UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

Form 10-Q

(Mark One)
☒ QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the Quarterly Period Ended June 30, 2006

OR

o TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF SECURITIES EXCHANGE ACT OF 1934

For the transition period from to

Commission file number 0-19125

Isis Pharmaceuticals, Inc.
(Exact name of Registrant as specified in its charter)

Delaware	**33-0336973**
(State or other jurisdiction of incorporation or organization)	(IRS Employer Identification No.)

1896 Rutherford Road, Carlsbad, CA 92008
(Address of principal executive offices, including zip code)

760-931-9200
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **None**

Securities registered pursuant to Section 12(g) of the Act:
Common Stock, $.001 Par Value

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No o

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer or a non-accelerated filer (as defined in Rule 12b-2 of the Exchange Act): Large Accelerated Filer o Accelerated Filer ☒ Non-Accelerated Filer o

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12(b)-2 of the Securities Exchange Act of 1934). Yes o No ☒

The number of shares of voting common stock outstanding as of August 03, 2006 was 73,878,381.

ISIS PHARMACEUTICALS, INC.
FORM 10-Q

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TRADEMARKS

Macugen® is a registered trademark of Eyetech Pharmaceuticals, Inc.
Vitravene® is a registered trademark of Novartis AG.
Affinitak™ is a trademark of Eli Lilly and Company.
Ibis Biosciences™ is a trademark of Isis Pharmaceuticals, Inc.
Ibis T5000™ is a trademark of Isis Pharmaceuticals, Inc.

ISIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED BALANCE SHEETS
(in thousands, except share data)

	June 30, 2006 (Unaudited)	December 31, 2005
ASSETS		
Current assets:		
Cash and cash equivalents (including cash and cash equivalents held by Symphony GenIsis, Inc. of $64.4 million and $0 at June 30, 2006 and December 31, 2005, respectively)	$ 105,359	$ 50,885
Short-term investments	32,581	43,504
Contracts receivable	2,618	3,918
Inventory	886	951
Other current assets	6,830	6,600
Total current assets	148,274	105,858
Property, plant and equipment, net	7,563	9,130
Licenses, net	22,602	23,770
Patents, net	18,688	18,773
Deposits and other assets	2,667	3,201
Long-term investments	2,125	5,641
Total assets	$ 201,919	$ 166,373
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 3,267	$ 2,095
Accrued compensation	1,628	3,706
Accrued liabilities	6,932	8,643
Current portion of long-term obligations	7,742	7,835

Current portion of deferred contract revenue	712	1,514
Total current liabilities	20,281	23,793
5 1/2% convertible subordinated notes	125,000	125,000
Long-term obligations, less current portion	11,173	14,915
Total liabilities	156,454	163,708
Noncontrolling interest in Symphony GenIsis, Inc	38,752	—
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 72,903,237 shares and 72,201,505 shares issued and outstanding at June 30, 2006 and December 31, 2005, respectively	73	72
Additional paid-in capital	795,026	770,263
Accumulated other comprehensive income	2,114	3,178
Accumulated deficit	(790,500)	(770,848)
Total stockholders' equity	6,713	2,665
Total liabilities, noncontrolling interest and stockholders' equity	$ 201,919	$ 166,373

See accompanying notes

ISIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS
(in thousands, except for per share amounts)
(Unaudited)

	Three Months Ended June 30,		Six Months Ended June 30,	
	2006	2005	2006	2005
Revenue:				
Research and development revenue under collaborative agreements	$ 4,322	$ 10,438	$ 8,791	$ 17,573
Licensing and royalty revenue	53	154	543	461
Total revenue	4,375	10,592	9,334	18,034
Operating expenses:				
Research and development	18,982	20,950	37,354	43,311
General and administrative	2,710	1,910	5,276	4,048
Compensation expense/(benefit) related to variable accounting of stock options	—	5	—	(628)
Restructuring activities	(215)	650	(178)	7,734
Total operating expenses	21,477	23,515	42,452	54,465
Loss from operations	(17,102)	(12,923)	(33,118)	(36,431)
Other income (expenses):				
Investment income	1,344	349	2,155	854
Interest expense	(2,285)	(7,085)	(4,560)	(13,740)
Gain on investments, net	2,263	—	2,263	—
Net loss before noncontrolling interest in Symphony GenIsis, Inc.	(15,780)	(19,659)	(33,260)	(49,317)
Loss attributed to noncontrolling interest in Symphony GenIsis, Inc.	13,608	—	13,608	—
Net loss applicable to common stock	$ (2,172)	$ (19,659)	$ (19,652)	$ (49,317)
Basic and diluted net loss per share	$ (0.03)	$ (0.34)	$ (0.27)	$ (0.86)
Shares used in computing basic and diluted net loss per share	72,822	57,524	72,601	57,523

See accompanying notes

ISIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)
(Unaudited)

	Six Months Ended June 30,	
	2006	2005
Net cash used in operating activities	(30,396)	(41,392)
Investing activities:		
Purchase of short-term investments	(28,611)	(3,069)
Proceeds from the sale of short-term investments	39,950	28,188
Purchase of property, plant and equipment	(438)	(498)
Proceeds from the sale of property, plant and equipment	—	1,165
Other assets	(943)	(1,896)
Strategic investments	4,397	—
Net cash provided by investing activities	14,355	23,890
Financing activities:		
Net proceeds from issuance of equity	3,401	372
Proceeds from long-term borrowings	—	5,000
Principal payments on debt and capital lease obligations	(3,836)	(7,132)
Proceeds from purchase of noncontrolling interest in Symphony GenIsis, Inc, net of fees	70,950	—
Net cash provided by financing activities	70,515	(1,760)
Net increase (decrease) in cash and cash equivalents	54,474	(19,262)
Cash and cash equivalents at beginning of period	50,885	27,250
Cash and cash equivalents (including cash and cash equivalents held by Symphony GenIsis, Inc. of $64.4 million and $0 at June 30, 2006 and December 31, 2005, respectively) at end of period	$ 105,359	$ 7,988
Supplemental disclosures of cash flow information:		
Interest paid	$ 4,272	$ 4,502
Warrant issued in conjunction with Symphony GenIsis, Inc. transaction	$ 18,590	$ —

See accompanying notes

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
June 30, 2006
(Unaudited)

1. Basis of Presentation

The unaudited interim consolidated financial statements for the three and six month periods ended June 30, 2006 and 2005 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2005. The financial statements include all adjustments, which Isis considers necessary for a fair presentation of the financial position at such dates and the operating results and cash flows for those periods. Results for the interim periods are not necessarily indicative of the results for the entire year. For more complete financial information, these financial statements, and notes thereto, should be read in conjunction with the audited financial statements for the year ended December 31, 2005 included in Isis' Annual Report on Form 10-K and 10-K/A filed with the Securities and Exchange Commission.

The condensed consolidated financial statements include the accounts of Isis and its wholly-owned subsidiaries, Isis Pharmaceuticals Singapore Pte Ltd., Isis USA Ltd., Hepasense, Ltd., Orasense, Ltd. and Ibis Biosciences, Inc. On July 25, 2005, Isis dissolved its Hepasense, Ltd. subsidiary. In addition to its wholly owned subsidiaries, the condensed consolidated financial statements include one variable interest entity, Symphony GenIsis, Inc., for which Isis is the primary beneficiary as defined by Financial Accounting Standards Board Interpretation ("FIN") No. 46 (revised 2003), *Consolidation of Variable Interest Entities, an Interpretation of ARB No. 51*. All significant intercompany balances and transactions have been eliminated.

2. Significant Accounting Policies

Revenue Recognition

Isis recognizes revenue when it has satisfied all contractual obligations and Isis is reasonably certain it can collect the receivable.

Research and development revenue under collaborative agreements

Isis recognizes research and development revenue under collaborative agreements as it incurs the related expenses, up to contractual limits. Isis defers payments received under these agreements that relate to future performance and records revenue as Isis earns it over the specified future performance period. Isis recognizes revenue that relates to nonrefundable, upfront fees over the period of the contractual arrangements as Isis satisfies its performance obligations. Isis recognizes revenue that relates to milestones, under existing arrangements, upon completion of the milestone's performance requirement. Isis recognizes revenue from arrangements entered into subsequent to June 30, 2003 in accordance with Emerging Issues Task Force Issue No. 00-21 ("EITF 00-21") *Accounting for Revenue Arrangements with Multiple Deliverables*. This issue addresses the timing and method of revenue recognition for revenue arrangements that include the delivery of more than one product or service. Isis sometimes enters into revenue arrangements that contain multiple deliverables. In these cases, Isis recognizes revenue from each element of the arrangement as long as Isis can determine a separate value for each element, Isis has completed its obligation to deliver or perform on that element, and Isis is reasonably assured of collecting the resulting receivable. Isis records revenue from government research grants and contracts during the period in which it incurs the related expenditures. Isis recognizes revenue from product sales as it ships the products.

Isis has implemented the provisions of Staff Accounting Bulletin No. 104 ("SAB 104"), which was issued in December 2003. SAB 104 updates portions of the interpretive guidance included in Topic 13 of the codification of Staff Accounting Bulletin No. 101 in order to make this interpretive guidance consistent with current authoritative accounting guidance and SEC rules and regulations. SAB 104 provides interpretation on selected revenue recognition issues and when revenue is properly recognizable. Revenue should not be recognized until it is realized or realizable and earned. It must meet the following criteria: 1) persuasive evidence of an arrangement exists, 2) delivery occurred or services were rendered, 3) the seller's price to the buyer is fixed or determinable and 4) collectibility is reasonably assured.

As part of Isis' Eli Lilly and Company ("Lilly") alliance, in 2001 Lilly provided Isis a $100.0 million interest-free loan to fund the companies' joint research collaboration. Isis discounted the loan amounts to their net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time Isis entered into the loan. Isis accreted the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan represented value Lilly gave to Isis to help fund the research collaboration. Isis accounted for this difference as deferred revenue and recognized it as revenue over the period of performance. In August 2005, in accordance with its terms, Isis converted this loan into 2.5 million shares of its common stock. Concurrent with the conversion, Isis extended the research collaboration.

Licensing and royalty revenue

Isis recognizes licensing and royalty revenue immediately, if collectibility is reasonably assured, for arrangements in which Isis is not required to provide services in the future.

Concentration of Credit Risk

Financial instruments that potentially subject Isis to concentrations of credit risk consist primarily of cash equivalents, short-term investments and receivables. Isis places its cash equivalents and certain of its short-term investments with high credit-quality financial institutions. Isis invests its excess cash primarily in money market instruments, and municipal and floating rate bonds. Isis and its audit committee established guidelines relative to credit ratings, diversification and maturities that seek to maintain safety and liquidity.

Cash, Cash Equivalents and Investments

Isis considers all liquid investments with maturities of ninety days or less when purchased to be cash equivalents. Cash and cash equivalents held by Symphony GenIsis primarily consist of investments in money market funds. Isis' short-term investments have initial maturities of greater than ninety days from date of purchase. Isis classifies its securities as "available-for-sale" in accordance with SFAS 115, *Accounting for Certain Investments in Debt and Equity Securities.* Isis carries these investments at fair market value with any unrealized gains and losses recorded as a separate component of stockholders' equity. Fair value is based upon market prices quoted on the last day of the fiscal quarter. Isis uses the specific identification method to determine the cost of debt securities sold. Isis includes gross realized gains and losses for securities sold in investment income.

In addition to investments in marketable securities, Isis has equity investments in privately- and publicly-held biotechnology companies. Isis holds ownership interests of less than 20% in each of the respective entities. In determining if and when a decrease in market value below cost in Isis' equity positions is other-than-temporary, Isis examines historical trends in the stock price, the financial condition of the issuer and the near term prospects of the issuer. When Isis determines that a decline in value is other-than-temporary, Isis recognizes an impairment loss in the period in which the other-than-temporary decline occurs. During the second quarter of 2006, Isis recorded a net gain on investments. This net gain on investments represented a gain of $2.7 million realized on the sale of a portion of the equity securities of Alnylam Pharmaceuticals, Inc. that Isis owns offset by a non-cash loss on investment of $465,000 related to the impairment of the Company's equity investment in Antisense Therapeutics Ltd.

Valuation of Inventory

Isis includes in inventory raw material costs for drugs that Isis manufactures for its partners under contractual terms, and that it uses primarily in its clinical development activities and drug products. Isis expenses these costs when it delivers its drugs to partners, or as it uses these drugs in its own clinical trials. Isis reflects its inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. Isis reviews inventory periodically and reduces its carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. Isis considers several factors in estimating the net realizable value, including shelf lives of raw materials, alternative uses for its drugs and clinical trial materials and historical write-offs. Total inventory, which consisted solely of raw materials, was $886,000 and $951,000 as of June 30, 2006 and December 31, 2005, respectively.

Licenses

Isis obtains licenses from third parties and capitalizes the costs related to exclusive licenses. Isis amortizes capitalized licenses over their estimated useful life or term of the agreement, which for current licenses is between 7 years and 15 years.

Patents

Isis capitalizes costs consisting principally of outside legal costs and filing fees related to obtaining patents. Isis reviews its capitalized patent costs regularly to determine that they include costs for patent applications that have future value. Isis evaluates costs related to patents that it is not actively pursuing for impairment and writes off any of these costs, if appropriate, which was $463,000 and $4.7 million for the first six months of 2006 and 2005, respectively. The charge in 2005 primarily consisted of charges related to restructuring activities. Isis amortizes patent costs over their estimated useful lives of 10 years, beginning with the date the patents are issued.

Fair Value of Financial Instruments

Isis has determined the estimated fair value of its financial instruments. The amounts reported for cash, accounts receivable, accounts payable and accrued expenses approximate fair value because of their short maturities. Isis reports its investment securities at their estimated fair value based on quoted market prices of comparable instruments.

Long-Lived Assets

Pursuant to the provisions of SFAS No. 144, *Accounting for the Impairment of Long-Lived Assets*, Isis evaluates carrying values of long-lived assets including property, plant and equipment and intangible assets, on at least a quarterly basis, and when events and circumstances indicate that these assets may be impaired. In the first half of 2006 and 2005, Isis incurred charges of $463,000 and $7.0 million, respectively. The charge in 2005 was primarily related to Isis' restructuring activities, which included the write-down of capitalized leasehold improvements in a building, which Isis vacated during March 2005.

Use of Estimates

The preparation of consolidated financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the amounts reported in the condensed consolidated financial statements and accompanying notes. Actual results could differ from those estimates.

Consolidation of Variable Interest Entities

Isis has implemented the provisions of FIN No. 46R, which addresses consolidation by business enterprises of variable interest entities either: (1) that do not have sufficient equity investment at risk to permit the entity to finance its activities without additional subordinated financial support, or (2) in which the equity investors lack an essential characteristic of a controlling financial interest. As of June 30, 2006, Isis had collaborative arrangements with five entities that it considers to be variable interest entities ("VIE") under FIN 46R.

In April 2006, Isis entered into a collaboration with Symphony Capital Partners, L.P. and a group of co-investors to fund the development of Isis' cholesterol-lowering drug, ISIS 301012, and two novel drugs from Isis' metabolic disease program. Symphony Capital formed Symphony GenIsis, Inc, capitalized with $75 million, to provide funding for the development of these three drugs in collaboration with Isis. Isis treats Symphony GenIsis as a VIE for which Isis is the primary beneficiary. As a result, beginning in the second quarter of 2006, Isis began including the financial condition and results of operations of Symphony GenIsis in its condensed consolidated financial statements. For a further discussion see Note 3 — *Strategic Alliances*.

As part of the collaboration between Isis and Ercole Biotech, Inc., during 2003 and early 2004, Isis paid Ercole $750,000 in exchange for a convertible promissory note. Isis expensed the payments when made. The promissory note will convert into securities that Ercole issues in a financing. Isis is not required to consolidate Ercole's results of operations under FIN No. 46 as Isis is not the primary beneficiary.

As part of the collaboration between Isis and Sarissa Inc., during February 2005, Isis licensed an anti-cancer antisense drug to Sarissa in exchange for a $1.0 million convertible promissory note. The promissory note will convert into securities that Sarissa issues in a financing. Isis has recognized a valuation allowance of $1.0 million to offset the debt instrument, as realization of this asset is uncertain. Isis is not required to consolidate Sarissa's results of operations under FIN No. 46 as Isis is not the primary beneficiary.

As part of the collaboration between Isis and iCo Therapeutics, Inc., during August 2005, Isis licensed iCo 007, an antisense drug, to iCo in exchange for a $500,000 upfront fee consisting of $250,000 in cash and a $250,000 convertible note. In December 2005, the Company entered into a manufacturing and supply agreement with iCo. Under the agreement, iCo will purchase drug manufactured by Isis for $700,000. iCo made a $525,000 prepayment to Isis consisting of $175,000 in cash and a $350,000 convertible note. The remaining $175,000 will be paid upon shipment of the drug. Isis previously recognized a valuation allowance for both notes as realization of these assets was uncertain. In May 2006, Isis received 869,025 shares of iCo common stock for the conversion of both convertible notes. Isis is not required to consolidate iCo's results of operations under FIN No. 46 as Isis is not the primary beneficiary.

As part of the collaboration between Isis and Achaogen, Inc., during January 2006, Isis licensed its proprietary aminoglycosides program in exchange for $1.5 million of Achaogen Series A Preferred stock. Isis has recognized a valuation allowance of $1.5 million to offset the equity instrument, as realization of this asset is uncertain. Isis is not required to consolidate Achaogen's results of operations under FIN No. 46 as Isis is not the primary beneficiary.

Stock-Based Compensation

On January 1, 2006, Isis adopted SFAS No. 123 (revised 2004), *Share-Based Payment*, ("SFAS 123(R)") which requires the measurement and recognition of compensation expense for all stock based payment awards made to employees and directors including employee stock options and employee stock purchases related to the Company's Employee Stock Purchase Plan ("ESPP") based on estimated fair values. SFAS 123(R) supersedes Isis' previous accounting under Accounting Principles Board Opinion No. 25, *Accounting for Stock Issued to Employees* ("APB 25") and SFAS 123, *Accounting for Stock-Based Compensation* ("SFAS 123"), beginning January 1, 2006. In March 2005, the Securities and Exchange Commission issued Staff Accounting Bulletin No. 107 ("SAB 107") relating to SFAS 123(R). Isis has applied the provisions of SAB 107 in its adoption of SFAS 123(R).

Isis adopted SFAS 123(R) using the modified prospective transition method, which requires the application of the accounting standard as of January 1, 2006, the first day of the Company's fiscal year 2006. Isis' Consolidated Statement of Operations as of and for the three and six months ended June 30, 2006 reflects the impact of SFAS 123(R). In accordance with the modified prospective transition method, Isis' Consolidated Statements of Operations for prior periods have not been restated to reflect, and do not include, the impact of SFAS 123(R).

SFAS 123(R) requires companies to estimate the fair value of share-based payment awards on the date of grant using an option-pricing model. The value of the portion of the award that is ultimately expected to vest is recognized as expense over the requisite service period as stock-based compensation

expense in Isis' Consolidated Statement of Operations. For the three and six months ended June 30, 2006, Isis' Consolidated Statement of Operations included compensation expense for share-based payment awards granted prior to, but not yet vested as of December 31, 2005, based on the grant date fair value estimated in accordance with the pro forma provisions of SFAS 123 and compensation expense for the share-based payment awards granted subsequent to December 31, 2005 based on the grant date fair value estimated in accordance with the provisions of SFAS 123(R). Isis recognizes compensation expense for all share-based payment awards using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front loaded over the vesting period. As stock-based compensation expense recognized in the Consolidated Statement of Operations for the first six months of fiscal 2006 is based on awards ultimately expected to vest, it has been reduced for estimated forfeitures. SFAS 123(R) requires forfeitures to be estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates. In Isis' pro forma information required under SFAS 123 for the periods prior to fiscal 2006, Isis accounted for forfeitures as they occurred.

As permitted by SFAS 123(R), Isis utilizes the Black-Scholes option-pricing model ("Black-Scholes model") as its method of valuation for share-based awards granted. The Black-Scholes model was previously utilized for Isis' pro forma information required under SFAS 123. Isis' determination of the fair value of share-based payment awards on the date of grant using an option-pricing model is affected by Isis' stock price as well as assumptions regarding a number of highly complex and subjective variables. These variables include, but are not limited to, Isis' expected stock price volatility over the term of the awards, and actual and projected employee stock option exercise behaviors. Option-pricing models were developed for use in estimating the value of traded options that have no vesting or hedging restrictions and are fully transferable. Because Isis' employee stock options have certain characteristics that are significantly different from traded options, and because changes in the subjective assumptions can materially affect the estimated value, in management's opinion, the existing valuation models may not provide an accurate measure of the fair value of Isis' employee stock options. Although the fair value of employee stock options is determined in accordance with SFAS 123(R) using an option-pricing model, that value may not be indicative of the fair value observed in a willing buyer/willing seller market transaction.

Prior to January 1, 2006, Isis had adopted the disclosure-only provision of SFAS 123. Accordingly, Isis had not previously recognized compensation expense for the Isis stock option plans and Isis' ESPP, except for compensation expense primarily related to the affected options from the 2003 option exchange program. Non-cash stock-based compensation expense recognized under SFAS 123(R) for the three and six months ended June 30, 2006 was $1.4 million and $2.8 million respectively. The non-cash stock-based compensation expense/(benefit) for the three and six months ended June 30, 2005 was $5,000 and ($628,000) respectively. This non-cash stock-based compensation expense/(benefit) resulted from the 2003 option exchange program.

In April 2003, Isis implemented an employee stock option exchange program that allowed employees during the offering period to surrender options granted prior to January 5, 2002. Employees exchanged 2.2 million options having a weighted-average exercise price of $14.89 for 1.0 million options having an exercise price of $5.15. The new options, fully vested as of January 31, 2006, expire on December 31, 2008. Isis previously accounted for the affected options using variable

accounting consistent with the provisions of APB 25 and FIN 44. As a result, Isis recorded non-cash compensation expense/(benefit) related to stock options on the Consolidated Statements of Operations.

See Note 6—*Stockholders' Equity* for additional information regarding Isis' share-based compensation plans and the impact of adopting SFAS 123(R).

Comprehensive Loss

SFAS No. 130, *Reporting Comprehensive Income*, requires Isis to report, in addition to net loss, comprehensive loss and its components. A summary follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2006	2005	2006	2005
Comprehensive loss:				
Change in unrealized gains (losses)	$ (3,634)	$ (403)	$ (1,073)	$ (2,482)
Net loss applicable to common stock	(2,172)	(19,659)	(19,652)	(49,317)
Comprehensive loss	$ (5,806)	$ (20,062)	$ (20,725)	$ (51,799)

Impact of Recently Issued Accounting Standards

In February 2006, the Financial Accounting Standards Board issued SFAS No. 155, *Accounting for Certain Hybrid Financial Instruments*, which amends SFAS No. 133, *Accounting for Derivative Instruments and Hedging Activities* and SFAS No. 140, *Accounting for Transfers and Servicing of Financial Assets and Extinguishments of Liabilities.* This Statement is intended to improve the financial reporting of certain hybrid financial instruments by requiring more consistent accounting that eliminates exemptions and provides a means to simplify the accounting for these instruments. This Statement is effective for all financial instruments acquired or issued after the beginning of an entity's first fiscal year that begins after September 15, 2006. Isis does not believe the adoption of SFAS 155 will have a material impact on its financial statements.

3. Strategic Alliances

Drug Discovery and Development

Rosetta Genomics, Inc.

In January 2006, Isis initiated a joint research collaboration with Rosetta Genomics to discover and develop antisense drugs that regulate microRNAs for the treatment of the most prevalent type of liver cancer, hepatocellular carcinoma. For each drug that meets specific success factors outlined in the collaboration, Isis and Rosetta will mutually agree on a development strategy for the drug. This collaboration has an initial term of two years.

Achaogen, Inc.

In January 2006, Isis licensed its proprietary aminoglycosides program to Achaogen, a biotechnology company pursuing unique strategies to combat drug-resistant pathogens. Aminoglycosides are a group of antibiotics that inhibit bacterial protein synthesis and are used to treat serious bacterial infections. The program Isis licensed to Achaogen resulted from research conducted in Isis' Ibis division to identify drugs to treat antibiotic-resistant infections.

In exchange for the exclusive, worldwide license to Isis' aminoglycoside program, Achaogen issued to Isis $1.5 million of Achaogen Series A Preferred stock. In addition, assuming Achaogen successfully develops and commercializes the first drug in the first major market, Isis will receive milestone payments totaling up to $34.5 million for the achievement of key clinical, regulatory and sales milestones. In addition, Isis will receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of the aminoglycoside program and products.

Symphony GenIsis, Inc.

On April 7, 2006, Isis entered into a series of related agreements in connection with a transaction with Symphony Capital and a group of co-investors to provide $75 million to fund the development of Isis' cholesterol-lowering drug, ISIS 301012, and two novel drugs from Isis' metabolic disease program. The financing will support ISIS 301012 through the completion of registration-supporting clinical studies in patients with familial hypercholesterolemia and the completion of Phase 2b clinical trials in patients with high cholesterol. The financing will also support development of the two novel diabetes drugs through initial proof of concept in human clinical trials. In addition to providing the financial support to move

these drugs forward, the transaction allows Isis to continue to control and manage the development of these three drugs through key development milestones.

Symphony Capital formed Symphony GenIsis, capitalized with $75 million, to provide funding for the development of these three drugs in collaboration with Isis. Isis licensed to Symphony GenIsis the intellectual property for its apoB-100, glucagon receptor (GCGR) and glucocorticoid receptor (GCCR) programs. Isis has received an exclusive purchase option from Symphony GenIsis' investors that will allow Isis to reacquire the intellectual property by purchasing all of Symphony GenIsis' equity at a predetermined price that reflects a compounded annual rate of return that averages 32% and is 27% at the end of the anticipated four-year collaborative development period. The purchase option exercise price may be paid in cash or a combination of cash and Isis common stock (up to 33% of the purchase price), at Isis' discretion.

In exchange for the purchase option, Isis granted to Symphony GenIsis Holdings LLC a five-year warrant to purchase 4.25 million shares of common stock at an exercise price of $8.93 per share, a 25% premium over Isis' prior 60 day average trading price, which was $7.14. To compensate Symphony Capital for structuring the transaction and to pay a portion of its expenses, Isis paid a structuring fee of $3.75 million. Using a Black-Scholes option pricing model, we estimated the fair value of the warrant, at the grant date, to be $18.6 million. Isis' determination of the fair value of the warrant on the date of grant using an option-pricing model is affected by Isis' stock price as well as assumptions regarding a number of highly complex and subjective variables. These variables include, but are not limited to, Isis' expected stock price volatility over the term of the warrant. Option-pricing models were developed for use in estimating the value of traded options that have no vesting or hedging restrictions and are fully transferable. Because the warrant has certain characteristics that are significantly different from traded options, and because changes in the subjective assumptions can materially affect the estimated value, in management's opinion, the existing valuation models may not provide an accurate measure of the fair value of the warrant, specifically the value determined may not be indicative of the fair value observed in a willing buyer/willing seller market transaction.

In accordance with FIN 46R, Isis has determined that Symphony GenIsis is a variable interest entity for which it is the primary beneficiary. As a result, Isis includes the financial condition and results of operations of Symphony GenIsis in its consolidated financial statements. Isis' consolidated financial statements now include the cash and cash equivalents held by Symphony GenIsis. Additionally, the consolidated financial statements include line items called "Noncontrolling interest in Symphony GenIsis." On the Consolidated Balance Sheet, this line item initially reflected the $75 million proceeds contributed into Symphony GenIsis less $4.1 million of structuring and legal fees and the $18.6 million fair value of the warrant issued by Isis to Symphony Capital. As Isis and Symphony GenIsis progress through their collaboration, this line item will be reduced by Symphony GenIsis' expenditures, which were $13.6 million in the second quarter of 2006, until the balance becomes zero. The reductions to the "Noncontrolling Interest in Symphony GenIsis" will be reflected in Isis' Consolidated Statement of Operations using a similar caption and will improve Isis' reported net loss.

ImQuest Pharmaceuticals, Inc.

In April 2006, Isis granted an exclusive worldwide license to ImQuest for the development and commercialization of ISIS 5320, a compound that has been shown to be a potent and specific inhibitor of HIV, the virus that causes AIDS. ImQuest plans to develop ISIS 5320 as a topical microbicide therapy to prevent the sexual transmission of HIV throughout the world, but especially in developing countries. In exchange for the exclusive worldwide license, Isis will receive royalties on sales of drugs resulting from ISIS 5320. In addition, if ImQuest sublicenses ISIS 5320, Isis is entitled to a portion of the consideration received.

Ibis Division

Bruker Daltonics, Inc.

In July 2006, Isis entered into a strategic alliance with Bruker Daltonics to manufacture and distribute of the Ibis T5000 biosensor system. Bruker will be the exclusive worldwide manufacturer of the Ibis T5000 biosensor system and will also be responsible for order processing, system installations and service in North America, Europe and the Middle East. In Europe and the Middle East, Bruker will have exclusive rights to sell Ibis T5000 systems and Ibis' infectious organism identification kits to government customers for defense, homeland security and other government applications, and non-exclusive rights to sell to all other customers, including clinical, pharmaceutical and academic researchers for all other applications except diagnostics. Outside of Bruker's exclusive markets, Ibis may sell Ibis T5000 systems and its infectious organism identification kits.

4. Segment Information and Concentration of Business Risk

Segment Information

The following is information for revenue and loss from operations by segment.

	Drug Discovery and Development	Ibis	Corporate	Total
Three Months Ended June 30, 2006				
Revenue:				
Research and development	$ 1,912	$ 2,410	$ —	$ 4,322
Licensing and royalty	53	—	—	53
Total segment revenue	$ 1,965	$ 2,410	$ —	$ 4,375
Income (Loss) from operations	$ (15,620)	$ (1,697)	$ 215	$ (17,102)
Three Months Ended June 30, 2005				
Revenue:				
Research and development	$ 7,541	$ 2,897	$ —	$ 10,438
Licensing and royalty	154	—	—	154
Total segment revenue	$ 7,695	$ 2,897	$ —	$ 10,592
Income (Loss) from operations	$ (11,873)	$ (395)	$ (655)	$ (12,923)

	Drug Discovery and Development	Ibis	Corporate	Total
Six Months Ended June 30, 2006				
Revenue:				
Research and development	$ 3,183	$ 5,608	$ —	$ 8,791
Licensing and royalty	543	—	—	543
Total segment revenue	$ 3,726	$ 5,608	$ —	$ 9,334
Income (Loss) from operations	$ (31,296)	$ (2,000)	$ 178	$ (33,118)
Six Months Ended June 30, 2005				
Revenue:				
Research and development	$ 12,351	$ 5,222	$ —	$ 17,573
Licensing and royalty	461	—	—	461
Total segment revenue	$ 12,812	$ 5,222	$ —	$ 18,034
Income (Loss) from operations	$ (27,818)	$ (1,507)	$ (7,106)	$ (36,431)

Isis does not include asset or liability information by reportable segment since Isis does not currently segregate this information by segment and it is not used for purposes of making decisions about allocating resources to the segments and assessing their performance.

Concentrations of Business Risk

Isis does not generate sales from products but has historically funded its operations in part from collaborations with corporate partners and various government agencies. A relatively small number of partners historically have accounted for a significant percentage of Isis' revenue. Revenue from significant partners as a percentage of total revenue was as follows:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2006	2005	2006	2005
Partner A	25%	22%	12%	13%
Partner B	25%	9%	21%	10%
Partner C	11%	2%	13%	4%
Partner D	11%	2%	8%	1%
Partner E	7%	14%	18%	13%
Partner F	1%	44%	9%	49%

For the three and six months ended June 30, 2006, Isis derived approximately 55% and 60%, respectively, of its revenue from agencies of the United States Government, including approximately 25% and 12%, respectively, of revenue from one significant customer.

Contract receivables from four significant partners comprised approximately 39%, 17%, 14%, and 13% of contract receivables at June 30, 2006. Contract receivables from four significant partners comprised 39%, 13%, 12%, and 12% of contract receivables at December 31, 2005.

5. Restructuring Activities

In connection with the decision to reorganize and refocus the Company's resources, in January 2005, Isis commenced several cost containment measures, including a reduction in workforce of approximately 160 employees, the consolidation of its facilities in the United States, and the closure of the Company's research and development laboratory in Singapore.

In the second quarter of 2006, Isis successfully negotiated a contract modification settlement with one of its vendors. The amount of the contract termination cost was $265,000 less than the amount that had been previously accrued; therefore Isis recognized a benefit for this amount in restructuring activities for the three months ended June 30, 2006.

Pursuant to SFAS No. 146, *Accounting for Costs Associated with Exit or Disposal Activities*, the following table sets forth the activity in the restructuring reserve, which is included in accrued liabilities at June 30, 2006 (in thousands).

	Facility Consolidation and Closure Related Costs	Contract Termination Costs	Other Costs	Total
Balance at March 31, 2006	$ 724	$ 765	$ 119	$ 1,608
Accrued and expensed	20	(265)	30	(215)
Charged against accrual	(153)	(500)	(36)	(689)
Balance at June 30, 2006	$ 591	$ —	$ 113	$ 704

6. Stockholders' Equity

Common Stock

In May 2006, after receiving approval from its stockholders, Isis amended its Restated Certificate of Incorporation to increase the authorized number of shares of its common stock from 100,000,000 shares to 200,000,000 shares.

Stock Option Plans

1989 Stock Option Plan and Other Employee Option Grants

The 1989 Stock Option Plan (the "1989 Plan") 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 its employees, directors, and consultants. The term of the plan is scheduled to end in January 2014. 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. As of June 30, 2006, 2,683,982 shares were available for future grant.

2000 Broad Based Equity Incentive Plan

The 2000 Broad-Based Equity Incentive Plan (the "2000 Plan") provides for the issuance of non-qualified stock options for the purchase of up to 5,990,000 shares of common stock to its 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. Options were fully vested on January 31, 2006. As of June 30, 2006, 2,130,485 shares were available for future grant.

2002 Non-Employee Directors' Stock Option Plan

In September 2001, Isis' Board of Directors adopted, and the stockholders subsequently approved, an amendment and restatement of the 1992 Non-Employee Directors' Stock Option Plan, which provides for the issuance of non-qualified stock options to Isis' non-employee directors. The name of the resulting new plan is the 2002 Non-Employee Directors' Stock Option Plan (the "2002 Plan"). In May 2006, after receiving approval from its stockholders, Isis amended its 2002 Non-Employee Directors' Stock Option Plan to increase the total number of shares reserved for issuance under the Directors' Plan from 600,000 shares to 850,000 shares. Options under this plan expire 10 years from the date of grant. Options granted become exercisable in four equal annual installments beginning one year after the date of grant. As of June 30, 2006, 414,000 shares were available for future grant.

Employee Stock Purchase Plan

Under the 2000 ESPP, Isis reserved 200,000 shares of common stock for issuance. In each of the subsequent years, an additional 200,000 shares of common stock were reserved for the ESPP, resulting in a total of 1.4 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 of the offering period or the end of each six-month purchase period. At June 30, 2006, 200,056 shares were available for purchase under this plan.

Stock Option Activity and Share-Based Compensation Expense

The following table summarizes stock option activity for the six months ended June 30, 2006 (in thousands, except per share and contractual life data):

	Number of Shares	Weighted Average Price Per Share	Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value

Outstanding at December 31, 2005	7,979	$ 7.86			
Granted	1,786	$ 5.49			
Exercised	(554)	$ 5.84			
Cancelled/forfeited/expired	(534)	$ 8.36			
Outstanding at June 30, 2006	8,677	$ 7.47	5.29	$	2,778
Exercisable at June 30, 2006	5,366	$ 8.57	4.57	$	881

The following table summarizes information concerning outstanding and exercisable options as of June 30, 2006 (in thousands, except contractual life and exercise price data):

	Options Outstanding			Options Exercisable	
Range of Exercise Prices	Number Outstanding	Weighted Average Remaining Contractual Life	Weighted Average Exercise Price	Number Exercisable	Weighted Average Exercise Price
$2.86 - $5.24	1,088	4.69	$ 4.83	688	$ 4.95
$5.25	1,402	6.51	$ 5.25	4	$ 5.25
$5.35 - $6.59	1,610	5.85	$ 5.92	667	$ 5.98
$6.60 - $6.81	1,480	5.52	$ 6.81	1,175	$ 6.81
$6.81 - $9.62	1,775	5.25	$ 7.93	1,512	$ 7.95
$9.75 - $22.83	1,322	3.57	$ 14.04	1,320	$ 14.04
	8,677	5.29	$ 7.47	5,366	$ 8.57

The weighted average fair values of options granted were $4.27 and $3.18 for the three and six months ended June 30, 2006, respectively, compared to $2.27 and $3.72 for the same periods in 2005. The total intrinsic value of options exercised during the three and six months ended June 30, 2006 was $289,000 and $1.3 million, respectively, which was determined as of the date of exercise. The amount of cash received from the exercise of stock options was $576,000 and $3.2 million for the three and six months ended June 30, 2006, respectively. As of June 30, 2006, there was $7.5 million of total unrecognized compensation cost related to non-vested share-based compensation plans. Total unrecognized compensation cost will be adjusted for future changes in estimated forfeitures. We expect to recognize that cost over a weighted average period of 1.4 years.

Share-based Valuation and Compensation Expense Information under SFAS 123(R)

Impact of the Adoption of SFAS 123(R)

The following table summarizes stock-based compensation expense related to employee stock options and employee stock purchases under SFAS 123(R) for the three and six months ended June 30, 2006 (in thousands, except per share data), which was allocated as follows:

	Three Months Ended June 30, 2006	Six Months Ended June 30, 2006
Research and development	$ 1,103	$ 2,256
General and administrative	$ 295	$ 516
Non-cash compensation expense related to stock options included in operating expenses	$ 1,398	$ 2,772
Basic and diluted net loss per share	$ 0.02	$ 0.04

Prior to the adoption of SFAS 123(R), Isis had adopted the disclosure-only provision of SFAS 123. Accordingly, Isis had not previously recognized compensation expense for the Isis stock option plans and the ESPP, except for compensation expense primarily related to the affected options from the 2003 option exchange program.

Prior to the adoption of SFAS 123(R), Isis presented deferred compensation as a separate component of stockholders' equity. In accordance with the provisions of SFAS 123(R), on January 1, 2006, Isis reclassified the balance in deferred compensation to additional paid-in capital on the balance sheet.

The table below reflects net loss along with basic and diluted net loss per share (in thousands, except per share amounts) assuming Isis determined compensation expense consistent with SFAS 123 for the three and six months ended June 30, 2005:

	Three Months Ended June 30, 2005	Six Months Ended June 30, 2005
Net loss applicable to common stock – as reported	$ (19,659)	$ (49,317)
Net loss applicable to common stock – pro forma	$ (20,374)	$ (52,294)
Basic and diluted net loss per share – as reported	$ (0.34)	$ (0.86)
Basic and diluted net loss per share – pro forma	$ (0.35)	$ (0.91)

Determining Fair Value

Valuation. Isis utilizes the Black-Scholes model as its method of valuation for share-based awards granted. Isis recognizes the value of the portion of the award that is ultimately expected to vest as expense over the requisite service period as stock-based compensation expense in Isis' Consolidated Statements of Operations. Isis recognizes compensation expense for all share-based payment awards using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front loaded over the vesting period.

Isis estimated the fair value of each stock option grant and the ESPP purchase rights on the date of grant using the Black-Scholes model with the following weighted-average assumptions:

Options:

	June 30,	
	2006	2005
Risk-free interest rate	4.9%	4.1%
Dividend yield	0.0%	0.0%
Volatility	68.7%	82.2%
Expected Life	4.6 years	4.8 years

ESPP:

	June 30,	
	2006	2005
Risk-free interest rate	4.4%	2.63%
Dividend yield	0.0%	0.0%
Volatility	45.8%	56.6%
Expected Life	6 months	6 months

Risk-Free Interest Rate. The risk-free interest rate assumption is based upon observed interest rates appropriate for the term of Isis' employee stock options or ESPP.

Dividend Yield. The dividend yield assumption is based on Isis' history and expectation of dividend payouts. Isis has not paid dividends in the past and does not expect to in the future.

Volatility. Isis used a weighted average of the historical stock price volatility of Isis' stock for the Black-Scholes model consistent with SFAS 123(R). Prior to fiscal 2006, Isis also used its historical stock price volatility in accordance with SFAS 123 for purposes of its pro forma information.

Expected Life. The expected life of employee stock options represents the average of the life of the options and the average vesting period, and is a derived output of the simplified method, as allowed under SAB 107.

Forfeitures. As stock-based compensation expense recognized in the Consolidated Statement of Operations is based on awards ultimately expected to vest, it has been reduced for estimated forfeitures. SFAS 123(R) requires forfeitures to be estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates. Forfeitures were estimated based on historical experience. In the Company's pro forma information required under SFAS 123 for the periods prior to fiscal 2006, the Company accounted for forfeitures as they occurred.

ITEM 2. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

In addition to historical information contained in this Report on Form 10-Q, this Report contains forward-looking statements regarding our business, the financial position of Isis Pharmaceuticals, Inc. and the therapeutic and commercial potential of our technologies and products in development. Any statement describing our goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, in developing and commercializing systems to identify infectious organisms that are effective and commercially attractive, and in the endeavor of building a business around such products. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning our programs are described in additional detail in our Annual Report on Form 10-K and 10-K/A for the year ended December 31, 2005, which are on file with the U.S. Securities and Exchange Commission, and those identified in the section of Item 2 entitled "Risk Factors" beginning on page 30 of this Report.

Overview

Since our inception in 1989, we have pioneered the science of antisense for the development of a new class of drugs. We have designed antisense drugs to treat a wide variety of diseases. Due to their gene selectivity, antisense drugs have the potential to be highly effective and less toxic than traditional drugs. We have made significant progress in understanding the capabilities of antisense drugs in treating disease. We have developed new chemistries and novel formulations to enhance the potency and utility of antisense drugs, and successfully turned our expertise into one marketed product and currently 15 drugs, which we continue to advance in preclinical and clinical development either internally or with our partners. Most of these are in Phase 1 and Phase 2 human clinical trials. Our internal drug development programs are aimed at treating cardiovascular, metabolic and inflammatory diseases. Our partners are focused in disease areas such as inflammatory, ocular, viral and neurodegenerative diseases, and cancer. We are expanding the therapeutic opportunities for antisense drugs by developing a variety of formulations to enhance patient convenience and compliance, as well as infrequent dose administration. Our

pipeline has matured to consist primarily of drugs based on our proprietary second generation chemistry. Our second generation antisense drugs offer a number of advantages over first generation drugs. Specifically, second generation drugs offer the potential for improved safety and increased potency. In addition, because second generation drugs have a longer half-life, they have the potential to produce a durable therapeutic response and to support more convenient, less frequent dosing.

To date, we and our partners have made important progress on all of our second generation drugs in development. In particular, we reported positive results from Phase 1, Phase 2 and animal studies of ISIS 301012, our apoB-100 inhibitor for the lowering of high cholesterol. In a Phase 1 study, ISIS 301012 produced rapid, dose-dependent and prolonged reductions in apoB-100, low-density lipoprotein cholesterol, or LDL, and very low-density lipoprotein, or VLDL, total cholesterol and triglycerides, and was well tolerated. These positive results supported the initiation of a Phase 2 development program for ISIS 301012. In a Phase 2 study of ISIS 301012 as a single-agent in patients with high cholesterol, ISIS 301012 continued to produce rapid, dose-dependent and prolonged reductions in apoB-100, LDL, VLDL, total cholesterol and triglycerides. At a dose of 200 mg/week for three months, ISIS 301012 achieved a median percent reduction from baseline of 47% in apoB-100, 42% in LDL, 34% in total cholesterol and 46% in triglycerides at day 99. ISIS 301012 was well tolerated in this study. We also recently announced that in a drug-drug interaction study, ISIS 301012 did not interact with simvastatin or ezetimibe, currently available lipid lowering drugs with which ISIS 301012 may be dosed in combination. In addition, the U.S. Food and Drug Administration has granted orphan drug status to ISIS 301012 for the treatment of patients with homozygous familial hypercholesterolemia.

For ISIS 113715, our PTP-1b inhibitor for the treatment of type 2 diabetes, we reported data from a Phase 2 study in diabetic patients in which ISIS 113715 improved glucose control, did not cause hypoglycemia and was well tolerated. We also recently announced the initiation of a study to examine ISIS 113715 in combination with other antidiabetic drugs. Our partnered drugs in development also met important milestones. For example, in the first quarter of 2006, OncoGenex Technologies Inc. announced encouraging data from a Phase 1 study of OGX-011 in patients with non-small cell lung cancer, which supports their ongoing Phase 2 study. Phase 2 studies evaluating OGX-011 in prostrate and breast cancers are also ongoing. Earlier this year, Eli Lilly and Company initiated Phase 1 studies of LY2275796, a cancer drug targeting eIF-4E and the second drug from our research collaboration.

We have a broad patent portfolio covering our technologies. We own or exclusively license approximately 1,500 issued patents, which we believe represents the largest antisense and RNA-oriented patent estate in the pharmaceutical industry. Our intellectual property is a strategic asset that we are exploiting to generate near-term revenue and that we expect will also provide us with revenue in the future. As of June 30, 2006, we had generated more than $76 million from our intellectual property licensing program that helps support our internal drug discovery and development programs.

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

Through our Ibis division, we plan to commercialize the Ibis T5000 biosensor system and infectious organism ID kits to government customers for use in biowarfare defense, epidemiological surveillance and forensics; and to non-government customers for use in pharmaceutical process control, hospital-associated infection control, and infectious disease diagnostics. We began executing our commercialization plans for the Ibis T5000 biosensor system in 2005 and to date have delivered three Ibis biosensor systems to our government partners, each for a different application. Our most recent delivery was to the Naval Health Research Center for use in epidemiological surveillance. Prior to that, we delivered Ibis T5000 systems to the Department of Homeland Security's National Bioforensic Analysis Center for use in microbial forensics and the United States Army Medical Research Institute for Infectious Disease for use in biowarfare defense. We plan to deliver Ibis T5000 biosensor systems to additional government customers in the second half of 2006. We also plan to begin shipping infectious organism ID kits in 2006.

Consistent with Ibis' commercialization strategy, in July 2006, Isis entered into a strategic alliance with Bruker Daltonics to manufacture and distribute the Ibis T5000 biosensor system. Bruker will be the exclusive worldwide manufacturer of the Ibis T5000 biosensor system and will also be responsible for order processing, system installations and service in North America, Europe and the Middle East. In Europe and the Middle East, Bruker will have exclusive rights to sell Ibis T5000 systems and Ibis' infectious organism identification kits to government customers for defense, homeland security and other government applications, and non-exclusive rights to sell to all other customers, including clinical, pharmaceutical and academic researchers for all other applications except diagnostics. Outside of Bruker's exclusive markets, Ibis may sell Ibis T5000 systems and infectious organism identification kits.

Much of the development of the Ibis T5000 system and related applications has been funded through government contracts and grants. As of June 30, 2006, we had earned $53.5 million in revenue from numerous government agencies. In addition, we have an additional $5.8 million committed under our existing contracts and grants. These agencies include the Defense Advanced Research Projects Agency (DARPA), Department of Homeland Security (DHS), the Centers for Disease Control (CDC), the Federal Bureau of Investigation (FBI), the United States Army Medical Research Institute of Infectious Diseases (USAMRIID), and the National Institute of Allergy and Infectious Diseases (the NIAID), a part of the National Institutes of Health (NIH).

We pursue early-stage antisense research programs, including RNA interference (RNAi), microRNA, and alternative splicing through research collaborations and partnerships, similar to our strategic alliances with Alnylam Pharmaceuticals, Inc. (Alnylam), Ercole and Rosetta.

Business Segments

We focus our business on two principal segments:

Drug Discovery and Development. We continue to utilize our proprietary technology to discover and characterize novel antisense inhibitors through which our scientists modify the properties of our antisense drugs for optimal use with particular targets and thus, produce a broad proprietary portfolio of compounds applicable to many disease targets. Further, our scientists have made significant advances in oligonucleotide chemistries, including what we call our second generation antisense drugs. Second generation, including generation 2.2, drugs provide increased potency, stability, oral bioavailability and an improved side effect profile. We and our partners are studying antisense drugs in intravenous, subcutaneous, intravitreal, enema, aerosol, intrathecal, oral and topical formulations.

Along with our partners, we currently have 15 drugs in development, of which five are in Phase 2 clinical development, three are in Phase 1 clinical development and seven are in preclinical development. Our partners are licensed to develop, with our support, nine of these 15 drugs, which substantially reduces our development costs.

Ibis Division. Our Ibis division has developed a revolutionary biosensor system, utilizing a U.S. government funded technology called T.I.G.E.R., or Triangulation Identification for Genetic Evaluation of Risk, that can simultaneously identify thousands of infectious organisms in a sample, without needing to know beforehand what might be present in the sample. Ibis plans to commercialize the Ibis T5000 biosensor system and related applications-specific infectious organism ID kits to government customers for use in biowarfare defense, epidemiological surveillance and forensics; and to non-government customers for use in pharmaceutical process control, hospital-associated infection control and infectious disease diagnostics.

Recent Events

Symphony GenIsis, Inc.

In April 2006, we entered into a series of related agreements in connection with a transaction with Symphony Capital and a group of co-investors to provide $75 million to fund the development of our cholesterol-lowering drug, ISIS 301012, and two novel drugs from our metabolic disease program. The financing will support ISIS 301012 through the completion of registration-supporting clinical studies in patients with familial hypercholesterolemia and the completion of Phase 2b clinical trials in patients with high cholesterol. The financing will also support development of the two novel diabetes drugs through initial proof of concept in human clinical trials. In addition to providing the financial support to move these drugs forward aggressively, the transaction allows us to continue to control and manage the development of these three drugs through key development milestones.

Symphony Capital formed Symphony GenIsis, Inc., capitalized with $75 million, to provide funding for the development of these three drugs in collaboration with us. We licensed to Symphony GenIsis the intellectual property for our apoB-100, glucagon receptor (GCGR) and glucocorticoid receptor (GCCR) programs. We have received an exclusive purchase option from Symphony GenIsis' investors that will allow us to reacquire the intellectual property by purchasing all of Symphony GenIsis' equity at a predetermined price that reflects a compounded annual rate of return that averages 32% and is 27% at the end of the anticipated four-year collaborative development period. The purchase option exercise price may be paid in cash or a combination of cash and our common stock (up to 33% of the purchase price), at our discretion.

In exchange for the purchase option, we granted to Symphony GenIsis Holdings LLC a five-year warrant to purchase 4.25 million shares of common stock at an exercise price of $8.93 per share, a 25% premium over our prior 60 day average trading price, which was $7.14. To compensate Symphony Capital for structuring the transaction and to pay a portion of its expenses, we paid a structuring fee of $3.75 million. Using a Black-Scholes option pricing model, the fair value of the warrant, at the grant date, was estimated to be $18.6 million. Our determination of the fair value of the warrant on the date of grant using an option-pricing model is affected by our stock price as well as assumptions regarding a number of highly complex and subjective variables. These variables include, but are not limited to, our expected stock price volatility over the term of the warrant. Option-pricing models were developed for use in estimating the value of traded options that have no vesting or hedging restrictions and are fully transferable. Because the warrant has certain characteristics that are significantly different from traded options, and because changes in the subjective assumptions can materially affect the estimated value, in management's opinion, the existing valuation models may not provide an accurate measure of the fair value of the warrant, specifically the value determined may not be indicative of the fair value observed in a willing buyer/willing seller market transaction.

In accordance with FIN 46R, we have determined that Symphony GenIsis is a variable interest entity for which we are the primary beneficiary. As a result, we include the financial condition and results of operations of Symphony GenIsis in our consolidated financial statements. Our consolidated financial statements now include the cash and cash equivalents held by Symphony GenIsis. Additionally, the consolidated financial statements include line items called "Noncontrolling interest in Symphony GenIsis." On the Consolidated Balance Sheet, this line item initially reflected the $75 million proceeds contributed into Symphony GenIsis less $4.1 million of structuring and legal fees and the $18.6 million fair value of the warrant issued by us to Symphony Capital. As we and Symphony GenIsis progress through our collaboration, this line item will be reduced by Symphony GenIsis' expenditures, which were $13.6 in the second quarter of 2006, until the balance becomes zero. The reductions to the "Noncontrolling Interest in Symphony GenIsis" will be reflected in our Consolidated Statement of Operations using a similar caption and will improve our reported net loss.

We anticipate that the amount recognized as a benefit in the Non-controlling Interest in Symphony GenIsis will be lower in the remaining quarters of 2006. In the second quarter of 2006, the amount recognized in the Non-controlling Interest in Symphony GenIsis included various one-time items that will not occur again during the last half of 2006. In 2007, as the development of the compounds under the Symphony collaboration continue to progress, we anticipate Symphony

GenIsis' expenditures to increase, and therefore the benefit to our net loss applicable to common stock to increase accordingly.

Azimuth Opportunity Ltd.

On May 30, 2006, we entered into an equity line of credit arrangement with Azimuth Opportunity Ltd. Specifically, we entered into a Common Stock Purchase Agreement with Azimuth, which provides that, upon the terms and subject to the conditions set forth therein, Azimuth is committed to purchase up to $75 million of our common stock, or 14,578,970 shares whichever occurs first, over the 18-month term of the purchase agreement. From time to time over the term of the purchase agreement, and at our sole discretion, we may present Azimuth with draw down notices constituting offers to purchase our common stock. The per share purchase price for these shares is at a discount ranging from 3.8% to 5.3%. In July 2006, we completed our first draw down of $5 million, selling 872,330 shares at a price of approximately $5.73 per share.

Critical Accounting Policies

We prepare our consolidated financial statements in conformity with accounting principles generally accepted in the United States of America. As such, we are required to make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. We discuss the development, selection and disclosure of such estimates with our audit committee each quarter. There are specific risks associated with these critical accounting policies that we describe in the following paragraphs. For all of these policies, we caution that future events rarely develop exactly as expected, and that best estimates routinely require adjustment. The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, require the following:

- Assessment of the propriety of revenue recognition and associated deferred revenue;
- Determination of the proper valuation of investments in marketable securities and other equity investments;
- Estimations to assess the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determination of the proper valuation of inventory;
- Determination of the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimation of our net deferred income tax asset valuation allowance;
- Determination of the appropriateness of the judgments and estimates used in allocating revenue and expenses to operating segments; and
- Estimations to determine the fair value of stock-based compensation, including the expected life of the option and the expected stock price volatility over the term of the expected life.

Descriptions of these critical accounting policies follow.

Revenue Recognition

We follow the provisions set forth by current accounting rules, which primarily include SAB 101, *Revenue Recognition in Financial Statements*, SAB 104, *Revenue Recognition*, and EITF 00-21, *Accounting for Revenue Arrangements with Multiple Deliverables*.

We generally recognize revenue when we have satisfied all contractual obligations and we are reasonably assured of collecting the resulting receivable. We are often entitled to bill our customers and receive payment from our customers in advance of recognizing the revenue under current accounting rules. In those instances where we have billed our customers or received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on the balance sheet.

We often enter into collaborations where we receive non-refundable up-front payments for prior or future expenditures. We recognize revenue related to up-front payments ratably over the period of the contractual arrangements as we satisfy our performance obligations. Occasionally, we are required to estimate the period of a contractual arrangement or our performance obligations when the agreements we enter into do not clearly define such information. Should different estimates prevail, revenue recognized could be materially different. We have made estimates of our continuing obligations on several agreements, including our collaborations with ATL, Lilly, OncoGenex, and Pfizer.

As part of our Lilly alliance, in 2001 Lilly provided us a $100.0 million interest-free loan to fund the companies' joint research collaboration. We took quarterly draw downs against this loan and discounted the amounts to their net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time we entered into the loan. We accreted the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan represented value Lilly gave to us to help fund the research collaboration. We accounted for this difference as deferred revenue and recognized it as revenue over the period of contractual performance. In August 2005, in accordance with its terms, we converted this loan into 2.5 million shares of our common stock. Concurrent with the conversion, we extended the research collaboration. As part of the conversion and collaboration extension, Lilly has agreed not to sell these shares until at least the fourth quarter of 2006, assuming the collaboration is not terminated earlier, in exchange for certain credits against milestones and royalties in the event of a stock price decline.

Our collaborations often include contractual milestones. When we achieve these milestones, we are entitled to payment, as defined by the underlying agreements. We generally recognize revenue related to milestones upon completion of the milestone's performance requirement, as long as we are reasonably assured of collecting the resulting receivable and we are not obligated to future performance related to the achievement of the milestone. To date, we have earned milestone payments totaling $1.2 million under our Pfizer collaboration. Additionally, in January 2006, Lilly initiated clinical trials of LY2275796 for which we received a $750,000 milestone payment.

We often enter into agreements to license our proprietary patent rights on an exclusive or non-exclusive basis in exchange for license and/or royalty fees. We generally recognize as revenue immediately those licensing and royalty fees for which we have no future performance obligations and are reasonably assured of collecting the resulting receivable.

We often enter into revenue arrangements that contain multiple deliverables. In these cases, we recognize revenue from each element of the arrangement as long as we are able to determine a separate value for each element, we have completed our obligation to deliver or perform on that element and we are reasonably assured of collecting the resulting receivable.

Valuation of Investments in Marketable Securities

We account for our investments in marketable securities in accordance with current accounting rules as set forth by SFAS 115, *Accounting for Certain Investments in Debt and Equity Securities.* We carry these investments at fair market value based upon market prices quoted on the last day of the

fiscal quarter. We record unrealized gains and losses as a separate component of stockholders' equity, and include gross realized gains and losses in investment income.

In addition to our investments in marketable securities, we also have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20% in each of the respective entities. In determining if and when a decrease in market value below our cost in our equity positions is other-than-temporary, we examine historical trends in the stock price, the financial condition of the issuer, near term prospects of the issuer, and our current need for cash. When we determine that a decline in value is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs. During the second quarter of 2006, we recorded a net gain on investments. This net gain on investments represented a gain of $2.7 million realized on the sale of a portion of the equity securities of Alnylam Pharmaceuticals, Inc. that we own offset by a non-cash loss on investment of $465,000 related to the impairment of our equity investment in ATL, which we believe is primarily a result of current financial market conditions related to biotechnology companies.

Valuation of Long-Lived Assets

We assess the value of our long-lived assets, which include property and equipment, patent costs, and licenses acquired from third parties, under the provisions set forth by SFAS 144, *Accounting for the Impairment or Disposal of Long-Lived Assets*. We evaluate our long-lived assets for impairment on at least a quarterly basis. During this process, we review our property and equipment listings, pending domestic and international patent applications, domestic and international issued patents, and licenses we have acquired from other parties. To determine if any impairment is present, we consider the following, among other factors:

- Evidence of decreases in market value;
- Changes in the extent or manner in which we use an asset;
- Adverse changes in legal factors or in the business climate that would affect the value of an asset;
- An adverse action or assessment by a regulator;
- An accumulation of costs significantly in excess of amounts originally expected to acquire or construct an asset;
- Current period operating or cash flow loss combined with a history of operating or cash flow losses associated with an asset used for the purpose of producing revenue; and
- Challenges or potential challenges to our existing patents, the likelihood of applications being issued and the scope of our issued patents.

Pursuant to the provisions of SFAS No. 144, *Accounting for the Impairment of Long-Lived Assets*, we evaluate carrying values of long-lived assets including property, plant and equipment and intangible assets, on at least a quarterly basis, and when events and circumstances indicate that these assets may be impaired. In the first half of 2006 and 2005, we incurred charges of $463,000 and $7.0 million, respectively. The charge in 2005 was primarily related to our restructuring activities, which included the write-down of capitalized leasehold improvements in a building, which we vacated during March 2005.

Valuation of Inventory

We include in inventory raw material costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We expense these costs when we deliver our drugs to partners, or as we use these drugs in our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce our carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value of our inventory, including shelf lives of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. Total inventory, which consisted solely of raw materials, was $886,000 and $951,000 as of June 30, 2006 and December 31, 2005, respectively.

Estimated Liability for Clinical Development Costs

We maintain accrued liabilities related to unbilled costs for ongoing preclinical studies and clinical trials. These costs primarily relate to third-party clinical management costs, laboratory costs and analysis, toxicology studies and investigator grants, among other costs. We have multiple drugs in concurrent preclinical studies and clinical trials at several clinical sites throughout the world. We expect that at any given time we will have liabilities outstanding for our preclinical and clinical development costs related to products or services for which our service providers have not yet billed us. In order to ensure that we have adequately provided for ongoing preclinical and clinical development costs during the period in which we incur such costs, we maintain an accrual to cover these costs. We update our estimate for this accrual on at least a quarterly basis. The assessment of these costs is a subjective process that requires judgment. The ultimate settlement of these costs may differ materially from the amounts we have accrued in our consolidated financial statements.

Valuation Allowance for Net Deferred Tax Assets

We recorded a valuation allowance to offset our net deferred tax assets because we are uncertain that we will realize these net tax assets. When and if circumstances warrant, we will assess the likelihood that our net deferred tax assets will more likely than not be recovered from future taxable income and record an appropriate reversal to the valuation allowance. Because we have had net operating losses since inception, we have established a 100% valuation allowance for our net deferred tax asset.

Segment Information

We provide segment financial information and results for our Drug Discovery and Development segment and our Ibis division based on the segregation of revenue and expenses used for management's assessment of operating performance and operating decisions. Expenses shared by the segments

require the use of judgments and estimates in determining the allocation of expenses to the two segments. Different assumptions or allocation methods could result in materially different results by segment.

Stock-Based Compensation

Prior to January 1, 2006, we adopted the disclosure-only provision of SFAS No. 123, *Accounting for Stock-Based Compensation*. Accordingly, we have not previously recognized compensation expense for our stock option plans and our ESPP, except for compensation expense primarily related to the variable accounting of options from the 2003 option exchange program.

Effective January 1, 2006, we adopted SFAS No. 123 (revised 2004), *Share-Based Payment,* which requires the measurement and recognition of compensation expense for all share-based payment awards made to employees and directors including employee stock options and employee stock purchases related to our ESPP based on estimated fair values. We elected to use the modified prospective transition method, which requires the application of the accounting standard as of January 1, 2006, the first day of our fiscal year 2006. Our Consolidated Statement of Operations as of and for the three and six months ended June 30, 2006 reflects the impact of SFAS 123(R). In accordance with the modified prospective transition method, our Consolidated Statements of Operations for prior periods have not been restated to reflect, and do not include, the impact of SFAS 123(R). As of June 30, 2006, there was $7.5 million of total unrecognized compensation cost related to non-vested share-based compensation plans. Total unrecognized compensation cost will be adjusted for future changes in estimated forfeitures. We expect to recognize that cost over a weighted average period of 1.4 years.

We utilize the Black-Scholes model and assumptions discussed in Note 6 for estimating the fair value of the share-based awards we granted. Compensation expense for all share-based payment awards will continue to be recognized using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front loaded over the vesting period. Our risk-free interest rate assumption is based upon observed interest rates appropriate for the term of our employee stock options and our ESPP. The dividend yield assumption is based on our history and expectation of dividend payouts. We have not paid dividends in the past and do not expect to in the future. We use a weighted average of the historical stock price volatility of our stock to calculate the expected volatility assumption required for the Black-Scholes model consistent with SFAS 123. The expected life of employee stock options represents the average of the life of the options and the average vesting period, and is a derived output of the simplified method, as allowed under SAB 107. We estimated forfeitures based on historical experience. For the periods prior to fiscal 2006, we accounted for forfeitures as they occurred in our pro forma information required under SFAS 123.

Results of Operations

Revenue

Total revenue for the three and six months ended June 30, 2006 was $4.4 million and $9.3 million, respectively, compared to $10.6 million and $18.0 million for the same periods in 2005. Our revenue fluctuates based on the timing of activities under contract. Our ability to maintain revenue at current levels will depend on new revenue sources and the expansion of existing revenue sources for the remainder of 2006.

The following table sets forth information on our revenue by segment (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2006	2005	2006	2005
Drug Discovery and Development:				
Research and development revenue	$ 1,912	$ 7,541	$ 3,183	$ 12,351
Licensing and royalty revenue	53	154	543	461
	$ 1,965	$ 7,695	$ 3,726	$ 12,812
Ibis Division				
Research and development revenue	$ 2,410	$ 2,897	$ 5,608	$ 5,222
Licensing and royalty revenue	—	—	—	—
	$ 2,410	$ 2,897	$ 5,608	$ 5,222
Total Revenue:				
Research and development revenue	$ 4,322	$ 10,438	$ 8,791	$ 17,573
Licensing and royalty revenue	53	154	543	461
	$ 4,375	$ 10,592	$ 9,334	$ 18,034

Drug Discovery and Development

Revenue for our drug discovery and development segment includes revenue from research and development under collaborative agreements and licensing and royalty revenue. Research and development revenue under collaborative agreements for the three and six months ended June 30, 2006 was $1.9 million and $3.2 million, respectively, compared to $7.5 million and $12.4 million for the same periods in 2005. The decrease for the three and six months ended June 30, 2006 compared to the same periods in 2005 reflects a decrease in revenue from collaborations. Revenue from collaborations was less in the first half of 2006 than in the first half of 2005 primarily due to a decrease in revenue associated with our collaboration with Lilly, which was extended in August 2005 to focus on a select number of targets. Revenue from collaborations also decreased as a result of revenue that we earned in the second quarter

of 2005 in connection with drug that we sold to our partner Oncogenex Technologies, Inc. Our revenue from licensing activities and royalties for the three and six months ended June 30, 2006 was $53,000 and $543,000, respectively, compared to $154,000 and $461,000 for the same periods in 2005.

Ibis Division

Our Ibis division generates research and development revenue from grants and contracts from United States government agencies, including DARPA, CDC, FBI, DHS, and NIAID, a part of the NIH. To date, Ibis has delivered its first three Ibis T5000 biosensor systems to its government partners for use in biowarfare defense, epidemiological surveillance and forensics. These deliveries represent Ibis' initial steps in commercializing its Ibis T5000 biosensor system and related applications-specific infectious organism ID kits. Our Ibis division generated revenue of $2.4 million and $5.6 million for the three and six months ended June 30, 2006, respectively, compared to revenue of $2.9 million and $5.2 million for the same periods in 2005. The increase in revenue for the first six months of 2006 primarily relates to an increase in the number and size of active government contracts that Ibis scientists were working on in the first half of 2006 compared to the same period in 2005. While the decrease for the three months ended June 30, 2006 compared to the same period in 2005 is a result of a decrease in Ibis' labor utilization. This decrease reflected a short-term shift of labor to lower margin contracts to support deployed Ibis T5000 biosensor systems and the preparations necessary to move towards commercialization. The success of these first beta sites are important to drive future commercial sales.

We receive our DARPA funding through a subcontract with San Diego-based Science Applications International Corporation or SAIC. Historically, we have generated the majority of our government-funded revenue through our collaboration with SAIC. This collaboration accounted for approximately 18% and 13% of our total revenue in the first half of 2006 and 2005, respectively, which represents 31% and 44% of our 2006 and 2005 Ibis division revenue, respectively. Our government-funded revenue may fluctuate, depending on the timing of when we enter into and commence work under various contracts with government agencies.

From inception through June 30, 2006, Ibis has earned $53.5 million in revenue from various government agencies to further the development of our Ibis T5000 biosensor system and application-specific infectious organism ID kits. An additional $5.8 million is committed under existing contracts and grants. We may receive additional funding under these contracts based upon a variety of factors, including the accomplishment of program objectives and the exercise of contract options by the contracting agencies. In addition, these agencies may terminate these contracts and grants at their convenience at any time, even if we have fully performed our obligations. Consequently, we may never receive the full amount of the potential value of these awards.

Operating Expenses

Total operating expenses for the three and six months ended June 30, 2006 were $21.5 million and $42.5 million, respectively, compared to $23.5 million and $54.5 million for the same periods in 2005. We achieved a 22% decrease in our operating expenses in the first half of 2006 compared to the same period in 2005 principally through a reorganization in early 2005 that focused our resources on key programs. The cost savings we achieved through the reorganization led to a decrease in R&D and G&A expenses for the first six months of 2006 as compared to the first six months of 2005 of $7.5 million, which excludes $2.8 million of non-cash compensation expense related to stock options. Also contributing to the decrease from the first half of 2005 to the same period in 2006 was a decrease in costs associated with restructuring activities of $7.9 million.

Included in our operating results for the three and six months ended June 30, 2006 is $1.4 million and $2.8 million, respectively, of non-cash compensation expense related to stock options as required by SFAS 123(R). Our operating expenses for the three and six months ended June 30, 2006 included non-cash compensation expense/(benefit) of $5,000 and $(628,000), respectively, as a result of variable accounting for stock options. In order to analyze and compare our results of operations to other similar companies, we believe that it is important to exclude non-cash compensation related to stock options and costs associated with restructuring activities, which are not part of ongoing operations. We believe these items are not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding these items.

Our research and development expenses consist of costs for antisense drug discovery, antisense drug development, manufacturing and operations, our Ibis division, and R&D support costs. The following table sets forth information on research and development costs (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2006	2005	2006	2005
Research and development expenses	$ 17,879	$ 20,950	$ 35,098	$ 43,311
Non-cash compensation expense related to stock options	1,103	—	2,256	—
Total research and development as reported	$ 18,982	$ 20,950	$ 37,354	$ 43,311

Our research and development expenses by segment were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2006	2005	2006	2005
Drug Discovery and Development	$ 15,708	$ 17,916	$ 30,800	$ 37,132
Ibis Division	3,274	3,034	6,554	6,179
Total research and development expenses	$ 18,982	$ 20,950	$ 37,354	$ 43,311

For the three and six months ended June 30, 2006, we incurred total research and development expenses, excluding stock compensation, of $17.9 million and $35.1 million, respectively, compared to $21.0 million and $43.3 million for the same periods in 2005. The $8.2 million decrease in the first six months of 2006 as compared to the same period in 2005, is attributed to cost savings achieved as a result of our restructuring activities, including significant reductions in personnel costs, as well as a reduction in costs associated with drug that we sold to our partner OncoGenex in the second quarter of 2005.

Antisense Drug Discovery

Antisense drug discovery costs for the three and six months ended June 30, 2006 were $3.2 million and $6.7 million, respectively, compared to $4.8 million and $10.0 million for the same periods in 2005. The decrease of $3.3 million for the first six months of 2006 compared to the same period in 2005 was principally the result of cost savings achieved as a result of our 2005 restructuring activities. These cost savings were primarily attributed to a decrease in personnel costs. We anticipate that our existing relationships and collaborations, as well as prospective new partners, will continue to help fund our research programs, as well as contribute to the advancement of the science by funding core antisense technology research.

Antisense Drug Development

The following table sets forth research and development expenses for our major antisense drug development projects (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2006	2005	2006	2005
Alicaforsen for Crohn's disease	$ —	$ 98	$ 2	$ 343
Other antisense development products	3,775	5,108	7,474	10,689
Development overhead costs	2,914	1,838	4,797	3,689
Total antisense drug development	$ 6,689	$ 7,044	$ 12,273	$ 14,721

Antisense drug development expenditures were $6.7 million and $12.3 million for the three and six months ended June 30, 2006, respectively, compared to $7.0 million and $14.7 million for the same periods in 2005. The decrease of $2.4 million for the first six months of 2006 compared to the same period in 2005 was primarily due to cost savings achieved as a result of our decision to focus our research and development resources on our most promising second generation drugs, including ISIS 301012 and ISIS 113715, a reduction of costs associated with drug that we sold to OncoGenex in the second quarter of 2005 and the decision to discontinue development of ISIS 104838, ISIS 14803 and alicaforsen for Crohn's disease. We expect our drug development expenses to fluctuate based on the timing and size of our clinical trials. We may conduct

multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Our Phase 1 and Phase 2 programs are really research programs that fuel our Phase 3 pipeline. When our products are in Phase 1 or Phase 2 clinical trials, they are in a dynamic state where we continually adjust the development strategy for each product. Although we may characterize a product as "in Phase 1" or "in Phase 2," it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product's particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous products in preclinical and early stage clinical research, the fluctuations in expenses from product-to-product, in large part, offset one another. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related cost. Our partners are developing, with our support, nine of our 15 drug candidates, which substantially reduces our development costs.

Manufacturing and Operations

Expenditures in our manufacturing and operations function consist primarily of personnel costs, specialized chemicals for oligonucleotide manufacturing, laboratory supplies and outside services. This function is responsible for providing drug supplies to antisense research and antisense drug development, including the analytical testing to satisfy good laboratory and good manufacturing practices requirements. These costs for the three and six months ended June 30, 2006 were $1.4 million and $3.2 million, respectively, as compared to $1.8 million and $3.3 million for the same periods in 2005.

Ibis Division

Our Ibis research and development expenses are primarily the result of our performance under our contracts with DARPA, CDC, FBI, DHS and NIAID, a part of the NIH, in support of our ongoing development of our Ibis T5000 biosensor system and application-specific infectious organism ID kits. Our Ibis division expenses include all contract-related costs we incur on behalf of government agencies in connection with the performance of our obligations under the respective contracts, including costs for equipment to which the government retains title. Research and development expenditures in our Ibis division include costs for scientists, pass-through equipment costs, laboratory supplies, chemicals and highly specialized information technology consultants to advance the research and development of our Ibis T5000 biosensor program technology. In 2006, Ibis is incurring costs to support deployed Ibis T5000 biosensor systems and the preparations necessary to move towards commercialization. The success of these first beta sites is important to drive future commercial sales. Further, we allocate a portion of R&D support costs and general and administrative costs to our Ibis division. Our Ibis division research and development expenses, excluding stock based compensation, for the three and six months ended June 30, 2006, were $3.1 million and $6.2 million, respectively, and essentially flat compared to $3.0 million and $6.2 million for the same periods in 2005. Ibis has deployed its first three Ibis T5000 biosensor systems to its government partners for use in biowarfare defense, epidemiological surveillance and forensics, and plans to deploy additional systems to its government partners this year. We also plan to begin shipping application specific infectious organism ID kits in 2006. We expect our costs, including our selling, general and administrative costs, for our Ibis division to increase as we continue to expand this business.

R&D Support

In our research and development expenses, we include support costs such as rent, repair and maintenance for buildings and equipment, utilities, depreciation of laboratory equipment and facilities, amortization of our intellectual property, information technology costs, procurement costs and waste disposal costs. We call these costs R&D support costs.

The following table sets forth information on R&D support costs (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2006	2005	2006	2005
Personnel costs	$ 1,553	$ 1,381	$ 2,997	$ 2,883
Occupancy	1,400	1,642	2,927	3,718
Depreciation and amortization	1,331	1,248	2,575	2,541
Insurance	265	295	520	594
Other	386	355	885	787
Total R&D support costs	$ 4,935	$ 4,921	$ 9,904	$ 10,523

R&D support costs for the three and six months ended June 30, 2006 were $4.9 million and $9.9 million, respectively, compared to $4.9 million and $10.5 million for the same periods in 2005. The decrease of $619,000 in the first half of 2006 as compared to the same period in 2005 was primarily due to decreased facilities and equipment depreciation and patent amortization costs resulting from our restructuring activities, which included consolidation and closure of facilities, and the write-down of equipment and patent costs.

Our R&D support costs by segment were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2006	2005	2006	2005
Drug Discovery and Development	$ 4,330	$ 4,289	$ 8,618	$ 9,123
Ibis Division	605	632	1,286	1,400
Total R&D support costs	$ 4,935	$ 4,921	$ 9,904	$ 10,523

General and Administrative

The following table sets forth information on general and administrative expenses (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2006	2005	2006	2005
General and administrative expenses	$ 2,415	$ 1,910	$ 4,760	$ 4,048
Non-cash compensation expense related to stock options	295	—	516	—
Total general and administrative as reported	$ 2,710	$ 1,910	$ 5,276	$ 4,048

General and administrative expenses, excluding stock-based compensation expense, for the three and six months ended June 30, 2006 were $2.4 million and $4.8 million, respectively, compared to $1.9 million and $4.0 million for the same periods in 2005. The increase of $712,000 in the first half of 2006 as compared to the same period in 2005 is the result of increased general and administrative expenses associated with the commercialization of the Ibis T5000 biosensor system, the addition of general and administrative expenses that are consolidated from Symphony GenIsis and legal fees incurred for the Ajinomoto arbitration. As Ibis continues to execute its commercialization plan, we expect general and administrative expense for Ibis to increase.

Our general and administrative expenses by segment were as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2006	2005	2006	2005
Drug Discovery and Development	$ 1,878	$ 1,652	$ 4,223	$ 3,498
Ibis Division	832	258	1,053	550
Total general and administrative expenses	$ 2,710	$ 1,910	$ 5,276	$ 4,048

Compensation Expense Related to the Variable Accounting of Stock Options

Compensation expense/(benefit) related to the variable accounting of stock options for the three and six months ended June 30, 2005 was $5,000 and $(628,000), respectively. Changes in compensation expense (benefit) were primarily related to the effects of using variable accounting to account for stock options associated with the employee stock option exchange program initiated in April 2003. We accounted for options affected by the employee stock option exchange program as variable stock options in accordance with APB Opinion No. 25 and FIN 44.

Restructuring Activities

During the three and six months ended June 30, 2006, we recorded a benefit of $215,000 and $178,000, respectively, compared to $650,000 and $7.7 million of expense for the same periods in 2005 for restructuring activities resulting from our decision to focus our resources on key programs. The 2005 charge for restructuring activities consisted of costs associated with employee terminations, the consolidation of our facilities, termination of certain contractual obligations, and the closure of our research and development laboratory in Singapore.

In the second quarter of 2006, we successfully negotiated a contract modification with one of our vendors. The amount of the contract modification was $265,000 less than the amount that had been previously accrued; therefore, we recognized a benefit for this amount in restructuring activities for the three and six months ended June 30, 2006.

Investment Income

Investment income for the three and six months ended June 30, 2006 totaled $1.3 million and $2.2 million, respectively, compared to $349,000 and $854,000 for the same periods in 2005. The increase in investment income for the first six months of 2006 over the same period in 2005 was primarily due to our higher average returns on our investments caused by higher interest rates for the first six months of 2006 compared to the first six months of 2005.

Interest Expense

Interest expense for the three and six months ended June 30, 2006 totaled $2.3 million and $4.6 million, respectively, compared to $7.1 million and $13.7 million for the same periods in 2005. This decrease was due to the effect of a lower debt balance during 2006 than during 2005 primarily related to the conversion of our $100 million Lilly loan in the third quarter of 2005.

Gain on Investments, net

Gain on investments for the three and six months ended June 30, 2006 was $2.3 million and $0 for the same periods in 2005. The gain on investments in 2006 reflects a gain of $2.7 million realized on the sale of a portion of the equity securities of Alnylam that we own offset by a non-cash loss of $465,000 related to the impairment of our equity investment in ATL. The impairment reflects the decrease in the market value of ATL's stock, which we believe is a result of current financial market conditions related to biotechnology companies.

Net Loss Applicable to Common Stock

Net loss applicable to common stock for the three and six months ended June 30, 2006 was $2.2 million and $19.7 million, respectively, compared with a net loss applicable to common stock of $19.7 million and $49.3 million, for the same periods in 2005. As a result of consolidating the results of Symphony GenIsis, we recognized a benefit of $13.6 million in the Non-controlling Interest in Symphony GenIsis for the three and six months ended June 30, 2006. This benefit that we recognized was a significant reason for the improvement in our net loss applicable to common stock in the first half of 2006 as compared to the same period in 2005. The decrease in the net loss applicable to common stock was also impacted by a decrease in our loss from operations, an increase from the gain on investments and a decrease in interest expense.

We anticipate that the amount recognized as a benefit in the Non-controlling Interest in Symphony GenIsis will be lower in the remaining quarters of 2006. In the second quarter of 2006, the amount recognized in the Non-controlling Interest in Symphony GenIsis included various one-time items that will not occur again during the last half of 2006. In 2007, as the development of the compounds under the Symphony collaboration continue to progress, we anticipate Symphony GenIsis' expenditures to increase, and therefore the benefit to our net loss applicable to common stock to increase accordingly.

Net Loss Per Share

Net loss per share for the three and six months ended June 30, 2006 was $0.03 and $0.27 per share, respectively, compared to a net loss per share for the same periods in 2005 of $0.34 and $0.86 per share. In August 2005, we issued approximately 12 million shares of common stock in a private placement that raised net proceeds of $48 million. Also in August 2005, we issued 2.5 million shares to Lilly in connection with the conversion of our $100 million Lilly loan. These additional shares combined with the substantial decrease in net loss applicable to common stock, were a significant reason for the decrease in net loss per share from the first half of 2005 to the same period in 2006.

Liquidity and Capital Resources

We have financed our operations with revenue from research and development under collaborative agreements and from affiliates. Additionally, we have earned licensing and royalty revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through June 30, 2006, we have earned approximately $492.5 million in revenue from contract research and development and the sale and licensing of our intellectual property. Since we were founded, we have raised net proceeds of approximately $645.8 million from the sale of equity securities. We have borrowed approximately $386.7 million under long-term debt arrangements to finance a portion of our operations.

At June 30, 2006, we had cash, cash equivalents and short-term investments of $137.9 million, which includes $64.4 million of cash and cash equivalents held by Symphony GenIsis. We had consolidated working capital of $128.0 million and a stockholders' equity of $6.7 million. In comparison, we had cash, cash equivalents and short-term investments of $94.4 million, working capital of $82.1 million and a stockholders' equity of $2.7 million as of December 31, 2005. The increase in our cash, cash equivalents and short-term investments and working capital were due primarily to the consolidation of the cash and cash equivalents held by Symphony GenIsis along with proceeds of $4.4 million that we received from the sale of a portion of our Alnylam equity securities offset by cash used to fund our operations, pursue patents, and to pay our debt and capital lease obligations.

As of June 30, 2006, our debt and other obligations totaled $143.9 million, compared to $147.8 million at December 31, 2005. We will continue to use lease financing as long as the terms are commercially attractive.

Based on reasonable assumptions for new sources of revenue and cash, we believe we have sufficient resources to meet our anticipated requirements through at least the end of 2008. The following table summarizes our contractual obligations as of June 30, 2006. The table provides a breakdown of when obligations become due. A more detailed description of the major components of our debt is provided in the paragraphs following the table:

	Payments Due by Period (in millions)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
5 1/2% Convertible Subordinated Notes	$ 125.0	$ —	$ 125.0	$ —	$ —
Silicon Valley Bank Term Loan	17.1	6.4	10.7	—	—
Capital Lease and Other Obligations	1.8	1.3	0.5	—	—
Operating Leases	21.4	3.5	4.2	2.8	10.9

Our contractual obligations consist primarily of our publicly traded convertible debt. In addition, we also have a term loan from Silicon Valley Bank, capital leases and other obligations.

In December 2003, we secured a $32.0 million term loan from Silicon Valley Bank to retire our existing debt to Boehringer Ingelheim, and Elan Corporation. We amortize the term loan over sixty months. The term loan requires equal monthly payments of principal plus accrued interest, and bears interest at the prime interest rate less applicable discounts based on the balances in the cash and investment accounts that we maintain at Silicon Valley Bank, which was 8.00% at June 30, 2006. The loan is secured by substantially all of our operating assets, excluding intellectual property, real estate, and certain equity investments. The loan is subject to certain liquidity requirements, including a requirement that we maintain a minimum balance in an account at Silicon Valley Bank at all times equal to the outstanding balance of the loan. The loan is convertible to a fixed interest rate at our option at any time at the then-applicable prime rate plus 1.25%. The carrying value of the term loan at June 30, 2006 was $17.1 million.

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 bear interest at 5.5%, which is payable semi-annually, and mature in May 2009. Holders of the subordinated notes can, at any time, convert the notes into shares of common stock at a conversion price of $16.625 per share. At June 30, 2006, the principal outstanding on the notes was $125.0 million.

In addition to contractual obligations, we had outstanding purchase orders as of June 30, 2006 for the purchase of services, equipment and materials as part of our normal course of business.

In May 2006, we obtained a $75 million equity financing commitment from Azimuth Opportunity Ltd. Under this arrangement, we may at our discretion, from time to time, sell registered shares of our common stock at a small discount, ranging from 3.8% to 5.3%, to the market price to Azimuth Opportunity over the 18-month term of the purchase agreement.

We plan to continue to enter into more collaborations with partners to provide for additional revenue and cash to us and we may be required to incur additional cash expenditures related to our obligations under any of the new agreements we may enter into. We currently intend to use our cash and short-term equivalents to finance our activities. However, we may also pursue other financing alternatives, like issuing additional shares of our common stock, issuing debt instruments, refinancing our existing debt, or securing lines of credit. Whether we use our existing capital resources or choose to obtain financing will depend on various factors, including the future success of our business, the prevailing interest rate environment and the condition of financial markets generally.

RISK FACTORS

Investing in our securities involves a high degree of risk. In addition to the other information in this report on Form 10-Q, you should carefully consider the risks described below before purchasing our securities. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment.

Risks Associated with our Businesses as a Whole

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

Because product discovery and development require substantial lead-time and money prior to commercialization, our expenses have exceeded our revenue since we were founded in January 1989. As of June 30, 2006, we had accumulated losses of approximately $790.5 million and stockholders' equity of approximately $6.7 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from interest income and research grants and the sale or licensing of patents. We currently have only one product, Vitravene, approved for commercial use. This product has limited sales potential. We expect to incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or services, or achieve or sustain future profitability.

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

All of our product candidates are undergoing clinical trials or are in the early stages of research and development. All of our products under development will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and a commitment of significant additional resources prior to their commercialization. Based on reasonable assumptions for new sources of revenue and cash, we believe we have sufficient resources to meet our anticipated requirements through at least the end of 2008. If we do not meet our goals to commercialize our products, or to license our drugs and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

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

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of

existing stockholders will be diluted and their price, as well as the price of our other securities, may decline. If adequate funds are not available, or not available on acceptable terms, we may have to cut back on one or more of our research, drug discovery or development programs. For example, in January 2005 we decided to terminate the development of two lower priority drugs, ISIS 14803 and ISIS 104838. Alternatively, we may obtain funds through arrangements with collaborative partners or others, which could require us to give up rights to certain of our technologies, product candidates or products.

If any of our collaborative partners fail to fund our collaborative programs or develop or sell any of our products under development, or if we cannot obtain additional partners, we may have to delay or stop progress on our product development programs.

To date, corporate partnering has played a key role in our strategy to fund our development programs and to add key development resources. We plan to continue to rely on additional collaborative arrangements to develop and commercialize our products. However, we may not be able to negotiate additional attractive collaborative arrangements, and, even if negotiated, the collaborative arrangements may not be successful.

We have entered into collaborative arrangements with third parties to develop many of our product candidates. We enter into these collaborations in order to:

- Fund our research and development activities;
- Access manufacturing by third parties;
- Seek and obtain regulatory approvals;
- Conduct clinical trials; and
- Successfully commercialize existing and future products.

If any of our partners fails to develop or sell any drug in which we have retained a financial interest, our business may suffer. These collaborations may not continue or result in commercialized drugs. Our collaborators can terminate their relationships with us under certain circumstances, some of which are outside of our control. For example, in November 2004 based on the outcome of both Phase 3 trials, Lilly discontinued its investment in Affinitak.

Other drugs in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics Limited, iCo Therapeutics, Inc., ImQuest Pharmaceuticals, Inc., OncoGenex Technologies Inc. and Lilly. We have received significant financial support from United States Government-funded grants and contracts for our Ibis division and the development of our Ibis T5000 biosensor system. The United States Government can unilaterally terminate these contracts and grants at its convenience at any time, even if we have fully performed our obligations. If any of these pharmaceutical companies or government partners stopped funding and/or developing these products, our business could suffer and we may not have the resources available to develop these products on our own.

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

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

If we cannot protect our patents or our proprietary rights, others may compete more directly against us.

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

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

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

If a third party claims that our products or technology infringe their patents or other intellectual property rights, we may have to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to needed intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of patents or applications held by others that relate to our business. This is especially true since patent applications in the United States are filed confidentially. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain unresolved.

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

For planning purposes, we estimate the timing of a variety of clinical, regulatory and other milestones, like when a certain product candidate will enter the clinic, when we will complete a clinical trial, or when we will file an application for marketing approval. We base our estimates on present facts and

a variety of assumptions. Many of the underlying assumptions are outside of our control. If we do not achieve milestones when we expect to, investors could be disappointed and the price of our securities would likely decrease.

The loss of key personnel, or the inability to attract and retain highly skilled personnel, could make it more difficult to run our business and reduce our likelihood of success.

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our executive officers. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. Failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel.

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding June 30, 2006, the market price of our common stock ranged from $3.75 to $9.50 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial results, technological innovations or new products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

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

We are developing our Ibis T5000 biosensor system in our facility located in Carlsbad, California. Additionally, we manufacture our research and clinical supplies in a separate manufacturing facility located in Carlsbad, California. The facilities and the equipment we use to develop the Ibis T5000 biosensor system and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Either of our facilities may be harmed by natural or man-made disasters, including, without limitation, earthquakes, floods and fires, and in the event they are affected by a disaster, our development and commercialization efforts would be delayed. Although we possess insurance for damage to our property and the disruption of our business from casualties, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all.

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

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

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders.

We also have implemented a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. These provisions, as well as Delaware law and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests. In addition, our board of directors has the authority to fix the rights and preferences of and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

If registration rights that we have previously granted are exercised or shares under our shelf registration statement are issued, then the price of our securities may be negatively affected.

We have granted registration rights to Lilly and Symphony GenIsis Holdings LLC, which cover approximately 6.75 million shares of our common stock, which we issued to Lilly upon the conversion of outstanding convertible securities or are issuable upon the exercise of the warrant we issued to Symphony GenIsis Holdings. We also registered for resale 12,000,000 shares of our common stock and 2,999,998 shares of our common stock issuable upon the exercise of the warrant, which we issued as part of our August 2005 private placement. In addition, on December 22, 2005, we filed a Form S-3 shelf registration statement with the SEC to register up to $200,000,000 worth of our common stock for possible issuance. The addition of these shares into the market may have an adverse effect on the price of our securities.

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

We have entered into a common stock purchase agreement with Azimuth Opportunity Ltd., which provides that, upon the terms and subject to the conditions set forth therein, Azimuth is committed to purchase up to $75 million of our common stock, or 14,578,970 shares, whichever occurs first over the 18-month term of the purchase agreement. From time to time over the term of the purchase agreement, and at our sole discretion, we may present Azimuth with draw down notices constituting offers to purchase our common stock. The per share purchase price for these shares is at a discount ranging from 3.8% to 5.3%. As a result, our existing common stockholders will experience immediate dilution upon the purchase of any shares of our common stock by Azimuth.

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

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

Risks Associated with our Drug Discovery and Development Business

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

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

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

If the results of clinical testing indicate that any of our drugs under development are not suitable for commercial use, or if additional testing is required to demonstrate suitability, we may need to abandon one or more of our drug development programs.

Drug discovery and development has inherent risks, including the risk that molecular targets prove not to be important in a particular disease; the risk that compounds that demonstrate attractive activity in preclinical studies do not demonstrate similar activity in human beings; the risk that a compound is not safe or effective for use in humans; and the risk that successful results in early human clinical trials may not be indicative of results in late-stage clinical trials. Antisense technology in particular is relatively new and unproven. We are applying most of our resources to create safe and effective drugs for human use. Any of the risks described above could prevent us from meeting this goal. In the past, we have invested in clinical studies of drugs that have not met the primary clinical end points in their Phase 3 studies.

In March 2003, we reported the results of a Phase 3 clinical trial of Affinitak in patients with late stage non-small cell lung cancer and in October 2004, we reported the results of a second similar Phase 3 clinical trial. In each case, Affinitak failed to demonstrate improved survival sufficient enough to support an NDA filing. In December 2004, we reported the results of our Phase 3 clinical trials of alicaforsen in patients with active Crohn's disease, in which alicaforsen did not demonstrate statistically significant induction of clinical remissions compared to placebo. Similar results could occur with the trials for our other drugs. If any of our drugs in clinical studies do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for this and other drugs and our stock price could decline.

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

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

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

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

We have licensed to Symphony GenIsis our intellectual property rights, including commercialization rights, to our product candidates in our apoB-100, GCGR, and GCCR programs in exchange for Symphony GenIsis' investment of $75.0 million to advance the clinical development of these programs. We are responsible for developing these product candidates in accordance with a specified development plan and related development budget. The Symphony

GenIsis development committee supervises our development activities. The development committee is comprised of an equal number of representatives from Isis and Symphony GenIsis. If the development committee cannot resolve a particular development issue, the issue will be referred to the chief executive officers of Isis and Symphony GenIsis. Any disagreements between Symphony GenIsis and us regarding a development decision may cause significant delays in the development and commercialization of our product candidates within our apoB-100, GCGR, and GCCR programs.

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

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

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

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

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

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

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

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

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

Our competitors are engaged in all areas of drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. Other companies are engaged in developing antisense technology. Our competitors may succeed in developing drugs or technologies that are more effective than any drugs or technologies that we are developing. These competitive developments could make our products obsolete or non-competitive.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical trials of new pharmaceutical products and in obtaining FDA and other regulatory approvals of products for use in health care. Accordingly, our competitors may succeed in obtaining regulatory approval for products earlier than we do. We will also compete with respect to marketing and sales capabilities, areas in which we have limited or no experience.

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

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

Risks Associated with our Ibis Division

We may not successfully develop or derive revenues from our business based on our Ibis T5000 biosensor system.

Our Ibis T5000 biosensor system is subject to the risks inherent in developing tools based on innovative technologies. Our product is at an early stage of development and requires additional research and development prior to marketing. If our potential customers fail to purchase our Ibis T5000 biosensor system due to competition or other factors, or if we fail to develop applications that lead to market acceptance, we could lose our investment in this technology and our Ibis T5000 biosensor system business could fail to meet our business and financial objectives.

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

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

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

In addition to Bruker, we may depend on third parties to commercialize our Ibis T5000 biosensor system, particularly in the areas of hospital-associated infection control and infectious disease diagnostics. If we are unable to reach agreements with suitable third parties, we may fail to meet our business objectives for the Ibis T5000 biosensor system. We may not successfully establish a relationship in these markets or be able to make alternative arrangements. Moreover, these relationships may not succeed, may require us to give up a part of our ownership interest, or may diminish our revenue targets on our Ibis instruments and ID kits.

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

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

For the six months ended June 30, 2006, Isis derived approximately 55% of its revenue from agencies of the United States government, including through our subcontract with SAIC. Because of the concentration of our contracts, we are vulnerable to adverse changes in our revenues and cash flows if a significant number of our United States Government contracts and subcontracts are simultaneously delayed or canceled for budgetary, performance or other reasons. If United States defense and other federal agencies choose to reduce their purchases under our contracts, exercise their right to terminate contracts, fail to exercise options to renew contracts or limit our ability to obtain new contract awards, our revenues and cash flows could be adversely affected.

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

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

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

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

Complex instruments such as our Ibis T5000 biosensor system typically require operating and reliability improvements following their initial introduction. As we continue to develop our Ibis T5000 biosensor system and its related

applications we will need to make sure our customers are satisfied with the sensor's reliability. Our efforts to satisfy our customer's needs for instrument reliability could result in greater than anticipated service expenses or divert other resources. Additionally, if we fail to resolve reliability issues as they develop, we could materially damage our reputation, which could prevent us from retaining our existing customers and attracting new customers.

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

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

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

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

The diagnostics industry is highly competitive. Currently, large reference laboratories, public health laboratories and hospitals perform the majority of diagnostic tests used by physicians and other health care providers. We expect that these laboratories will compete vigorously to maintain their dominance in the diagnostic testing market. In order to achieve market acceptance of our Ibis T5000 biosensor system, we will be required to demonstrate that it provides accurate, cost-effective and/or time saving alternatives to tests performed by traditional laboratory procedures and products made by our competitors.

Improvements in preventing major diseases could reduce the need for our Ibis T5000 biosensor instruments and ID kits, which in turn could reduce our revenues.

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

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

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

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

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

If we or our partners are required to obtain regulatory approval for our Ibis T5000 biosensor system applications, we may not successfully obtain approval.

Depending on their intended use, our Ibis T5000 biosensor systems may be regulated as a medical device by the FDA and comparable agencies of other countries and require either premarket approval (PMA) or 510(k) clearance from the FDA, prior to marketing. The 510(k) clearance process usually takes from three to twelve months from submission, but can take longer. The premarket approval process is much more costly, lengthy, uncertain and generally takes from six months to two years or longer from submission. In addition, commercialization of any diagnostic or other product that our licensees or collaborators or we develop would depend upon successful completion of preclinical testing and clinical trials. Preclinical testing and clinical trials are long, expensive and uncertain processes, and we do not know whether we, our licensees or any of our collaborators, would be permitted or able to undertake clinical trials of any potential products. It may take us or our licensees or collaborators many years to complete any such testing, and failure could occur at any stage. Preliminary results of trials do not necessarily predict final results, and acceptable results in early trials may not be repeated in later trials. We or our collaborators may encounter delays or rejections of potential products based on changes in regulatory policy for product approval during the period of product development and regulatory agency review.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to changes in interest rates primarily from our long-term debt arrangements and, secondarily, investments in certain short-term investments. We invest our excess cash in highly liquid short-term investments that are typically held for the duration of the term of the respective instrument. We do not utilize derivative financial instruments, derivative commodity instruments or other market risk sensitive instruments, positions or transactions to manage exposure to interest rate changes. Accordingly, we believe that, while the securities we hold are subject to changes in the financial standing of the issuer of such securities, we are not subject to any material risks arising from changes in interest rates, foreign currency exchange rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments.

ITEM 4. CONTROLS AND PROCEDURES

As of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended. Based on this

evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of June 30, 2006. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to June 30, 2006.

An evaluation was also performed under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of any change in our internal control over financial reporting that occurred during our last fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting. That evaluation did not identify any change in our internal control over financial reporting that occurred during our latest fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

We maintain disclosure controls and procedures that are designed to ensure that information required to be disclosed in our Exchange Act reports is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable and not absolute assurance of achieving the desired control objectives.

PART II – OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

Ajinomoto Co., Inc. v. Isis Pharmaceuticals, Inc. On or about January 27, 2005, Ajinomoto Co., Inc., or Ajinomoto, filed a Demand for Arbitration against us with the American Arbitration Association in San Diego, California. The Demand relates to a February 17, 1994 license agreement between Ajinomoto and us, that licensed certain intellectual property, including United States Patent No. 5,013,830, or the '830 patent, in

exchange for initial payments, royalties and certain milestone payments relating to the development of products covered by the license. Ajinomoto alleges that several products developed by us are covered by the '830 patent, and thus by the license. Ajinomoto seeks a determination of products covered by the license, along with an accounting of any sums due as a result. In October 2005, we filed our answering statement. We believe that Ajinomoto's claims are without merit, and we intend to vigorously defend our position. Ajinomoto and Isis agreed to a bifurcated arbitration process in which the arbitrator would first hear contract arguments and will then hear the patent arguments, if necessary, at a later date. The contract argument portion of the arbitration proceeding took place on February 22, 2006 resulting in an Arbitrator's Interim Award. This Interim award as anticipated is not determinative of all issues in dispute. Isis and Ajinomoto recently participated in a mediation conference and have reached an agreement in-principle that will fully resolve all issues in dispute, including all past and potential future issues. Isis expects to reach a definitive agreement in September 2006. Accordingly, Isis has recorded a $600,000 charge representing its estimated liability under this definitive agreement.

ITEM 2. UNREGISTERED SALES OF EQUITY SECURITIES AND USE OF PROCEEDS

Not applicable

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

ITEM 4. SUBMISSION OF MATTERS TO A VOTE OF SECURITY HOLDERS

On May 3, 2006, we held our Annual Meeting of Stockholders in Carlsbad, California for the following purposes:

(1) To elect two directors to serve as Class III directors of the Company until the 2009 Annual Meeting of Stockholders and one director to serve as a Class I director for the Company until the 2007 Annual Meeting of Stockholders. For Director number one, Richard D. DiMarchi, the number of votes for and withheld was 65,964,319 and 537,969, respectively. For Director number two, Joseph Klein III, the number of votes for and withheld was 65,984,148 and 518,140, respectively. For Director number three, Frederick T. Muto, the number of votes for and withheld was 65,554,704 and 947,584, respectively.

(2) To approve an amendment of the Company's Restated Certificate of Incorporation to increase the authorized number of shares of Common Stock from 100,000,000 shares to 200,000,000 shares. The number of votes for, against and abstaining was 58,704,237; 7,707,183 and 90,687, respectively.

(3) To approve an amendment of the 2002 Non-Employee Director's Stock Option Plan to (i) increase the total number of shares reserved for issuance under the Director's Plan from 600,000 shares to 850,000 shares and (ii) increase the annual non-discretionary stock option grant for Isis' non-employee directors from 10,000 shares to 12,500 shares. The number of votes for, against, abstaining and broker non-votes was 38,792,848; 4,966,617; 108,609 and 22,634,214, respectively.

(4) To ratify the appointment of Ernst & Young LLP as the Company's independent registered public accounting firm for the fiscal year ending December 31, 2006. The number of votes for, against and abstaining was 66,121,881; 305,675 and 74,731, respectively.

ITEM 5. OTHER INFORMATION

Not applicable

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Stock Purchase Agreement between the Registrant and Azimuth Opportunity Ltd. Dated May 30, 2006 (1).
10.2	Amended and Restated 2002 Non-Employee Director's Stock Option Plan (2).
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.

(1) Filed as an exhibit to the Company's current report on Form 8-K, filed with the SEC on May 31, 2006 and incorporated herein by reference.

(2) Filed as an exhibit to the Company's current report on Form 8-K, filed with the SEC on May 5, 2006 and incorporated herein by reference.

Isis Pharmaceuticals, Inc.

(Registrant)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

Signatures	Title	Date
/s/ Stanley T. Crooke Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	August 9, 2006
/s/ B. Lynne Parshall B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	August 9, 2006

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this quarterly report;

3. Based on my knowledge, the consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, consolidated results of operations and consolidated cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: August 9, 2006

/s/ Stanley T. Crooke

Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

EXHIBIT 31.2

CERTIFICATION

I, B. Lynne Parshall, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this quarterly report;

3. Based on my knowledge, the consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, consolidated results of operations and consolidated cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: August 9, 2006

/s/ B. Lynne Parshall

B. Lynne Parshall, J.D.
Chief Financial Officer

Exhibit 32.1

CERTIFICATION

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, Stanley T. Crooke, the Chief Executive Officer of Isis Pharmaceuticals, Inc., (the "Company"), and B. Lynne Parshall, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Quarterly Report on Form 10-Q for the period ended June 30, 2006, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

2. The information contained in the Periodic Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Periodic Report and the results of operations of the Company for the period covered by the Periodic Report.

Dated: August 9, 2006

/s/ Stanley T. Crooke	/s/ B. Lynne Parshall
Stanley T. Crooke, M.D., Ph.D.	B. Lynne Parshall, J.D.
Chief Executive Officer	Chief Financial Officer

A signed original of this written statement required by Section 906 has been provided to Isis Pharmaceuticals, Inc. and will be retained by Isis Pharmaceuticals, Inc. and furnished to the Securities and Exchange Commission or its staff upon request.