period</b>	<b>Redemption Price</b>
February 15, 2012 to February 14, 2013	100.750%
February 15, 2013 to February 14, 2014	100.375%
February 15, 2014 and thereafter	100.000%

We will give notice of redemption not less than 30 nor more than 60 days prior to the redemption date to all record holders of Notes at their addresses set forth in the register of the registrar. This notice will state, among other things:

- that you have a right to convert the Notes called for redemption, and the conversion rate then in effect;
- the date on which your right to convert the Notes called for redemption will expire; and

- whether we have elected to settle our obligation upon conversion by delivering shares of our common stock, cash or a combination of cash and shares of our common stock, and, in the event that we have elected to deliver all or a portion of our conversion obligation in cash, the date on which the conversion period will begin.

If we do not redeem all of the Notes, the trustee will select the Notes to be redeemed in principal amounts of \$1,000 or integral multiples of \$1,000 by lot, pro rata or by another method the trustee considers fair and appropriate. If any Notes are to be redeemed in part only, we will issue a new Note in principal amount equal to the unredeemed principal portion thereof. If a portion of your Notes is selected for partial redemption and you convert a portion of your Notes, the converted portion will be deemed to be taken from the portion selected for redemption.

Additionally, we will not be required to:

- issue, register the transfer of, or exchange any Notes during the period of 15 days before the mailing of the notice of redemption, or
- register the transfer of or exchange any Notes so selected for redemption, in whole or in part, except the unredeemed portion of any Notes being redeemed in part.

We may not redeem the Notes if we have failed to pay interest on the Notes and such failure to pay is continuing.

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## Repurchase at the Option of the Holder

### *Optional Put*

On February 15, 2014, February 15, 2017 and February 15, 2022, you will have the right to require us to repurchase, at the repurchase price described below, all or part of your Notes for which you have properly delivered and not withdrawn a written repurchase notice. The Notes submitted for repurchase must be \$1,000 in principal amount or whole multiples thereof.

The repurchase price will be payable in cash and will equal 100% of the principal amount of the Notes being repurchased, plus accrued and unpaid interest (including additional interest, if any) to, but excluding, the repurchase date. However, if the repurchase date is after a record date and on or prior to the corresponding interest payment date, the interest (including additional interest, if any) will be paid on the repurchase date to the holder of record on the record date.

We may be unable to repurchase your Notes upon your exercise of your repurchase right. Our ability to repurchase Notes in cash in the future may be limited by the terms of our then-existing borrowing agreements. Accordingly, we cannot assure you that we would have the financial resources, or would be able to arrange financing, to pay the repurchase price in cash.

We will give notice at least 20 business days prior to each repurchase date to all record holders at their addresses shown in the register of the registrar and to beneficial owners as required by applicable law. This notice will state, among other things, the procedures that you must follow to require us to repurchase your Notes.

To exercise your repurchase right, you must deliver at any time from 9:00 a.m., New York City time, on the date that is 20 business days prior to the applicable repurchase date to 5:00 p.m., New York City time, on the business day immediately preceding the applicable repurchase date, a written notice to the paying agent of your exercise of your repurchase right (together with the Notes to be repurchased, if certificated Notes have been issued). The repurchase notice must state:

- if you hold a beneficial interest in a global Note, your repurchase notice must comply with appropriate DTC procedures; if you hold certificated Notes, the Notes certificate numbers;
- the portion of the principal amount of your Notes to be repurchased, which must be in \$1,000 multiples; and
- that the Notes are to be repurchased by us pursuant to the applicable provisions of the Notes and the indenture.

You may withdraw your repurchase notice at any time prior to 5:00 p.m., New York City time, on the business day immediately preceding the applicable repurchase date, by delivering a written notice of withdrawal to the paying agent. If a repurchase notice is given and withdrawn during that period, we will not be obligated to repurchase the Notes listed in the repurchase notice. The withdrawal notice must state:

- if you hold a beneficial interest in a global Note, your withdrawal notice must comply with appropriate DTC procedures; if you hold certificated Notes, the certificate numbers of the withdrawn Notes;
- the principal amount of the withdrawn Notes; and
- the principal amount, if any, which remains subject to the repurchase notice.

Payment of the repurchase price for Notes for which a repurchase notice has been delivered and not withdrawn is conditioned upon book-entry transfer or delivery of the Notes, together with necessary endorsements, to the paying agent, as the case may be. Payment of the repurchase price for the Notes will be made promptly following the later of the repurchase date and the time of book-entry transfer or delivery of the Notes, as the case may be.

If the paying agent holds on the business day immediately following the repurchase date cash sufficient to pay the repurchase price of the Notes that holders have elected to require us to repurchase, then, as of the repurchase date:

- those Notes will cease to be outstanding and interest (including additional interest, if any) will cease to accrue, whether or not book-entry transfer of the Notes has been made or the Notes have been delivered to the paying agent, as the case may be; and
- all other rights of the Notes holders will terminate, other than the right to receive the repurchase price upon delivery or transfer of the Notes.

In connection with any repurchase, we will, to the extent applicable:

- comply with the provisions of Rule 13e-4 and any other tender offer rules under the Exchange Act that may be applicable at the time of the offer to repurchase the Notes;
- file a Schedule TO or any other schedule required in connection with any offer by us to repurchase the Notes; and
- comply with all other federal and state securities laws in connection with any offer by us to repurchase the Notes.

### ***Fundamental Change Put***

If a fundamental change (as defined below) occurs at any time prior to the maturity of the Notes, you will have the right to require us to repurchase, at the repurchase price described below, all or part of your Notes for which you have properly delivered and not withdrawn a written repurchase notice. The Notes submitted for repurchase must be \$1,000 in principal amount or whole multiples thereof.

The repurchase price will be payable in cash and will equal 100% of the principal amount of the Notes being repurchased, plus accrued and unpaid interest (including additional interest, if any) to, but excluding, the repurchase date. However, if the repurchase date is after a record date and on or prior to the corresponding interest payment date, the interest (including additional interest, if any) will be paid on the repurchase date to the holder of record on the record date.

We may be unable to repurchase your Notes in cash upon a fundamental change. Our ability to repurchase the Notes with cash in the future may be limited by the terms of our then-existing borrowing agreements. In addition, the occurrence of a fundamental change could cause an event of default under the terms of our then-existing borrowing agreements. We cannot assure you that we would have the financial resources, or would be able to arrange financing, to pay the repurchase price in cash.

A “fundamental change” will be deemed to have occurred when any of the following has occurred:

- (1) the consummation of any transaction (including, without limitation, any merger or consolidation) the result of which is that any “person” acquires more than 50% of our capital stock that is at the time entitled to vote by the holder thereof in the election of our board of directors (or comparable body);
- (2) the first day on which a majority of the members of our board of directors are not continuing directors;
- (3) the adoption of a plan relating to our liquidation or dissolution;
- (4) the consolidation or merger of us with or into any other person, or the sale, lease, transfer, conveyance or other disposition, in one or a series of related transactions, of all or substantially all of our assets and those of our subsidiaries taken as a whole to any “person” (as this term is used in Section 13(d)(3) of the Exchange Act), other than:
  - (a) any transaction

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- that does not result in any reclassification, conversion, exchange or cancellation of outstanding shares of our capital stock; and
  - pursuant to which the holders of 50% or more of the total voting power of all shares of our capital stock entitled to vote generally in elections of directors immediately prior to such transaction have the right to exercise, directly or indirectly, 50% or more of the total voting power of all shares of our capital stock entitled to vote generally in elections of directors of the continuing or surviving person immediately after giving effect to such transaction; or
- (b) any merger primarily for the purpose of changing our jurisdiction of incorporation and resulting in a reclassification, conversion or exchange of outstanding shares of common stock solely into shares of common stock of the surviving entity; or
- (5) the termination of trading of our common stock, which will be deemed to have occurred if our common stock or other common stock into which the Notes are convertible is neither listed for trading on a United States national securities exchange nor approved for listing on the Nasdaq Global Select Market, the Nasdaq Global Market or any similar United States system of automated dissemination of quotations of securities prices, and no American Depositary Shares or similar instruments for such common stock are so listed or approved for listing in the United States.

However, a fundamental change will be deemed not to have occurred if more than 90% of the consideration in the transaction or transactions (other than cash payments for fractional shares and cash payments made in respect of dissenters’ appraisal rights) which otherwise would constitute a fundamental change under clause (1) or (4) above consists of shares of common stock, depositary receipts or other certificates representing common equity interests traded or to be traded immediately following such transaction on a national securities exchange or quoted on the Nasdaq Global Select Market or the Nasdaq Global



Market and, as a result of the transaction or transactions, the Notes become convertible into such common stock, depository receipts or other certificates representing common equity interests (and any rights attached thereto) and other applicable consideration.

“Continuing directors” means, as of any date of determination, any member of our board of directors who:

- was a member of the board of directors on the date of the indenture; or
- was nominated for election or elected to the board of directors with the approval of a majority of the continuing directors who were members of the board at the time of new director’s nomination or election.

The definition of “fundamental change” includes a phrase relating to the sale, lease, transfer, conveyance or other disposition, in one or a series of related transactions, of all or substantially all of our assets and those of our subsidiaries taken as a whole. Although there is a developing body of case law interpreting the phrase “substantially all,” there is no precise established definition of the phrase under applicable law. Accordingly, the ability of a holder of Notes to require us to repurchase the Notes as a result of a sale, lease, transfer, conveyance or other disposition of less than all of our assets and those of our subsidiaries taken as a whole to another person or group may be uncertain.

Within 20 days after the occurrence of a fundamental change, we will provide to all record holders of the Notes on the date of the fundamental change at their addresses shown in the register of the registrar and to beneficial owners to the extent required by applicable law, the trustee and the paying agent, a written notice of the occurrence of the fundamental change and the resulting repurchase right. Such notice will state, among other things, the event causing the fundamental change, the conversion rate then in effect and the procedures you must follow to require us to repurchase your Notes.

The repurchase date will be a date specified by us in the notice of a fundamental change that is not less than 15 or more than 35 calendar days after the date of the notice of a fundamental change.

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To exercise your repurchase right, you must deliver, prior to 5:00 p.m., New York City time, on the business day immediately preceding the repurchase date, a written notice to the paying agent of your exercise of your repurchase right (together with the Notes to be repurchased, if certificated Notes have been issued). The repurchase notice must state:

- if you hold a beneficial interest in a global Note, your repurchase notice must comply with appropriate DTC procedures; if you hold certificated Notes, the Notes certificate numbers;
- the portion of the principal amount of the Notes to be repurchased, which must be \$1,000 or whole multiples thereof; and
- that the Notes are to be repurchased by us pursuant to the applicable provisions of the Notes and the indenture.

You may withdraw your repurchase notice at any time prior to 5:00 p.m., New York City time, on the business day immediately preceding the repurchase date by delivering a written notice of withdrawal to the paying agent. If a repurchase notice is given and withdrawn during that period, we will not be obligated to repurchase the Notes listed in the repurchase notice. The withdrawal notice must state:

- if you hold a beneficial interest in a global Note, your withdrawal notice must comply with appropriate DTC procedures; if you hold certificated Notes, the certificate numbers of the withdrawn Notes;
- the principal amount of the withdrawn Notes; and
- the principal amount, if any, which remains subject to the repurchase notice.

Payment of the repurchase price for Notes for which a repurchase notice has been delivered and not withdrawn is conditioned upon book-entry transfer or delivery of the Notes, together with necessary endorsements, to the paying agent, as the case may be. Payment of the repurchase price for the Notes will be made promptly following the later of the repurchase date and the time of book-entry transfer or delivery of the Notes, as the case may be.

If the paying agent holds on the business day immediately following the repurchase date cash sufficient to pay the repurchase price of the Notes that holders have elected to require us to repurchase, then, as of the repurchase date:

- the Notes will cease to be outstanding and interest (including additional interest, if any) will cease to accrue, whether or not book-entry transfer of the Notes has been made or the Notes have been delivered to the paying agent, as the case may be; and
- all other rights of the holders of Notes will terminate, other than the right to receive the repurchase price upon delivery or transfer of the Notes.

In connection with any repurchase, we will, to the extent applicable:

- comply with the provisions of Rule 13e-4 and any other tender offer rules under the Exchange Act that may be applicable at the time of the offer to repurchase the Notes;
- file a Schedule TO or any other schedule required in connection with any offer by us to repurchase the Notes; and
- comply with all other federal and state securities laws in connection with any offer by us to repurchase the Notes.

This fundamental change repurchase right could discourage a potential acquirer of Isis. However, this fundamental change repurchase feature is not the result of management’s knowledge of any specific effort to obtain control of us by means of a merger, tender offer, solicitation or otherwise, or part of a plan by management to adopt a series of anti-takeover provisions.

Our obligation to repurchase the Notes upon a fundamental change would not necessarily afford you protection in the event of a highly leveraged or other transaction involving us that may adversely affect holders. We

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also could, in the future, enter into certain transactions, including certain recapitalizations, that would not constitute a fundamental change but would increase the amount of our (or our subsidiaries') outstanding debt. The incurrence of significant amounts of additional debt could adversely affect our ability to service our then existing debt, including the Notes.

### **Consolidation, Merger and Sale of Assets by Isis**

The indenture provides that we may not, in a single transaction or a series of related transactions, consolidate with or merge with or into any other person or sell, convey, transfer or lease our property and assets substantially as an entirety to another person, unless:

- either (a) we are the continuing corporation or (b) the resulting, surviving or transferee person (if other than us) is a corporation or limited liability company organized and existing under the laws of the United States, any state thereof or the District of Columbia and such person assumes, by a supplemental indenture in a form reasonably satisfactory to the trustee, and a supplemental agreement, all of our obligations under the Notes, the indenture and the registration rights agreement;
- immediately after giving effect to such transaction, no default or event of default has occurred and is continuing;
- if as a result of such transaction the Notes become convertible into common stock or other securities issued by a third party, such third party fully and unconditionally guarantees all obligations of us or such successor under the Notes, the indenture and the registration rights agreement; and
- we have delivered to the trustee specific certificates and opinions of counsel if so requested by the trustee.

In the event of any transaction described in and complying with the conditions listed in the immediately preceding paragraph in which Isis is not the continuing corporation, the successor person formed or remaining will succeed, and be substituted for, and may exercise every right and power of, Isis, and Isis will be discharged from its obligations, under the Notes, the indenture and the registration rights agreement.

This covenant includes a phrase relating to the sale, conveyance, transfer and lease of the property and assets of Isis "substantially as an entirety." There is no precise, established definition of the phrase "substantially as an entirety" under New York law, which governs the indenture and the Notes, or under the laws of Delaware, our state of incorporation. Accordingly, the ability of a holder of the Notes to require us to repurchase the Notes as a result of a sale, conveyance, transfer or lease of less than all of the property and assets of Isis may be uncertain.

An assumption by any person of our obligations under the Notes and the indenture might be deemed for U.S. federal income tax purposes to be an exchange of the Notes for new Notes by the holders thereof, resulting in recognition of gain or loss for such purposes and possibly other adverse tax consequences to the holders. Holders should consult their own tax advisors regarding the tax consequences of such an assumption.

### **Events of Default; Notice and Waiver**

The following are events of default under the indenture:

- we fail to pay any interest (including additional interest, if any) on the Notes when due and such failure continues for a period of 30 calendar days;
- we fail to pay principal of the Notes when due at maturity, or we fail to pay the redemption price or repurchase price, in respect of any Notes when due, whether or not the payment is prohibited by the subordination provisions of the indenture;
- we fail to deliver our common stock (including any additional shares), or cash in lieu thereof, or a combination of the foregoing, upon the conversion of any Notes and such failure continues for 15 days following the scheduled settlement date for such conversion;

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- we fail to provide notice of the anticipated effective date or actual effective date of a fundamental change on a timely basis as required in the indenture;
  - we fail to perform or observe any other term, covenant or agreement in the Notes or the indenture for a period of 60 calendar days after written notice of such failure is given to us by the trustee or to us and the trustee by the holders of at least 25% in aggregate principal amount of the Notes then outstanding; or
  - specific events involving our bankruptcy, insolvency or reorganization or the bankruptcy, insolvency or reorganization of any of our wholly-owned "significant subsidiaries" (which term will have the meaning specified in Rule 1-02(w) of Regulation S-X).

We are required to notify the trustee promptly upon becoming aware of the occurrence of any default under the indenture known to us. The trustee is then required within 90 calendar days of becoming aware of the occurrence of any default to give to the registered holders of the Notes notice of all uncured defaults known to it. However, the trustee may withhold notice to the holders of the Notes of any default, except defaults in payment of principal, interest (including additional interest, if any) on the Notes, if the trustee, in good faith, determines that the withholding of such notice is in the interests of the holders. We are also required to deliver to the trustee, on or before a date not more than 120 calendar days after the end of each fiscal year, a written statement as to compliance with the indenture, including whether or not any default has occurred.

If an event of default specified in the last bullet point listed above occurs and continues with respect to us or any of our wholly-owned significant subsidiaries, the principal amount of the Notes and accrued and unpaid interest (including additional interest, if any) on the outstanding Notes will automatically become due and payable. If any other event of default occurs and is continuing, the trustee or the holders of at least 25% in aggregate principal amount of the outstanding Notes may declare the principal amount of the Notes and accrued and unpaid interest (including additional interest, if any) on the outstanding Notes to be due and payable. Upon such a declaration, such principal and interest will be due and payable immediately. Thereupon, the trustee may, in its discretion, proceed to protect and enforce the rights of the holders of the Notes by appropriate judicial proceedings.

However, the indenture provides that, to the extent elected by us, the sole remedy for an event of default relating to the failure to comply with the reporting obligations in the indenture and for any failure to comply with the requirements of Section 314(a)(1) of the Trust Indenture Act, as applicable, will for the first 120 days after the occurrence of such an event of default consist exclusively of the right to receive special interest on the Notes at an annual rate equal to 0.25% of the principal amount of the Notes. The special interest will be paid semi-annually in arrears, with the first semi-annual payment due on the first interest payment date following the date on which the special interest began to accrue on any Notes. The special interest will accrue on all outstanding Notes from and including the date on which an event of default relating to a failure to comply with the reporting obligations in the indenture first occurs to but not including the 120<sup>th</sup> day thereafter) or such earlier date on which the event of default will have been cured or waived). On such 120<sup>th</sup> day (or earlier, if the event of default relating to reporting obligations is cured or waived prior to such 120<sup>th</sup> day), such special interest will cease to accrue and, if the event of default relating to reporting obligations has not been cured or waived prior to such 120<sup>th</sup> day, the Notes will be subject to acceleration as provided above. The provisions of the indenture described in this paragraph will not affect the rights of holders in the event of the occurrence of any other event of default. In the event we do not elect to pay special interest upon an event of default in accordance with this paragraph, the Notes will be subject to acceleration as provided above. In no event will the special interest as described above, together with any additional interest payable in the event of a registration default as described under “— Registration Rights,” exceed 0.50%.

If we elect to pay special interest as the sole remedy for an event of default relating to the failure to comply with reporting obligations in the indenture and for any failure to comply with the requirements of Section 314(a)(1) of the Trust Indenture Act, as applicable, in accordance with the immediately preceding paragraph, we will notify all holders of Notes and the trustee and paying agent of such election on or before the close of business on the date on which such event of default first occurs.

After a declaration of acceleration, but before a judgment or decree for payment of the money due has been obtained by the trustee, the holders of a majority in aggregate principal amount of the Notes outstanding, by written notice to us and the trustee, may rescind and annul such declaration if:

- we have paid (or deposited with the trustee a sum sufficient to pay) (1) all overdue interest (including

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additional interest, if any) on all Notes; (2) the principal amount of any Notes that have become due otherwise than by such declaration of acceleration; (3) to the extent that payment of such interest is lawful, interest upon overdue interest (including additional interest, if any); and (4) all sums paid or advanced by the trustee under the indenture and the reasonable compensation, expenses, disbursements and advances of the trustee, its agents and counsel; and

- all events of default, other than the non-payment of the principal amount and any accrued and unpaid interest (including additional interest, if any) that have become due solely by such declaration of acceleration, have been cured or waived.

The holders of a majority in aggregate principal amount of the outstanding Notes have the right to direct the time, method and place of any proceedings for any remedy available to the trustee, subject to limitations specified in the indenture.

No holder of the Notes may pursue any remedy under the indenture, except in the case of a default in the payment of principal or interest (including additional interest, if any) on the Notes, unless:

- the holder has given the trustee written notice of an event of default;
- the holders of at least 25% in aggregate principal amount of the outstanding Notes make a written request to the trustee to pursue the remedy, and offer reasonable security or indemnity against any costs, liability or expense of the trustee;
- the trustee fails to comply with the request within 60 calendar days after receipt of the request and offer of security or indemnity; and
- the trustee does not receive an inconsistent direction from the holders of a majority in aggregate principal amount of the outstanding Notes.

#### **Waiver**

The holders of a majority in aggregate principal amount of the Notes outstanding may, on behalf of the holders of all the Notes, waive any past default or event of default under the indenture and its consequences, except:

- our failure to pay principal of or interest (including additional interest, if any) on any Notes when due;
- our failure to convert any Notes into common stock (or cash or a combination of common stock and cash, if we so elect) as required by the indenture;
- our failure to pay the redemption price on the redemption date in connection with a redemption by us or the repurchase price on the repurchase date in connection with a holder exercising its repurchase rights; or
- our failure to comply with any of the provisions of the indenture that would require the consent of the holder of each outstanding Note affected.

#### **Modification**

##### ***Changes Requiring Approval of Each Affected Holder***

The indenture (including the terms and conditions of the Notes) may not be modified or amended without the written consent or the affirmative vote of the holder of each Note affected by such change to:

- extend the maturity of any Notes;
- reduce the rate or extend the time for payment of interest (including additional interest, if any) on any Notes;
- reduce the principal amount of any Notes;

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- reduce any amount payable upon redemption or repurchase of any Notes;
- impair the right of a holder to institute suit for payment of any Notes;
- change the currency in which any Notes is payable;
- change the redemption provisions in a manner adverse to the holders;
- change our obligation to repurchase any Notes at the option of the holder in a manner adverse to the holders;
- change our obligation to repurchase any Notes upon a fundamental change in a manner adverse to the holders;
- reduce the number of additional shares to which a holder would be entitled upon conversion in connection with a non-stock change of control;
- affect the right of a holder to convert any Notes into shares of our common stock (or, if we so elect, cash or a combination of cash and shares of our common stock) or reduce the amount of cash, number of shares of our common stock or any other property receivable upon conversion pursuant to the terms of the indenture;
- modify the subordination provisions of the indenture in a manner that materially adversely affects the holders of the Notes;
- subject to specified exceptions, modify specific provisions of the indenture relating to modification of the indenture or waiver under the indenture; or
- reduce the percentage of the Notes required for consent to any modification of the indenture that does not require the consent of each affected holder.

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### ***Changes Requiring Majority Approval***

The indenture (including the terms and conditions of the Notes) may be modified or amended, except as described above, with the written consent or affirmative vote of the holders of a majority in aggregate principal amount of the Notes then outstanding.

### ***Changes Requiring No Approval***

The indenture (including the terms and conditions of the Notes) may be modified or amended by us and the trustee, without the consent of the holder of any Notes, to, among other things:

- provide for conversion rights of holders of the Notes and our repurchase obligations in connection with a fundamental change in the event of any reclassification of our common stock, merger or consolidation, or sale, conveyance, transfer or lease of our property and assets substantially as an entirety;
- secure the Notes;
- provide for the assumption of our obligations to the holders of the Notes in the event of a merger or consolidation, or sale, conveyance, transfer or lease of our property and assets substantially as an entirety;
- surrender any right or power conferred upon us;
- add to our covenants for the benefit of the holders of the Notes;
- cure any ambiguity or correct or supplement any inconsistent or otherwise defective provision contained in the indenture; provided that such modification or amendment does not adversely affect the interests of the holders of the Notes in any material respect; provided, further, that any amendment made solely to conform the provisions of the indenture to the description of the Notes contained in this prospectus will not be deemed to adversely affect the interests of the holders of the Notes;
- make any provision with respect to matters or questions arising under the indenture that we may deem necessary or desirable and that will not be inconsistent with provisions of the indenture; provided that such change or modification does not, in the good faith opinion of our board of directors, adversely affect the interests of the holders of the Notes in any material respect;

- increase the conversion rate; provided, that the increase will not adversely affect the interests of the holders of the Notes;
- comply with the requirements of the SEC in order to effect or maintain the qualification of the indenture under the Trust Indenture Act;
- add guarantees of obligations under the Notes;
- make any changes or modifications necessary in connection with the registration of the Notes under the Securities Act as contemplated in the registration rights agreement; provided that such change or modification does not adversely affect the interests of the holders of the Notes in any material respect; and
- provide for a successor trustee.

#### ***Other***

No modification or amendment may be made to the subordination provisions of the indenture that adversely affects the rights of any holder of senior indebtedness then outstanding unless the holders of such senior indebtedness (or any group or representative thereof authorized to give consent) consent to such change.

The consent of the holders of Notes is not necessary under the indenture to approve the particular form of any proposed modification or amendment. It is sufficient if such consent approves the substance of the proposed modification or amendment. After a modification or amendment under the indenture becomes effective, we are required to mail to the holders a notice briefly describing such modification or amendment. However, the failure to give such notice to all the holders, or any defect in the notice, will not impair or affect the validity of the modification or amendment.

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#### ***Notes Not Entitled to Consent***

Any Notes held by us or by any person directly or indirectly controlling or controlled by or under direct or indirect common control with us will be disregarded (from both the numerator and the denominator) for purposes of determining whether the holders of the requisite aggregate principal amount of the outstanding Notes have consented to a modification, amendment or waiver of the terms of the indenture.

#### **Repurchase and Cancellation**

We may, to the extent permitted by law, repurchase any Notes in the open market or by tender offer at any price or by private agreement. Any Notes repurchased by us may, at our option, be surrendered to the trustee for cancellation. Any Notes surrendered for cancellation may not be reissued or resold and will be promptly cancelled.

#### **Rule 144A Information**

We will furnish to the holders or beneficial holders of the Notes or the common stock issued upon conversion and prospective purchasers, upon their request, the information, if any, required under Rule 144A(d)(4) under the Securities Act until such time as such securities are no longer “restricted securities” within the meaning of Rule 144 under the Securities Act, assuming these securities have not been owned by an affiliate of ours.

#### **Information Concerning the Trustee and Common Stock Transfer Agent and Registrar**

We have appointed Wells Fargo Bank, NA, the trustee under the indenture, as paying agent, conversion agent, Notes registrar and custodian for the Notes. The trustee or its affiliates may also provide other services to us in the ordinary course of their business. The indenture contains specific limitations on the rights of the trustee, if it or any of its affiliates is then our creditor, to obtain payment of claims in certain cases or to realize on certain property received on any claim as security or otherwise. The trustee and its affiliates will be permitted to engage in other transactions with us. However, if the trustee or any affiliate continues to have any conflicting interest and a default occurs with respect to the Notes, the trustee must eliminate such conflict or resign.

American Stock Transfer and Trust Company is the transfer agent and registrar for our common stock.

#### **Governing Law**

The Notes and the indenture are governed by, and construed in accordance with, the laws of the State of New York.

#### **Calculations in Respect of the Notes**

Except as otherwise provided herein, we will be responsible for making all calculations called for under the Notes. These calculations include, but are not limited to, determinations of the sale price of our common stock, accrued interest payable on the Notes and the conversion rate and conversion price. We or our agents will make all these calculations in good faith and, absent manifest error, such calculations will be final and binding on holders of the Notes. We will provide a schedule of these calculations to each of the trustee and the conversion agent, and each of the trustee and conversion agent is entitled to rely upon the accuracy of our calculations without independent verification. The trustee will forward these calculations to any holder of the Notes upon the request of that holder.

The Notes are issued:

- in fully registered form;
- without interest coupons; and
- in denominations of \$1,000 principal amount and integral multiples of \$1,000.

***Global Notes, Book-Entry Form***

The Notes will be evidenced by one or more global Notes. We will deposit the global Notes with DTC and register the global Notes in the name of Cede & Co. as DTC's nominee. We initially issued the notes in the form of a global security, bearing a legend relating to restrictions on transfer, which was deposited with the trustee as custodian for DTC and registered in the name of Cede & Co. as DTC's nominee. Except as set forth below, a global Note may be transferred, in whole or in part, only to another nominee of DTC or to a successor of DTC or its nominee.

Beneficial interests in a global Note may be held through organizations that are participants in DTC (called "participants"). Transfers between participants will be effected in the ordinary way in accordance with DTC rules and will be settled in clearing house funds. The laws of some states require that certain persons take physical delivery of securities in definitive form. As a result, the ability to transfer beneficial interests in the global Notes to such persons may be limited.

Beneficial interests in a global Note held by DTC may be held only through participants, or certain banks, brokers, dealers, trust companies and other parties that clear through or maintain a custodial relationship with a participant, either directly or indirectly (called "indirect participants"). So long as Cede & Co., as the nominee of DTC, is the registered owner of a global Note, Cede & Co. for all purposes will be considered the sole holder of such global Notes. Except as provided below, owners of beneficial interests in a global Note will:

- not be entitled to have certificates registered in their names;
- not receive physical delivery of certificates in definitive registered form; and
- not be considered holders of the global Notes.

We will pay principal of, premium, if any, and interest (including additional interest, if any) on, and the redemption price and the repurchase price of, a global Note to Cede & Co., as the registered owner of the global Notes, by wire transfer of immediately available funds on the maturity date, each interest payment date or the redemption or repurchase date, as the case may be. Neither we, the trustee nor any paying agent will be responsible or liable:

- for any aspect of the records relating to, or payments made on account of, beneficial ownership interests in a global Note; or
- for maintaining, supervising or reviewing any records relating to the beneficial ownership interests.

DTC has advised us that it will take any action permitted to be taken by a holder of the Notes, including the presentation of the Notes for conversion, only at the direction of one or more participants to whose account with DTC interests in the global Notes are credited, and only in respect of the principal amount of the Notes represented by the global Notes as to which the participant or participants has or have given such direction.

DTC has advised us that it is:

- a limited purpose trust company organized under the laws of the State of New York, and a member of the Federal Reserve System;
- a "clearing corporation" within the meaning of the Uniform Commercial Code; and

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- a "clearing agency" registered pursuant to the provisions of Section 17A of the Exchange Act.

DTC was created to hold securities for its participants and to facilitate the clearance and settlement of securities transactions between participants through electronic book-entry changes to the accounts of its participants. Participants include securities brokers, dealers, banks, trust companies and clearing corporations and other organizations. Some of the participants or their representatives, together with other entities, own DTC. Indirect access to the DTC system is available to others such as banks, brokers, dealers and trust companies that clear through or maintain a custodial relationship with a participant, either directly or indirectly.

DTC has agreed to the foregoing procedures to facilitate transfers of interests in a global Note among participants. However, DTC is under no obligation to perform or continue to perform these procedures, and may discontinue these procedures at any time. We will issue the Notes in definitive certificated form if DTC notifies us that it is unwilling or unable to continue as depository or DTC ceases to be a clearing agency registered under the Exchange Act and a successor depository is not appointed by us within 90 days. In addition, beneficial interests in a global Note may be exchanged for definitive certificated Notes upon request by or on behalf of DTC in accordance with customary procedures following the request of a beneficial owner seeking to enforce its rights under such Notes or the indenture. The indenture permits us to determine at any time and in our sole discretion that Notes will no longer be represented by global Notes. DTC has advised us that, under its current practices, it would notify its participants of our request, but will only withdraw beneficial interests from the global Note at the request of each DTC participant. We would issue definitive certificates in exchange for any such beneficial interests withdrawn.

Neither we, the trustee, registrar, paying agent nor conversion agent will have any responsibility or liability for the performance by DTC or its participants or indirect participants of their respective obligations under the rules and procedures governing their operations.

***Restrictions on Transfer, Legends***

The Notes and shares of common stock that are issued upon conversion will be subject to specific restrictions on transfer, as described below under “Notice to Investors.” The Notes and share certificates will bear a legend regarding such transfer restrictions.

## Registration Rights

In connection with our initial issuance of the notes to the initial purchasers, we entered a resale registration rights agreement with the initial purchasers of the Notes for the benefit of the holders of the Notes. Pursuant to the agreement we filed with the SEC, a shelf registration statement covering resales by holders of the Notes and the common stock issuable upon conversion of the Notes, and we will, at our expense use reasonable best efforts to keep the registration statement effective until the earliest of:

- the date when the holders of transfer restricted Notes and shares of common stock issued upon conversion of the Notes are able to sell under Rule 144(k) under the Securities Act all such securities immediately without restriction; or
- the date when all transfer restricted Notes and shares of common stock issued upon conversion of the Notes are registered under the shelf registration statement and sold pursuant thereto; or
- the date when all transfer restricted Notes and shares of common stock issued upon conversion of the Notes have ceased to be outstanding (whether as a result of redemption, repurchase and cancellation, conversion or otherwise).
- Each holder who sells securities pursuant to the shelf registration statement generally will be:
  - required to be named as a selling security holder in the related prospectus;
  - required to deliver a prospectus to each purchaser;
  - subject to certain of the civil liability provisions under the Securities Act in connection with the holder’s sales; and

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- bound by the provisions of the registration rights agreement that are applicable to the holder (including certain indemnification rights and obligations).

We may suspend the holder’s use of the prospectus for a period not to exceed 45 days in any 90-day period, and not to exceed an aggregate of 90 days in any 360-day period, if:

- the prospectus would, in our reasonable judgment, contain a material misstatement or omission as a result of an event that has occurred and is continuing; and
- we reasonably determine that the disclosure of this material non-public information would have a material adverse effect on us and our subsidiaries taken as a whole.

However, if the disclosure relates to a previously undisclosed proposed or pending material business transaction, the disclosure of which would impede our ability to consummate such transaction, we may extend the suspension period from 45 days to 60 days.

If at any time after the effectiveness target date, the registration statement ceases to be effective or fails to be usable and (1) we do not cure the registration statement within five business days by a post-effective amendment or a report filed pursuant to the Exchange Act or (2) if applicable, we do not terminate the suspension period, described above, by the 45th or 60th day, as the case may be, or the suspension periods exceed an aggregate of 90 days in any 360-day period (each, a “registration default”), then additional interest will accrue on the Notes, from and including the day following the registration default to but excluding the day on which the registration default has been cured. Additional interest, if any, will be paid semiannually in arrears, in cash, on each February 15 and August 15, and will accrue at a rate per year equal to:

- 0.25% of the principal amount of Notes to and including the 90th day following such registration default; and
- 0.50% of the principal amount of Notes from and after the 91st day following such registration default.

In no event will additional interest as described above, together with any special interest payable in the event of our failure to comply with the reporting obligations in the indenture or with the requirements of Section 314(a)(1) of the Trust Indenture Act, as applicable, as described under “— Events of Default; Notice and Waiver,” exceed 0.50%. Once you convert your Notes, you will cease to be entitled to receive any additional interest, but you will receive on the next payment date additional interest accrued through the date of conversion.

If a shelf registration statement covering the resales of the Notes and common stock into which the Notes are convertible is not effective, the Notes may not be sold or otherwise transferred except in accordance with the provisions set forth under “Notice to Investors.”

## DESCRIPTION OF CAPITAL STOCK

Our authorized capital stock consists of

- Series B Convertible Exchangeable 5% Preferred Stock, 4,605 shares of which were authorized and none of which were issued and outstanding at December 31, 2006;
- Series C Junior Participating Preferred Stock, 1,000,000 shares of which were authorized and none of which was issued and outstanding at December 31, 2006; and

## 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 December 31, 2006, there were no Series B Convertible Exchangeable 5% Preferred Stock shares outstanding. We do not intend to issue any of the remaining authorized but unissued Series B Convertible Exchangeable 5% Preferred Stock.

### Series C Junior Participating Preferred Stock

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

## Common Stock

At December 31, 2006, we had 200,000,000 shares of common stock authorized, of which 82,283,693 were issued and outstanding, respectively. As of December 31, 2006, 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 21,924,862.

## Equity Compensation Plans

The following table sets forth information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of December 31, 2006.

Plan Category	Number of Shares to be Issued Upon Exercise of Outstanding Options	Weighted Average Exercise Price of Outstanding Options	Number of Shares Remaining Available for Future Issuance
Equity compensation plans approved by stockholders(a)	5,553,631	\$ 7.17	2,969,510 (c)
Equity compensation plans not approved by stockholders(b)	2,102,436	\$ 8.62	2,201,431
Total	7,656,067	\$ 7.57	5,170,941

- (a) Consists of three Isis plans: 1989 Stock Option Plan, 2002 Non-Employee Directors’ Stock Option Plan and the 2000 Employee Stock Purchase Plan.
- (b) Consists of the 2000 Broad-Based Equity Incentive Plan, more fully described below.
- (c) Of these shares, 100,054 remained available for purchase under the 2000 Employee Stock Purchase Plan as of December 31, 2006. The 2000 Employee Stock Purchase Plan incorporates an evergreen formula pursuant to which on each January 1 for the first 9 anniversaries, we automatically increase the aggregate number of shares reserved for issuance under the plan by 200,000 shares.

### 1989 Stock Option Plan and Other Employee Option Grants

In June 1989 and as amended, our Board of Directors adopted, and our stockholders subsequently approved, a stock option plan that provides for the issuance of non-qualified and incentive stock options for the purchase of up to 13,200,000 shares of common stock to our employees, directors, and consultants. The term of the plan is scheduled to end in January 2014. The 1989 Plan does not allow us to grant stock bonuses or restricted stock awards and prohibits us from repricing any options outstanding under the plan unless our stockholders approve the repricing. Options granted after December 31, 1995 vest over a four-year period, with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted before January 1, 1996 generally vested over a five-year period. Options granted after May 26, 2004 have a term of seven years while options granted before May 26, 2004 have a term of ten years. At December 31, 2006, a total of 5,186,631 options were outstanding, options to purchase 2,297,379 shares were exercisable, and 2,495,456 shares were available for future grant.

### 2000 Broad Based Equity Incentive Plan



In January 2000, we adopted the 2000 Broad-Based Equity Incentive Plan (the "2000 Plan"), which provides for the issuance of non-qualified stock options for the purchase of up to 5,990,000 shares of common stock under the 2000 Plan for issuance to our employees, directors, and consultants. Typically options expire 10 years from the date of grant. Options granted under this plan generally vest over a four-year period, with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted under this plan pursuant to the April 2003 stock option exchange program expire on December 31, 2008 and vested 33.34% on January 1, 2004 and then at the rate of 2.78% per month during the option holder's employment or service as a consultant, employee or director. At December 31, 2006, a total of 2,102,436 options were outstanding, 2,004,775 shares were exercisable, and 2,201,431 shares were available for future grant.

#### *Change of Control Under 1989 Plan and 2000 Plan*

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

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

then any surviving corporation or acquiring corporation will assume any stock awards outstanding under the 2000 Plan and the 1989 Plan or will substitute similar stock awards (including an award to acquire the same consideration paid to the shareholders in the transaction for those outstanding under the 2000 Plan and the 1989 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar stock awards for those outstanding under the 2000 Plan and the 1989 Plan, then with respect to stock awards held by participants whose continuous service has not terminated, such stock awards automatically vest in full (and, if applicable, the time during which such stock awards may be exercised) and the stock awards will terminate if not exercised (if applicable) at or prior to such event. With respect to any other stock awards outstanding under the 2000 Plan and the 1989 Plan, such stock awards will terminate if not exercised (if applicable) prior to such event.

In addition, as of December 31, 2006, options to purchase approximately 97,661 shares granted under the 2000 Plan will be accelerated in full if a transaction described above occurs, even if the surviving corporation assumes such award.

#### *2002 Non-Employee Directors' Stock Option Plan*

In September 2001, our Board of Directors adopted, and our stockholders subsequently approved, an amendment and restatement of the 1992 Non-Employee Directors' Stock Option Plan, which provides for the issuance of non-qualified stock options to our non-employee directors. The name of the resulting new plan is the 2002 Non-Employee Directors' Stock Option Plan, and it has an aggregate of 850,000 shares of common stock authorized for issuance. Options under this plan expire 10 years from the date of grant. Options granted become exercisable in four equal annual installments beginning one year after the date of grant. At December 31, 2006, a total of 367,000

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options were outstanding, 199,500 of the shares issued under this plan were exercisable and 374,000 shares were available for future grant.

#### *Employee Stock Purchase Plan*

In 2000, our Board of Directors adopted, and our stockholders subsequently approved, the 2000 Employee Stock Purchase Plan and Isis reserved 200,000 shares of common stock for issuance thereunder. In each of the subsequent years, an additional 200,000 shares of common stock were reserved for the 2000 Employee Stock Purchase Plan, resulting in a total of 1.4 million shares authorized in the plan. The plan permits full-time employees to purchase common stock through payroll deductions (which cannot exceed 10% of each employee's compensation) at the lower of 85% of fair market value at the beginning or end of the six-month offering period. At December 31, 2006, 100,054 shares were available for purchase under this plan.

### **Warrants**

#### *Symphony Warrants*

In April 2006, we granted the members of Symphony GenIsis Holdings LLC warrants to purchase 4.25 million shares of common stock at an exercise price of \$8.93 per share. These warrants expire on April 7, 2011. At December 31, 2006, all of these warrants remained issued and outstanding. If we enter into a merger or acquisition in which the surviving or resulting "parent" entity is an entity other than us, then the holders of these warrants may exchange the warrants for a new warrant exercisable in return for shares or common stock of the surviving entity as follows:

- if the terms of such merger or acquisition provide for consideration that consists solely of stock of the surviving entity, and the surviving entity has a class of common stock traded on a major national exchange or foreign exchange ("Public Common Shares"), then any replacement warrants issued to the holders will be solely for such publicly traded common shares, at an exchange ratio reflecting the stock consideration paid at the time of such change in control; or
- if the terms of such merger or acquisition will provide for consideration that consists of cash or a combination of cash and Public Common Shares of the surviving entity, then any replacement warrants issued to the holders will be solely for Public Common Shares of the surviving entity, at an exchange ratio reflecting the total consideration paid by the surviving entity at the time of such change in control, as if the total consideration (including cash) for each share of our common stock was instead paid only in Public Common Shares of the surviving entity at the time of such change of control; or
- if the surviving entity is a private corporation, closely held company or other entity that does not have a class of Public Common Shares, then the holders of the warrants may elect, to surrender all outstanding warrants to us in consideration of a cash payment for each share of our common stock

subject to purchase under the warrants in an amount equal to 40% of the per share cash consideration to be received by a holder of one share of our common stock to be tendered in the merger or acquisition, subject to an aggregate limit of \$22,000,000.

#### Private Placement Warrants

In connection with the August 2005 private placement financing, investors received warrants to purchase shares of common stock at an exercise price of \$5.2395 per share. These warrants expire on August 23, 2010, but provide a call right in favor of Isis to the extent that the price per share of our common stock exceeds \$14.41 per share for twenty (20) consecutive trading days, subject to certain circumstances. Isis cannot exercise this call right prior to August 2008. At December 31, 2006, of these warrants, warrants to purchase 2,499,998 shares of common stock remained issued and outstanding.

#### Existing Convertible Subordinated Notes

In May 2002, we completed a \$125.0 million convertible debt offering, which raised proceeds of approximately \$120.9 million, net of \$4.1 million in issuance costs. The subordinated notes mature in 2009 and bear interest at

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5.5%, which is payable semi-annually. We may, at our option, redeem these convertible notes, in whole or in part, at a redemption price described below, plus any accrued and unpaid interest to the redemption date.

<u>Period</u>	<u>Redemption Price*</u>
May 3, 2005 to April 30, 2006	103.143%
May 1, 2006 to April 30, 2007	102.357%
May 1, 2007 to April 30, 2008	101.571%
May 1, 2008 to April 30, 2009	100.786%

\* Expressed as a percentage of principal amount

At December 31, 2006, the principal and accrued interest outstanding on the notes was \$125.0 million and \$1.1 million, respectively. We do not include these convertible notes in the computation of diluted net loss per share because the effect would be anti-dilutive. In January 2007, through privately negotiated transactions, we repurchased approximately \$44.1 million aggregate principal amount of the total outstanding of our 5.5% convertible notes. As of March 12, 2007, there is approximately \$80.9 million in aggregate principal amount of the notes outstanding. The notes outstanding as of March 12, 2007 are convertible, at the option of the note holders, into approximately 4,866,165 shares of common stock at a conversion price of \$16.625 per share.

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#### CERTAIN U.S. FEDERAL TAX CONSIDERATIONS

The following is a summary of certain U.S. federal income and, in the case of “non-U.S. holders” (as defined below), estate tax consequences of the ownership of the notes and the shares of our common stock, if any, into which the notes may be converted, as of the date hereof. Except where noted, this summary deals only with a note or common stock held as a “capital asset” (generally, property held for investment) and does not represent a detailed description of the U.S. federal income and estate tax consequences applicable to you if you are subject to special treatment under the U.S. federal income or estate tax laws, including if you are:

- a dealer in securities or currencies;
- a financial institution;
- a regulated investment company;
- a real estate investment trust;
- a tax-exempt organization;
- an insurance company;
- a person holding the notes or our common stock as part of a hedging, integrated, conversion or constructive sale transaction or a straddle;
- a trader in securities that has elected the mark-to-market method of accounting for your securities;
- a person liable for alternative minimum tax;
- a person who is an investor in a pass-through entity;
- a “U.S. holder” (as defined below) whose “functional currency” is not the U.S. dollar;
- a “controlled foreign corporation”;

- a “passive foreign investment company”;
- a U.S. expatriate; or
- certain former citizens or long-term residents of the United States.

The summary is based upon the provisions of the Internal Revenue Code of 1986, as amended, referred to as the Code, and U.S. Treasury regulations, rulings and judicial decisions as of the date hereof. Those authorities may be changed, perhaps retroactively, so as to result in U.S. federal income and estate tax consequences different from those summarized below. This summary does not address all aspects of U.S. federal income and estate taxes and does not deal with all tax considerations that may be relevant to holders in light of their personal circumstances.

For purposes of this discussion, a U.S. holder is a beneficial owner of a note or share of common stock that is:

- an individual citizen or resident of the United States for U.S. federal income tax purposes;
- a corporation (or any other entity treated as a corporation for U.S. federal income tax purposes) created or organized in or under the laws of the United States, any state thereof or the District of Columbia;
- an estate the income of which is subject to U.S. federal income taxation regardless of its source;
- a trust if it (1) is subject to the primary supervision of a court within the United States and one or more United States persons have the authority to control all substantial decisions of the trust or (2) has a valid election in effect under applicable U.S. Treasury regulations to be treated as a United States person.

The term “non-U.S. holder” means a beneficial owner of a note or share of our common stock (other than a partnership) that is not a U.S. holder.

If a partnership (or other entity taxable as a partnership) holds the notes, the tax treatment of a partner (or interest holder) will generally depend upon the status of the partner (or interest holder) and the activities of the partnership (or other such entity taxable as a partnership). If you are a partnership or other entity taxable as a partnership that holds the notes or our common stock, or a partner or interest holder of such a partnership or other entity, you should consult your own tax advisors.

**If you are considering the purchase of notes, you should consult your own tax advisors concerning the particular U.S. federal income and estate tax consequences to you of the ownership of the notes or our common stock, if any, into which the notes may be converted, as well as the consequences to you arising under the laws of any other taxing jurisdiction.**

**TO ENSURE COMPLIANCE WITH TREASURY DEPARTMENT CIRCULAR 230, EACH PERSON RECEIVING THIS PROSPECTUS IS HEREBY NOTIFIED THAT: (A) ANY DISCUSSION OF FEDERAL TAX ISSUES IN THIS PROSPECTUS IS NOT INTENDED OR WRITTEN TO BE RELIED UPON, AND CANNOT BE RELIED UPON, BY HOLDERS FOR THE PURPOSE OF AVOIDING PENALTIES THAT MAY BE IMPOSED ON HOLDERS UNDER THE INTERNAL REVENUE CODE OF 1986, AS AMENDED AND (B) SUCH DISCUSSION IS INCLUDED HEREIN BY US IN CONNECTION WITH THE PROMOTION OR MARKETING (WITHIN THE MEANING OF TREASURY DEPARTMENT CIRCULAR 230) OF THE TRANSACTIONS OR MATTERS ADDRESSED HEREIN. HOLDERS RECEIVING THIS PROSPECTUS SHOULD SEEK U.S. FEDERAL, STATE, LOCAL AND FOREIGN TAX ADVICE BASED ON THE HOLDER’S PARTICULAR CIRCUMSTANCES FROM AN INDEPENDENT TAX ADVISOR.**

#### **U.S. Holders**

The following discussion is a summary of certain U.S. federal income tax consequences that will apply to you if you are a U.S. holder of notes.

#### ***Payment of Interest***

This discussion assumes that the notes will not be issued with more than a *de minimis* amount of original issue discount. In such case, interest on a note will generally be taxable to you as ordinary income at the time it is paid or accrued in accordance with your usual method of accounting for tax purposes.

#### ***Market Discount***

If you purchase a note for an amount that is less than its stated redemption price at maturity, the amount of the difference will be treated as “market discount” for U.S. federal income tax purposes, unless the difference is less than a specified *de minimis* amount. Under the market discount rules, you will be required to treat any payment, other than stated interest, on, or any gain on the sale, exchange, retirement or other disposition of, a note as ordinary income to the extent of the market discount that you have not previously included in income and is treated as having accrued on the note at the time of its payment or disposition. Any unrecognized market discount will carry over to common stock received upon conversion of the notes. In addition, you may be required to defer, until the maturity of the note or its earlier disposition in a taxable transaction, the deduction of all or a portion of the interest expense on any indebtedness attributable to the note.

Any market discount will be considered to accrue ratably during the period from the date of acquisition to the maturity date of the note, unless you elect to accrue on a constant interest method. Your election to accrue market discount on a constant interest method is to be made for the taxable year in which you acquired the note, applies only to that note and may not be revoked without the consent of the Internal Revenue Service. You may elect to include market discount in income currently as it accrues, on either a ratable or constant interest method, in which case the rule described above regarding deferral of interest deductions will not apply. Your election to include market discount in income currently, once made, applies to all market discount obligations acquired by you on or after the first taxable year to which your election applies and may not be revoked without the consent of the Internal Revenue Service. You should consult your own tax advisor before making either election described in this paragraph.

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### ***Amortizable Bond Premium***

If you purchase a note for an amount in excess of the sum of all amounts payable on the note after the purchase date other than stated interest, you will be considered to have purchased the note at a “premium.” You generally may elect to amortize the premium over the remaining term of the note on a constant yield method as an offset to interest when includible in income under your regular accounting method. If you do not elect to amortize bond premium, that premium will decrease the gain or increase the loss you would otherwise recognize on disposition of the note. Your election to amortize premium on a constant yield method will also apply to all debt obligations held or subsequently acquired by you on or after the first day of the first taxable year to which the election applies. You may not revoke the election without the consent of the Internal Revenue Service. You should consult your own tax advisor before making this election.

### ***Sale, Exchange, Redemption, or other Disposition of Notes***

Except as provided below under “— Conversion of Notes Solely into Common Stock” you will generally recognize gain or loss upon the sale, exchange, redemption or other disposition of a note equal to the difference between the amount realized (less accrued but unpaid interest which will be taxable as such to the extent not previously included in income) upon the sale, exchange, redemption or other disposition and your adjusted tax basis in the note. Your adjusted tax basis in a note will generally be equal to the amount you paid for the note increased by market discount that you previously included in income and reduced by any bond premium that you elect to amortize and any cash payments on the note other than stated interest. Any gain or loss recognized on a taxable disposition of the note will be capital gain or loss subject to the market discount discussion above. If you are an individual and have held the note for more than one year, such capital gain will be subject to reduced rates of taxation. Your ability to deduct capital losses may be limited.

### ***Conversion of Notes Solely into Common Stock***

You will not recognize any income, gain or loss on the conversion of your notes solely into shares of common stock except to the extent of cash received in lieu of a fractional share of common stock and cash attributable to accrued but unpaid interest which will be taxable as such to the extent not previously included in income. The amount of gain or loss recognized with respect to a fractional share will be equal to the difference between the amount of cash you receive in respect of such fractional share, and the portion of your tax basis in the note that is allocable to the fractional share. The tax basis of the shares of common stock received upon a conversion will equal the adjusted tax basis of the note that was converted, reduced by the portion of the tax basis that is allocable to any fractional share, and increased by the amount of any accrued but unpaid interest that is deemed paid by reason of conversion. Your holding period for shares of common stock will include the period during which you held the note, except that the holding period of any common stock deemed received with respect to accrued but unpaid interest will commence on the day after conversion.

### ***Conversion of the Notes into Cash***

If a U.S. holder converts a note and we deliver solely cash, the holder will recognize gain or loss in the same manner as if such holder had disposed of the note in a taxable disposition as described under “— Sale, Exchange, Redemption, or other Disposition of Notes” above.

### ***Conversion of the Notes into Common Stock and Cash***

If a U.S. holder converts a note and we deliver a combination of our common stock and cash (and such cash is not delivered merely in lieu of a fractional share), we intend to take the position (and the following discussion assumes) that the conversion will be treated as a recapitalization for U.S. federal income tax purposes, although the tax treatment is uncertain.

Assuming such treatment, a U.S. holder will recognize gain, but not loss, equal to the excess of the sum of the fair market value of our common stock and cash received other than amounts attributable to accrued interest (which will be treated as described under “— Payment of Interest” above), over such holder’s adjusted tax basis in the note, but in no event will the gain recognized exceed the amount of cash received (excluding cash attributable to accrued interest or received in lieu of a fractional share).

In such circumstances, a U.S. holder’s tax basis in our common stock received upon a conversion of a note (other than common stock received with respect to accrued interest, but including any basis allocable to a fractional

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share) will equal the tax basis of the note that was converted, reduced by the amount of cash received (excluding cash received in lieu of a fractional share and cash attributable to accrued interest), and increased by the amount of gain, if any, recognized (other than with respect to a fractional share). The receipt of cash in lieu of a fractional share will be treated in the same manner as described under “— Conversion of Notes Solely into Common Stock” above.

A U.S. holder’s holding period for our common stock received upon conversion will include the period during which such holder held the notes, except that the holding period of any common stock received with respect to accrued but unpaid interest will commence on the day after conversion.

If the conversion were not treated as a recapitalization, the cash payment received on conversion would be treated as proceeds from a sale of a portion of the note, and taxed in the manner described under “— Sale, Exchange, Redemption, or other Disposition of Notes” above. In such case, the holder’s tax basis in the note would be allocated pro rata between the common stock and cash received, in accordance with their fair market value.

U.S. holders should consult their tax advisors regarding the tax treatment of the receipt of cash and our common stock for notes upon conversion.

### ***Constructive Distributions***

The conversion rate of the notes will be adjusted in certain circumstances. Under Section 305(c) of the Code, adjustments (or failures to make adjustments) that have the effect of increasing your proportionate interest in our assets or earnings may in some circumstances result in a deemed distribution to you. Adjustments to the conversion rate made pursuant to a bona fide reasonable adjustment formula that has the effect of preventing the dilution of the interest of the holders of the notes, however, will generally not be considered to result in a deemed distribution to you. Certain of the possible conversion rate adjustments provided in the notes may not qualify as being pursuant to a bona fide reasonable adjustment formula. If such adjustments are made, the U.S. holders of notes may be deemed to have received a distribution even though they have not received any cash or property as a result of such adjustments. Any deemed distributions will be includible in your income in the manner described under “—Taxation of Distributions on Common Stock” below. It is not clear whether a constructive dividend deemed paid to you would be eligible for the preferential rates of U.S. federal income tax applicable in respect of certain dividends received. It is also unclear whether corporate holders would be entitled to claim the dividends received deduction with respect to any such constructive dividends.

### ***Potential Application of the Rules Applicable to Contingent Payment Debt Instruments***

If we fail to register or maintain an effective registration statement for the resale of the notes or the common stock issuable upon conversion of the notes, we will be obligated to pay to a holder amounts in excess of the stated interest and principal on the notes. If those contingent payments were considered in determining the yield on the notes under the rules that apply to contingent payment debt instruments, holders would generally be required to accrue interest income at a rate higher than the stated interest rate on the notes and to treat as ordinary income (rather than capital gain) any gain recognized on a sale, exchange, repurchase or retirement of the notes before the resolution of the contingency. Because we believe that the likelihood of occurrence of the circumstances requiring such additional interest is “remote” within the meaning of applicable Treasury Regulations and that the notes are not subject to the contingent payment debt rules, we do not intend to treat that contingency as affecting the yield of the notes for these purposes. Our determination that that contingency is remote is binding on you for federal income tax purposes unless you disclose your contrary position in a timely-filed tax return for the taxable year in which you acquire a note. However, our determination is not binding on the Internal Revenue Service and is not free from doubt. You should consult your own tax advisors with respect to the tax considerations related to such payments or potential payments and the potential application of the contingent payment debt rules to the notes and the consequences thereof.

### ***Possible Effect of the Adjustment to Conversion Rate Upon a Fundamental Change***

In certain situations, we may be obligated to adjust the conversion rate of the notes (as described above under “Description of Notes — Conversion Rights — Conversion Procedures — Conversion Rate Adjustments”). The treatment of such adjustment for tax purposes is uncertain. It is possible that such adjustment could be treated as a contingent payment of additional interest, it is possible that such adjustment

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could be treated as a constructive distribution since it takes the form of an adjustment to the conversion rate, and it is possible that such adjustment could result in a deemed taxable exchange to a holder and the modified note could be treated as newly issued at that time. Each holder should consult his own tax advisor as to the effect of such adjustment. Although the issue is not free from doubt, we intend to take the position that the likelihood of the occurrence of a fundamental change is “remote” within the meaning of applicable Treasury Regulations and that the notes should not be treated as contingent payment debt instruments because of this adjustment. It is possible that the Internal Revenue Service could disagree with this treatment and seek to treat the notes as contingent payment debt instruments, which would require current accrual of income in excess of stated interest, recognition of gain or loss on conversion and the treatment as ordinary income rather than capital gain of income realized on the taxable disposition of a note. Our determination that the likelihood of a fundamental change is remote is binding on you for federal income tax purposes unless you disclose your contrary position in a timely-filed tax return for the taxable year in which you acquire a note. However, our determination is not binding on the Internal Revenue Service and is not free from doubt. You should consult your own tax advisors with respect to the tax considerations related to adjustments to the conversion rate and the potential application of the contingent payment debt rules to the notes and the consequences thereof.

### ***Taxation of Distributions on Common Stock***

Distributions paid on our common stock received upon a conversion of a note, other than certain pro rata distributions of common stock, will be treated as a dividend to the extent paid out of current or accumulated earnings and profits (as determined under U.S. federal income tax principles) and will be included in income by the U.S. holder and taxable as ordinary income when received. If a distribution exceeds our current and accumulated earnings and profits, the excess will be first treated as a tax-free return of the U.S. holder’s investment, up to the U.S. holder’s basis in the common stock. Any remaining excess will be treated as a capital gain. Dividends received by individual U.S. holders in tax years prior to 2011 will be eligible to be taxed at reduced rates if the holder meets certain holding period and other applicable requirements. Dividends received by a corporate U.S. holder will be eligible for the dividends-received deduction if the holder meets certain holding period and other applicable requirements.

### ***Sale or Other Disposition of Common Stock***

Subject to the discussion above concerning market discount, gain or loss realized by a U.S. holder on the sale or other disposition of our common stock received upon a conversion of a note will be capital gain or loss for U.S. federal income tax purposes, and will be long-term capital gain or loss if the U.S. holder’s holding period for the common stock is more than one year. The amount of the U.S. holder’s gain or loss will be equal to the difference between the U.S. holder’s tax basis in the common stock disposed of and the amount realized on the disposition. If you are an individual U.S. holder, long-term capital gains will be subject to reduced rates of taxation. Your ability to deduct capital losses may be limited.

### ***Information Reporting and Backup Withholding***

Information reporting requirements generally will apply to payments of interest on the notes and dividends on shares of common stock and to the proceeds of a sale of a note or share of common stock paid to you unless you are an exempt recipient such as a corporation. A backup withholding tax (currently at a rate of 28%) will apply to those payments if you fail to provide your taxpayer identification number, or certification of foreign or other exempt status, or if you fail to report in full interest and dividend income.

Any amounts withheld under the backup withholding rules will be allowed as a refund or a credit against your U.S. federal income tax liability provided the required information is timely furnished to the Internal Revenue Service.

## Non-U.S. Holders

The following is a summary of the U.S. federal tax consequences that will apply to you if you are a non-U.S. holder of notes or shares of common stock.

### *Payments of Interest*

The 30% U.S. federal withholding tax will not apply to any payment to you of interest on a note under the “portfolio interest rule” provided that:

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- interest paid on the note is not effectively connected with your conduct of a trade or business in the United States;
  - you do not actually (or constructively) own 10% or more of the total combined voting power of all classes of our voting stock within the meaning of the Code and applicable U.S. Treasury regulations;
  - you are not a “controlled foreign corporation” that is related to us, directly or indirectly, through stock ownership;
  - you are not a bank whose receipt of interest on a note is described in Section 881(c)(3)(A) of the Code; and
  - either (a) you provide your name and address on an Internal Revenue Service Form W-8BEN (or other applicable form), and certify, under penalties of perjury, that you are not a United States person or (b) you hold your notes through certain foreign intermediaries and satisfy the certification requirements of applicable U.S. Treasury regulations.

Special certification rules apply to non-U.S. holders that are pass-through entities rather than corporations or individuals.

If you cannot satisfy the requirements described above, payments of interest made to you will be subject to the 30% U.S. federal withholding tax, unless you provide us with a properly executed:

- IRS Form W-8BEN (or other applicable form) claiming an exemption from or reduction in withholding under the benefit of an applicable income tax treaty; or
- IRS Form W-8ECI (or other applicable form) stating that interest paid on the notes is not subject to withholding tax because it is effectively connected with your conduct of a trade or business in the United States.

The 30% U.S. federal withholding tax generally will not apply to any gain that you realize on the sale, exchange, retirement or other disposition of a note.

If you are engaged in a trade or business in the United States and interest on the notes is effectively connected with the conduct of that trade or business and, if required by an applicable income tax treaty, is attributable to a U.S. permanent establishment, then you will be subject to U.S. federal income tax on that interest on a net income basis (although you will be exempt from the 30% U.S. federal withholding tax, provided the certification requirements discussed above in “— Payments of Interest” are satisfied) generally in the same manner as if you were a United States person as defined under the Code. In addition, if you are a foreign corporation, you may be subject to a branch profits tax equal to 30% (or lower applicable income tax treaty rate) of such interest, subject to adjustments.

As described more fully under “Description of Notes — Registration Rights of the Noteholders,” upon the occurrence of certain enumerated events we may be required to pay additional amounts to you. Payments of such additional amounts may be subject to federal withholding.

### *Dividends and Constructive Dividends*

Any dividends paid to you with respect to the shares of common stock (and any deemed dividends resulting from certain adjustments, or failure to make adjustments, to the conversion rate including, without limitation, adjustments in respect of taxable dividends to holders of our common stock, see “— U.S. Holders — Constructive Distributions” above) will be subject to withholding tax at a 30% rate (or lower applicable income tax treaty rate). In the case of any constructive dividend, it is possible that this tax would be withheld from any amount owed to you, including, but not limited to, interest, shares of your common stock or sales proceeds subsequently paid or credited to you. However, dividends that are effectively connected with the conduct of a trade or business within the United States and, if required by an applicable income tax treaty, are attributable to a U.S. permanent establishment, are not subject to the withholding tax, but instead are subject to U.S. federal income tax on a net income basis at applicable graduated individual or corporate rates. Certain certification requirements and disclosure requirements must be complied with in order for effectively connected income to be exempt from withholding. Any such effectively connected income received by a foreign corporation may, under certain circumstances, be subject to an additional branch profits tax at a 30% rate (or lower applicable income tax treaty rate).

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A non-U.S. holder of shares of common stock who wishes to claim the benefit of an applicable treaty rate is required to satisfy applicable certification and other requirements. If you are eligible for a reduced rate of U.S. federal withholding tax pursuant to an income tax treaty, you may obtain a refund of any excess amounts withheld by filing an appropriate claim for refund with the Internal Revenue Service.

### ***Conversion of Notes into Solely Common Stock***

Neither gain nor loss will be recognized by non-U.S. holders on the exchange of notes solely into shares of our common stock upon conversion, except to the extent of cash received in lieu of a fractional share (which will be treated as described below under “— Sale, Exchange, Redemption or Other Disposition of Notes or Shares of Common Stock”) and common stock attributable to accrued interest, if any (which will be treated as described above under “— Payments of Interest”).

### ***Sale, Exchange, Redemption or Other Disposition of Notes or Shares of Common Stock***

Any gain realized upon the sale, exchange, redemption or other disposition of a note or share of common stock generally will not be subject to U.S. federal income tax unless:

- that gain is effectively connected with your conduct of a trade or business in the United States (and, if a tax treaty applies, is attributable to a U.S. permanent establishment);
- you are an individual who is present in the United States for 183 days or more in the taxable year of that disposition, and certain other conditions are met; or
- we are or have been a “U.S. real property holding corporation” for U.S. federal income tax purposes.

If your gain is described in the first bullet point above, you generally will be subject to U.S. federal income tax on the net gain derived from the sale. If you are a corporation, then any such effectively connected gain received by you may also, under certain circumstances, be subject to the branch profits tax at a 30% rate (or lower applicable income tax treaty rate).

If you are an individual described in the second bullet point above, you will be subject to a flat 30% U.S. federal income tax on the gain derived from the sale, which may be offset by U.S. source capital losses, even though you are not considered a resident of the United States.

We believe that we are not and do not anticipate becoming a “U.S. real property holding corporation” for U.S. federal income tax purposes.

Such holders are urged to consult their tax advisers regarding the tax consequences of the acquisition, ownership and disposition of the notes or the common stock.

### ***U.S. Federal Estate Tax***

Your estate will not be subject to U.S. federal estate tax on notes held by you at the time of your death, provided that any payment to you on the notes would be eligible for exemption from the 30% U.S. federal withholding tax under the “portfolio interest rule” described above under “— Payments of Interest” without regard to the statement requirement described in the last bullet point and, at the time of your death, payments with respect to the note would not have been effectively connected with the conduct by you of a trade or business in the United States. However, shares of common stock held by you at the time of your death will be included in your gross estate for U.S. federal estate tax purposes unless an applicable estate tax treaty provides otherwise.

### ***Information Reporting and Backup Withholding***

Generally, we must report to the Internal Revenue Service and to you the amount of interest and dividends paid to you and the amount of tax, if any, withheld with respect to those payments. Copies of the information returns reporting such interest payments and any withholding may also be made available to the tax authorities in the country in which you reside under the provisions of an applicable income tax treaty.

In general, you will not be subject to backup withholding with respect to payments of interest or dividends that we make to you provided that we do not have actual knowledge or reason to know that you are a United States person, as defined under the Code, and we have received from you the statement described above in the last bullet point under “— Payments of Interest.”

In addition, no information reporting or backup withholding will be required regarding the proceeds of the sale of a note made within the United States or conducted through certain U.S.-related financial intermediaries, if the

payor receives the statement described above and does not have actual knowledge or reason to know that you are a U.S. person, as defined under the Code, or you otherwise establish an exemption.

Any amounts withheld under the backup withholding rules generally will be allowed as a refund or a credit against your U.S. federal income tax liability provided the required information is timely furnished to the Internal Revenue Service.

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

## EXPERTS

Ernst & 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, 2006, and management's assessment of the effectiveness of our internal control over financial reporting as of December 31, 2006, as set forth in their reports, which are incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements and management's assessment are incorporated by reference in reliance on Ernst & Young LLP's reports, given on their authority as experts in accounting and auditing.

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## WHERE YOU CAN FIND MORE INFORMATION

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission. Certain information in the registration statement has been omitted from this prospectus in accordance with the rules of the SEC. We are a public company and file proxy statements and annual, quarterly and special reports and other information with the SEC. You can inspect and copy the registration statement as well as the reports, proxy statements and other information we have filed with the SEC at the public reference room maintained by the SEC at the SEC's public reference room at 100 F Street, N.E., Room 1580, Washington, D.C. 20549. You may obtain information on the operation of the public reference room by calling the SEC at 1-800-SEC-0330. The SEC also maintains an Internet site that contains reports, proxy statements and other information regarding registrants (including us) that file electronically with the SEC ([www.sec.gov](http://www.sec.gov)).

## INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" certain of our publicly-filed documents into this prospectus, which means that information included in those documents is considered part of this prospectus. Information that we file with the SEC after the effective date of the registration statement of which this prospectus is a part will automatically update and supersede this information. We incorporate by reference the documents listed below and any future filings made with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, until the offering is completed.

The following documents filed with the SEC are incorporated by reference in this prospectus:

- our Annual Report on Form 10-K for the year ended December 31, 2006;
- our Current Reports on Form 8-K, filed with the SEC on January 22, 2007, January 24, 2007 and March 6, 2007;
- our Notice of Annual Meeting and Proxy Statement for the 2006 Annual Meeting of Stockholders, filed with the SEC on March 22, 2006;
- the description of our Preferred Share Purchase Rights Plan contained in our Current Report on Form 8-K filed with the SEC on December 13, 2000, as updated by our Form 8-K filed with the SEC on April 8, 2005; and
- the description of our common stock contained in our Registration Statement on Form 8-A filed with the SEC on April 12, 1991, as updated by our Certificate of Amendment of our Restated Certificate of Incorporation filed with our Quarterly Report on Form 10-Q for the period ended June 30, 2001 and our Certificate of Amendment of our Restated Certificate of Incorporation filed with our Quarterly Report on Form 10-Q for the period ended March 31, 2006.

We will furnish without charge to you, on written or oral request, a copy of any or all of the documents incorporated by reference, other than exhibits to those documents. You should direct any requests for documents to Vice President of Finance at our principal executive offices at 1896 Rutherford Road, Carlsbad, California 92008, telephone number (760) 931-9200.

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

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## Part II

### INFORMATION NOT REQUIRED IN PROSPECTUS

#### Item 14. Other Expenses of Issuance and Distribution

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

SEC registration fee	\$	4,989
Legal fees and expenses	\$	10,000
Accounting fees and expenses	\$	10,000



Miscellaneous	\$ 5,011
Total	<u>\$ 30,000</u>

## Item 15. Indemnification of Officers and Directors

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

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

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

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

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

## Item 16. Exhibits

Exhibit Number	Description of Document
1.1	— Purchase Agreement, dated January 17, 2007, among the Registrant and the Initial Purchasers identified therein.(8)
4.1	— Amended and Restated Certificate of Incorporation filed June 19, 1991.(1)
4.2	— Certificate of Amendment to Restated Certificate of Incorporation filed May 3, 2006.(2)
4.3	— Bylaws.(3)
4.4	— Certificate of Designation of the Series C Junior Participating Preferred Stock.(4)
4.5	— Specimen Common Stock Certificate.(1)
4.6	— Form of Right Certificate.(4)
4.7	— Subscription, Joint Development and Operating Agreement dated January 14, 2000 among the Registrant, Elan Corporation, plc, Elan International Services, Ltd. and Hepasense, Ltd. (with certain confidential information deleted), together with the related Securities Purchase Agreement, Convertible Promissory Note, Warrant to Purchase Shares of Common Stock, Registration Rights Agreement and License Agreements.(5)
4.8	— Registration Rights Agreement, dated May 1, 2002, among the Registrant, UBS Warburg LLC, Robertson Stephens, Inc., Needham & Company, Inc., and Roth Capital Partners, LLC.(6)
4.9	— Indenture, dated as of May 1, 2002, between the Registrant and Wells Fargo Bank Minnesota, National Association, as Trustee, with respect to the \$125,000,000 5½% Convertible Subordinated Notes due 2009.(6)
4.10	— Form of 5½% Convertible Subordinated Note due 2009.(6)
4.11	— Securities Purchase Agreement, dated August 19, 2005, by and among the Registrant and the purchasers listed on Exhibit A thereto.(7)
4.12	— Form of Warrant dated August 23, 2005.(7)
4.13	— Indenture, dated January 23, 2007, between the Registrant and Wells Fargo Bank, N.A., a national banking association, as trustee, including Form of 2 5/8% Convertible Subordinated Note due 2027. (8)
4.14	— Registration Rights Agreement, dated January 23, 2007, among the Registrant and the Initial Purchasers identified therein. (8)
4.15	— Registration Rights Agreement between the Registrant and Symphony GenIsis Holdings LLC dated April 7, 2006 (with certain confidential information deleted). (9)
4.16	— Form of Warrant dated April 7, 2006 issued to Symphony GenIsis Holdings LLC. (9)
5.1	— Opinion of Grantland E. Bryce.
12.1	— Statement Regarding Computation of Ratio of Earnings to Fixed Charges.
23.1	— Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm.
23.2	— Consent of Grantland E. Bryce. Reference is made to Exhibit 5.1.

- 24.1 — Power of Attorney. Reference is made to page II-5.  
25.1 — Statement of Eligibility of Trustee.

- (1) Filed as an exhibit to the Registrant's Registration Statement on Form S-1 (No. 33-39640) or amendments thereto and incorporated herein by reference.
- (2) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2006.
- (3) Filed as an exhibit to the Registrant's report on Form 10-Q/A for the quarter ended June 30, 2001 and incorporated herein by reference.
- (4) Filed as an exhibit to Registrant's Report on Form 8-K dated December 8, 2000 and incorporated herein by reference.
- (5) Filed as an exhibit to the Registrant's Report on Form 8-K dated January 28, 2000, as amended on October 5, 2001, and incorporated herein by reference.

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- (6) Filed as an exhibit to the Registrant's Registration Statement on Form S-3 (No. 333-89066), originally filed on May 24, 2002, or amendment thereto and incorporated by reference.
- (7) Filed as an exhibit to Registrant's Current Report on Form 8-K dated August 22, 2005 and incorporated herein by reference.
- (8) Filed as an exhibit to the Registrant's Current Report on Form 8-K, filed with the SEC on May 5, 2006 and incorporated herein by reference.
- (9) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2006.

### Item 17. Undertakings

(a) The undersigned registrant hereby undertakes:

- (1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement
  - (i) to include any prospectus required by Section 10(a)(3) of the Securities Act of 1933;
  - (ii) to reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. However any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20 percent change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective registration statement;
  - (iii) to include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement;

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

- (2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment will be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time will be deemed to be the initial bona fide offering thereof.
- (3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.
- (4) That, for the purpose of determining liability under the Securities Act of 1933 to any purchaser:

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

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

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

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

- (i) Any preliminary prospectus or prospectus of the undersigned registrant relating to the offering required to be filed pursuant to Rule 424;
- (ii) Any free writing prospectus relating to the offering prepared by or on behalf of the undersigned registrant or used or referred to by the undersigned registrant;
- (iii) The portion of any other free writing prospectus relating to the offering containing material information about the undersigned registrant or its securities provided by or on behalf of the undersigned registrant; and
- (iv) Any other communication that is an offer in the offering made by the undersigned registrant to the purchaser.

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

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

The undersigned registrant hereby undertakes that:

- (1) For purposes of determining any liability under the Securities Act of 1933, the information omitted from the form of prospectus filed as part of this registration statement in reliance upon Rule 430A and contained in a form of prospectus filed by the registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act will be deemed to be part of this registration statement as of the time it was declared effective.
- (2) For purposes of determining any liability under the Securities Act of 1933, each post-effective amendment that contains a form of prospectus will be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time will be deemed to be the initial bona fide offering thereof.

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

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## SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this Registration Statement to be signed on its behalf by the undersigned thereunto duly authorized, in the city of Carlsbad, County of San Diego, State of California, on the 19th day of March, 2007.

**ISIS PHARMACEUTICALS, INC.**

By: /s/ B. Lynne Parshall

B. Lynne Parshall

*Executive Vice President and Chief Financial Officer*

## POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints STANLEY T. CROOKE and B. LYNNE PARSHALL, and each of them, as his or her true and lawful attorney-in-fact and agents, with full power of substitution and resubstitution, for the undersigned and in his or her name, place and stead, in any and all capacities, to sign any or all amendments (including post-effective amendments) to this Registration Statement and to sign any Registration Statement that is to be effective on filing pursuant to Rule 462(b) promulgated under the Securities Act of

1933, and all post-effective amendments thereto, and to file the same, with all exhibits thereto, and all documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power of authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, each acting alone, or his or her substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

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

Signatures	Title	Date
<u>/s/ Stanley T. Crooke</u> Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board and Chief Executive Officer (Principal executive officer)	March 19, 2007
<u>/s/ B. Lynne Parshall</u> B. Lynne Parshall	Executive Vice President, Chief Financial Officer and Director (Principal financial and accounting officer)	March 19, 2007
<u>/s/ Spencer R. Berthelsen</u> Spencer R. Berthelsen	Director	March 19, 2007
<u>/s/ Richard D. DiMarchi</u> Richard D. DiMarchi	Director	March 19, 2007
<u>Joseph Klein</u>	Director	
<u>/s/ Frederick T. Muto</u> Frederick T. Muto	Director	March 19, 2007
<u>/s/ John C. Reed</u> John C. Reed	Director	March 19, 2007
<u>/s/ Joseph H. Wender</u> Joseph H. Wender	Director	March 19, 2007

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## EXHIBIT INDEX

Exhibit Number	Description of Document
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4.2	— Certificate of Amendment to Restated Certificate of Incorporation filed May 3, 2006.(2)
4.3	— Bylaws.(3)
4.4	— Certificate of Designation of the Series C Junior Participating Preferred Stock.(4)
4.5	— Specimen Common Stock Certificate.(1)
4.6	— Form of Right Certificate.(4)
4.7	— Subscription, Joint Development and Operating Agreement dated January 14, 2000 among the Registrant, Elan Corporation, plc, Elan International Services, Ltd. and Hepasense, Ltd. (with certain confidential information deleted), together with the related Securities Purchase Agreement, Convertible Promissory Note, Warrant to Purchase Shares of Common Stock, Registration Rights Agreement and License Agreements.(5)
4.8	— Registration Rights Agreement, dated May 1, 2002, among the Registrant, UBS Warburg LLC, Robertson Stephens, Inc., Needham & Company, Inc., and Roth Capital Partners, LLC.(6)
4.9	— Indenture, dated as of May 1, 2002, between the Registrant and Wells Fargo Bank Minnesota, National Association, as Trustee, with respect to the \$125,000,000 5½% Convertible Subordinated Notes due 2009.(6)
4.10	— Form of 5½% Convertible Subordinated Note due 2009.(6)
4.11	— Securities Purchase Agreement, dated August 19, 2005, by and among the Registrant and the purchasers listed on Exhibit A thereto.(7)
4.12	— Form of Warrant dated August 23, 2005.(7)
4.13	— Indenture, dated January 23, 2007, between the Registrant and Wells Fargo Bank, N.A., a national banking association, as trustee, including Form of 2 5/8% Convertible Subordinated Note due 2027. (8)
4.14	— Registration Rights Agreement, dated January 23, 2007, among the Registrant and the Initial Purchasers identified therein. (8)
4.15	— Registration Rights Agreement between the Registrant and Symphony GenIsis Holdings LLC dated April 7, 2006 (with certain confidential information deleted). (9)
4.16	— Form of Warrant dated April 7, 2006 issued to Symphony GenIsis Holdings LLC. (9)

5.1	—	Opinion of Grantland E. Bryce.
12.1	—	Statement Regarding Computation of Ratio of Earnings to Fixed Charges.
23.1	—	Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm.
23.2	—	Consent of Grantland E. Bryce. Reference is made to Exhibit 5.1.
24.1	—	Power of Attorney. Reference is made to page II-5.
25.1	—	Statement of Eligibility of Trustee.

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- (1) Filed as an exhibit to the Registrant's Registration Statement on Form S-1 (No. 33-39640) or amendments thereto and incorporated herein by reference.
  - (2) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2006.
  - (3) Filed as an exhibit to the Registrant's report on Form 10-Q/A for the quarter ended June 30, 2001 and incorporated herein by reference.
  - (4) Filed as an exhibit to Registrant's Report on Form 8-K dated December 8, 2000 and incorporated herein by reference.
  - (5) Filed as an exhibit to the Registrant's Report on Form 8-K dated January 28, 2000, as amended on October 5, 2001, and incorporated herein by reference.
  - (6) Filed as an exhibit to the Registrant's Registration Statement on Form S-3 (No. 333-89066), originally filed on May 24, 2002, or amendment thereto and incorporated by reference.
  - (7) Filed as an exhibit to Registrant's Current Report on Form 8-K dated August 22, 2005 and incorporated herein by reference.
  - (8) Filed as an exhibit to the Registrant's Current Report on Form 8-K, filed with the SEC on May 5, 2006 and incorporated herein by reference.
  - (9) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2006.
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March 19, 2007

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

Ladies and Gentlemen:

You have requested my opinion with respect to certain matters in connection with the filing by Isis Pharmaceuticals, Inc., a Delaware corporation (the "Company"), of a Registration Statement on Form S-3 (the "Registration Statement") with the Securities and Exchange Commission pursuant to which the Company is registering under the Securities Act of 1933, as amended, the resale by the holders thereof of a total of \$162.5 million aggregate principal amount of 2 5/8% Convertible Subordinated Notes due 2027 (the "Notes") and the shares of common stock issuable upon conversion thereof (the "Shares"). The Notes were issued pursuant to the Indenture dated January 23, 2007 between the Company and Wells Fargo Bank, N.A. (the "Indenture").

In connection with this opinion, I have examined copies of the Indenture, the Notes and such other documents and have made such other inquiries and investigations of law as I have deemed necessary or appropriate to enable me to render the opinion expressed below. I have assumed the genuineness and authenticity of all documents submitted to me as originals and the conformity to originals of all documents where due execution and delivery are a prerequisite to the effectiveness thereof.

Except with respect to my opinion as to the enforceability of the Notes, which is provided solely with respect to the laws of the State of New York, my opinion is expressed only with respect to the federal laws of the United States of America, the laws of the State of California and the General Corporation Law of the State of Delaware. I express no opinion as to whether the laws of any particular jurisdiction other than those identified above are applicable to the subject matter hereof.

On the basis of the foregoing and in reliance thereon, I am of the opinion that (i) the Notes constitute valid and binding obligations of the Company, except as may be limited by applicable bankruptcy, insolvency, reorganization, moratorium, fraudulent transfer and other similar laws of general application relating to or affecting creditors' rights, by general principles of equity, and by an implied covenant of good faith, and (ii) following the issuance upon conversion of the Notes in accordance with their terms, the Shares will be validly issued, fully paid and nonassessable.

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

Sincerely,

/s/ Grantland E. Bryce

Grantland E. Bryce  
Vice President, Legal and  
General Counsel

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**COMPUTATION OF RATIO OF EARNINGS TO FIXED CHARGES**  
**(in thousands, except ratio of earnings to fixed charges)**

The following table sets forth our ratio of earnings to fixed charges for the years ended December 31, 2002, 2003, 2004, 2005 and 2006. As earnings were inadequate to cover the combined fixed charges, we have provided the coverage deficiency amounts. For purposes of this computation, earnings are defined as net loss excluding the preferred stock dividend requirement on our Series A and Series B preferred stock. Fixed charges are the sum of (i) interest costs including the amortization of deferred financing costs; and (ii) the portion of operating lease rental expense that is representative of the interest factor of 12%.

	Years Ended December 31,				
	2002	2003	2004	2005	2006
Net loss before accretion of dividend on preferred stock and noncontrolling interest in Symphony GenIsis, Inc.	\$ (72,242)	\$ (94,996)	\$ (142,503)	\$ (72,401)	\$ (68,924)
Interest expense on indebtedness	\$ 16,562	\$ 18,680	\$ 22,592	\$ 20,313	\$ 9,029
Interest expense on portion of rent expense representative of interest	\$ 1,113	\$ 1,099	\$ 1,022	\$ 1,012	\$ 1,383
<b>Earnings</b>	<b>\$ (54,567)</b>	<b>\$ (75,217)</b>	<b>\$ (118,889)</b>	<b>\$ (51,076)</b>	<b>\$ (58,512)</b>
Interest expense on indebtedness	\$ 16,562	\$ 18,680	\$ 22,592	\$ 20,313	\$ 9,029
Interest expense on portion of rent expense representative of interest	\$ 1,113	\$ 1,099	\$ 1,022	\$ 1,012	\$ 1,383
<b>Total Fixed Charges</b>	<b>\$ 17,675</b>	<b>\$ 19,779</b>	<b>\$ 23,614</b>	<b>\$ 21,325</b>	<b>\$ 10,412</b>
Ratio of earnings to fixed charges	—	—	—	—	—
Coverage deficiency	\$ (72,242)	\$ (94,996)	\$ (142,503)	\$ (72,401)	\$ (68,924)

**CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM**

We consent to the reference to our firm under the caption "Experts" in the Registration Statement (Form S-3) to be filed on or about March 20, 2007, and related Prospectus of Isis Pharmaceuticals, Inc. for the registration of \$162,500,000 2 5/8% Convertible Subordinated Notes due 2027 and 11,111,116 shares of its common stock issuable upon conversion of the notes and to the incorporation by reference therein of our reports dated March 6, 2007, with respect to the consolidated financial statements of Isis Pharmaceuticals, Inc., Isis Pharmaceuticals, Inc. management's assessment of the effectiveness of internal control over financial reporting, and the effectiveness of internal control over financial reporting of Isis Pharmaceuticals, Inc. included in its Annual Report (Form 10-K) for the year ended December 31, 2006, filed with the Securities and Exchange Commission.

/s/ ERNST & YOUNG LLP

San Diego, California  
March 14, 2007

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**UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

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**FORM T-1**

STATEMENT OF ELIGIBILITY  
UNDER THE TRUST INDENTURE ACT OF 1939 OF A  
CORPORATION DESIGNATED TO ACT AS TRUSTEE

- 
- o CHECK IF AN APPLICATION TO DETERMINE ELIGIBILITY OF A TRUSTEE PURSUANT TO  
SECTION 305(b) (2)

**WELLS FARGO BANK, NATIONAL ASSOCIATION**

(Exact name of trustee as specified in its charter)

**A National Banking Association**  
(Jurisdiction of incorporation or  
organization if not a U.S. national  
bank)

**94-1347393**  
(I.R.S. Employer  
Identification No.)

**101 North Phillips Avenue**  
**Sioux Falls, South Dakota**  
(Address of principal executive offices)

**57104**  
(Zip code)

**Wells Fargo & Company**  
**Law Department, Trust Section**  
**MAC N9305-175**  
**Sixth Street and Marquette Avenue, 17<sup>th</sup> Floor**  
**Minneapolis, Minnesota 55479**  
**(612) 667-4608**  
(Name, address and telephone number of agent for service)

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**ISIS PHARMACEUTICALS, INC.**

(Exact name of obligor as specified in its charter)

**Delaware**  
(State or other jurisdiction of  
incorporation or organization)

**33-0336973**  
(I.R.S. Employer  
Identification No.)

**1896 Rutherford Road**  
**Carlsbad, CA**  
(Address of principal executive offices)

**92008**  
(Zip code)

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**2 5/8 % Convertible Subordinated Notes due 2027**

(Title of the indenture securities)

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Item 1. General Information. Furnish the following information as to the trustee:

- (a) Name and address of each examining or supervising authority to which it is subject.

Comptroller of the Currency  
Treasury Department  
Washington, D.C.

Federal Deposit Insurance Corporation  
Washington, D.C.

Federal Reserve Bank of San Francisco  
San Francisco, California 94120

(b) Whether it is authorized to exercise corporate trust powers.

The trustee is authorized to exercise corporate trust powers.

Item 2. Affiliations with Obligor. If the obligor is an affiliate of the trustee, describe each such affiliation.

None with respect to the trustee.

No responses are included for Items 3-14 of this Form T-1 because the obligor is not in default as provided under Item 13.

Item 15. Foreign Trustee. Not applicable.

Item 16. List of Exhibits. List below all exhibits filed as a part of this Statement of Eligibility.

Exhibit 1.	A copy of the Articles of Association of the trustee now in effect.*
Exhibit 2.	A copy of the Comptroller of the Currency Certificate of Corporate Existence and Fiduciary Powers for Wells Fargo Bank, National Association, dated February 4, 2004.**
Exhibit 3.	See Exhibit 2
Exhibit 4.	Copy of By-laws of the trustee as now in effect.***
Exhibit 5.	Not applicable.
Exhibit 6.	The consent of the trustee required by Section 321(b) of the Act.
Exhibit 7.	A copy of the latest report of condition of the trustee published pursuant to law or the requirements of its supervising or examining authority.
Exhibit 8.	Not applicable.
Exhibit 9.	Not applicable.

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\* Incorporated by reference to the exhibit of the same number to the trustee's Form T-1 filed as exhibit 25 to the Form S-4 dated December 30, 2005 of Hornbeck Offshore Services LLC file number 333-130784-06.

\*\* Incorporated by reference to the exhibit of the same number to the trustee's Form T-1 filed as exhibit 25 to the Form T-3 dated March 3, 2004 of Trans-Lux Corporation file number 022-28721.

\*\*\* Incorporated by reference to the exhibit of the same number to the trustee's Form T-1 filed as exhibit 25 to the Form S-4 dated May 26, 2005 of Penn National Gaming Inc. file number 333-125274.

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#### SIGNATURE

Pursuant to the requirements of the Trust Indenture Act of 1939, as amended, the trustee, Wells Fargo Bank, National Association, a national banking association organized and existing under the laws of the United States of America, has duly caused this statement of eligibility to be signed on its behalf by the undersigned, thereunto duly authorized, all in the City of Minneapolis and State of Minnesota on the 19th day of March 2007.

WELLS FARGO BANK, NATIONAL ASSOCIATION

/s/ Lynn M. Steiner  
Lynn M. Steiner  
Vice President

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#### EXHIBIT 6

March 19, 2007

Securities and Exchange Commission  
Washington, D.C. 20549

Gentlemen:

In accordance with Section 321(b) of the Trust Indenture Act of 1939, as amended, the undersigned hereby consents that reports of examination of the undersigned made by Federal, State, Territorial, or District authorities authorized to make such examination may be furnished by such authorities to the Securities and Exchange Commission upon its request therefor.

Very truly yours,

WELLS FARGO BANK, NATIONAL ASSOCIATION

/s/ Lynn M. Steiner

Lynn M. Steiner

Vice President

EXHIBIT 7

Consolidated Report of Condition of  
Wells Fargo Bank National Association  
of 101 North Phillips Avenue, Sioux Falls, SD 57104  
And Foreign and Domestic Subsidiaries,  
at the close of business December 31, 2006, filed in accordance with 12 U.S.C. §161 for National Banks.

	<b>Dollar Amounts In Millions</b>
<b>ASSETS</b>	
Cash and balances due from depository institutions:	
Noninterest-bearing balances and currency and coin	\$ 15,071
Interest-bearing balances	1,332
Securities:	
Held-to-maturity securities	0
Available-for-sale securities	37,720
Federal funds sold and securities purchased under agreements to resell:	
Federal funds sold in domestic offices	4,141
Securities purchased under agreements to resell	1,130
Loans and lease financing receivables:	
Loans and leases held for sale	33,751
Loans and leases, net of unearned income	252,936
LESS: Allowance for loan and lease losses	2,088
Loans and leases, net of unearned income and allowance	250,848
Trading Assets	3,060
Premises and fixed assets (including capitalized leases)	4,045
Other real estate owned	557
Investments in unconsolidated subsidiaries and associated companies	419
Intangible assets	
Goodwill	8,995
Other intangible assets	18,458
Other assets	19,144
Total assets	<u>\$ 398,671</u>

<b>LIABILITIES</b>	
Deposits:	
In domestic offices	\$ 272,350
Noninterest-bearing	76,347
Interest-bearing	196,003
In foreign offices, Edge and Agreement subsidiaries, and IBFs	39,196
Noninterest-bearing	12
Interest-bearing	39,184
Federal funds purchased and securities sold under agreements to repurchase:	
Federal funds purchased in domestic offices	4,271
Securities sold under agreements to repurchase	5,631

	<b>Dollar Amounts In Millions</b>
Trading liabilities	2,145
Other borrowed money (includes mortgage indebtedness and obligations under capitalized leases)	7,119
Subordinated notes and debentures	10,164
Other liabilities	17,464
Total liabilities	<u>\$ 358,340</u>

Minority interest in consolidated subsidiaries

61

EQUITY CAPITAL

Perpetual preferred stock and related surplus	0
Common stock	520
Surplus (exclude all surplus related to preferred stock)	24,751
Retained earnings	14,549
Accumulated other comprehensive income	450
Other equity capital components	0
Total equity capital	<u>40,270</u>
Total liabilities, minority interest, and equity capital	<u>\$ 398,671</u>

I, Karen B. Nelson, Vice President of the above-named bank do hereby declare that this Report of Condition has been prepared in conformance with the instructions issued by the appropriate Federal regulatory authority and is true to the best of my knowledge and belief.

Karen B. Nelson  
Vice President

We, the undersigned directors, attest to the correctness of this Report of Condition and declare that it has been examined by us and to the best of our knowledge and belief has been prepared in conformance with the instructions issued by the appropriate Federal regulatory authority and is true and correct.

Avid Modijtabai  
John Stumpf  
Carrie Tolstedt

Directors

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