UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-Q/A

(Mark One)

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

For the Quarterly Period Ended March 31, 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 x 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 x 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 x

The number of shares of voting common stock outstanding as of May 3, 2006 was 72,768,057.

EXPLANATORY NOTE

Isis Pharmaceuticals, Inc. (the "Company") is filing this Amendment to its Quarterly Report on Form 10-Q for the quarter ended March 31, 2006, filed with the Securities Exchange Commission on May 10, 2006 ("Original Filing"), to modify Part I, Item 1, *Consolidated Financial Statements*, to reclassify cash equivalents that were inadvertently classified as short term investments in the Company's Consolidated Balance Sheet at March 31, 2006. The Company's working capital and total of cash, cash equivalents and short-term investments were accurately stated in all items of the Original Filing. Although we are including in this Amendment the complete text of the Consolidated Financial Statements, the only changes to the Consolidated Financial Statements

from those previously filed with the Original Filing are as follows:

- *Condensed Consolidated Balance Sheets*, (page 3 of the Original Filing) was amended to reclassify certain cash equivalents from Short-term investments to Cash and cash equivalents.

- *Condensed Consolidated Statements of Cash Flows* (page 5 of the Original Filing) was amended to reflect the change in the Consolidated Balance Sheet at March 31, 2006 as described above.

Additionally, Item 6. of Part II, *Exhibits*, of this Amendment has been revised to contain currently-dated certifications from our Chief Executive Officer and Chief Financial Officer, as required by Sections 302 and 906 of the Sarbanes-Oxley Act of 2002. The certifications of our Chief Executive Officer and Chief Financial Officer are attached to this Form 10-Q/A as Exhibits 31.1, 31.2 and 32.1, respectively.

As this Amendment only relates to the Consolidated Financial Statements, the previously issued Management's Discussion and Analysis in the Original Filing is unchanged. This Amendment does not reflect events occurring after the filing of our Quarterly Report on Form 10-Q or include, or otherwise modify or update, the disclosure contained therein in any way except as expressly indicated above. Accordingly, this Amendment should be read in conjunction with the Original Filing and the Company's filings made with the Securities and Exchange Commission subsequent to the Original Filing.

This report on Form 10-Q/A contains forward-looking statements regarding our business, our financial position 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 our 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 for the year ended December 31, 2005, which is 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 26 of the Original Filing.

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

	March 31, 2006 (Unaudited) (as amended)	December 31, 2005

ASSETS		
Current assets:		
Cash and cash equivalents	$ 38,604	$ 50,885
Short-term investments	39,957	43,504
Contracts receivable	3,503	3,918
Inventory	749	951
Other current assets	7,918	6,600
Total current assets	90,731	105,858
Property, plant and equipment, net	8,208	9,130
Licenses, net	23,186	23,770
Patents, net	18,875	18,773
Deposits and other assets	2,883	3,201
Long-term investments	6,754	5,641
Total assets	$ 150,637	$ 166,373
LIABILITIES AND STOCKHOLDERS' EQUITY (DEFICIT)		
Current liabilities:		
Accounts payable	$ 2,483	$ 2,095
Accrued compensation	1,517	3,706
Accrued liabilities	7,871	8,643
Current portion of long-term obligations	7,863	7,835
Current portion of deferred contract revenue	1,111	1,514
Total current liabilities	20,845	23,793
5 ½% convertible subordinated notes	125,000	125,000
Long-term obligations, less current portion	12,942	14,915
Stockholders' equity (deficit):		
Common stock, $0.001 par value; 100,000,000 shares authorized, 72,681,425 shares and 72,201,505 shares issued and outstanding at March 31, 2006 and December 31, 2005, respectively	73	72
Additional paid-in capital	774,366	770,263
Accumulated other comprehensive income	5,739	3,178
Accumulated deficit	(788,328)	(770,848)
Total stockholders' equity (deficit)	(8,150)	2,665
Total liabilities and stockholders' equity (deficit)	$ 150,637	$ 166,373

See accompanying notes

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

	Three Months Ended March 31,	
	2006	2005
Revenue:		
Research and development revenue under collaborative agreements	$ 4,468	$ 7,135
Licensing and royalty revenue	490	307
Total revenue	4,958	7,442
Operating expenses:		
Research and development (including non-cash compensation expense related to stock options of $1.2 million and $0 in 2006 and 2005, respectively)	18,372	22,361
General and administrative (including non-cash compensation expense related to stock options of $221,000 and $0 in 2006 and 2005, respectively)	2,566	2,137
Compensation benefit related to variable accounting of stock options	—	(633)
Restructuring activities	36	7,084
Total operating expenses	20,974	30,949
Loss from operations	(16,016)	(23,507)
Other income (expenses):		
Investment income	811	504
Interest expense	(2,275)	(6,655)
Net loss applicable to common stock	$ (17,480)	$ (29,658)

Basic and diluted net loss per share	$ (0.24)	$ (0.52)
Shares used in computing basic and diluted net loss per share	72,377	57,521

See accompanying notes

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

	Three Months Ended March 31,	
	2006 (as amended)	2005
Net cash used in operating activities	$ (16,166)	$ (22,032)
Investing activities:		
Purchase of short-term investments	(19,270)	(3,306)
Proceeds from the sale of short-term investments	23,000	8,985
Purchase of property, plant and equipment	(117)	(277)
Proceeds from the sale of property, plant and equipment	—	165
Other assets	(514)	(1,173)
Net cash provided by investing activities	3,099	4,394
Financing activities:		
Net proceeds from issuance of equity	2,731	353
Proceeds from long-term borrowings	—	5,000
Principal payments on debt and capital lease obligations	(1,945)	(2,959)
Net cash provided by financing activities	786	2,394
Net increase (decrease) in cash and cash equivalents	(12,281)	(15,244)
Cash and cash equivalents at beginning of period	50,885	27,250
Cash and cash equivalents at end of period	$ 38,604	$ 12,006
Supplemental disclosures of cash flow information:		
Interest paid	$ 409	$ 522

See accompanying notes

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
March 31, 2006
(Unaudited)

1. Basis of Presentation

The unaudited interim consolidated financial statements for the three-month periods ended March 31, 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.

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 federal research grants 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 auction and 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 Short-Term Investments

Isis considers all liquid investments with maturities of ninety days or less when purchased to be cash equivalents. 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 in investment income. Isis determined that there were no other-than-temporary declines in value of its investments during the three months ended March 31, 2006 and 2005.

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 $749,000 and $951,000 as of March 31, 2006 and December 31, 2005, respectively.

Licenses

Isis obtains licenses from third parties and capitalizes the cost 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. 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 the 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 quarter of 2006 and 2005, Isis incurred a charge related to restructuring activities of $25,000 and $1.6 million, respectively. The charge in 2005 was primarily related to 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 Financial Accounting Standards Board Interpretation ("FIN") No. 46, *Consolidation of Variable Interest Entities, an Interpretation of ARB No. 51*, 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 March 31, 2006, Isis had collaborative arrangements with four entities that it considers to be variable interest entities ("VIE") under FIN 46. Additionally, 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 has formed Symphony GenIsis, Inc, capitalized with $75 million, to provide funding for the development of these three drugs in collaboration with Isis. Isis will treat Symphony GenIsis as a VIE for which Isis is the primary beneficiary. As a result, beginning in the second quarter of 2006, Isis will include the financial condition and results of operations of Symphony GenIsis in its condensed consolidated financial statements. For a further discussion see Note 7 — *Subsequent Events*.

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. The note will convert into securities that iCo issues in a financing. Isis has recognized a valuation allowance of $250,000 to offset the note, as realization of this asset is uncertain. 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, which will convert into iCo stock upon iCo's completion of a financing. The remaining $175,000 will be paid upon shipment of the drug. Isis has recognized a valuation allowance of $350,000 to offset the note, as realization of this asset is uncertain. Isis is not required to consolidate iCo's results of operations under FIN No. 46 as Isis is not the primary beneficiary. In May 2006, Isis received 869,025 shares of iCo common stock for the conversion of both convertible notes.

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"), for the period 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 months ended March 31, 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 months ended March 31, 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 three 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 months ended March 31, 2006 was $1.4 million. Non-cash stock-based compensation benefit of $633,000 for the three months ended March 31, 2005 was related to 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—*Stock-Based Compensation Plans* 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 March 31,	
	2006	2005
Comprehensive loss:		
Change in unrealized gains (losses)	$ 2,561	$ (2,079)
Net loss applicable to common stock	(17,480)	(29,658)
Comprehensive loss	$ (14,919)	$ (31,737)

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 aimed at improving 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.

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 in vitro and in vivo 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.

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 March 31, 2006				
Revenue:				
Research and development	$ 1,270	$ 3,198	$ —	$ 4,468
Licensing and royalty	490	—	—	490
Total segment revenue	$ 1,760	$ 3,198	$ —	$ 4,958
Loss from operations	$ (15,449)	$ (531)	$ (36)	$ (16,016)
Three Months Ended March 31, 2005				
Revenue:				
Research and development	$ 4,810	$ 2,325	$ —	$ 7,135
Licensing and royalty	307	—	—	307
Total segment revenue	$ 5,117	$ 2,325	$ —	$ 7,442
Loss from operations	$ (15,944)	$ (1,112)	$ (6,451)	$ (23,507)

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 March 31,	
	2006	2005
Partner A	29%	11%
Partner B	18%	12%
Partner C	15%	57%
Partner D	14%	7%

For the three months ended March 31, 2006 and 2005, Isis derived approximately 64% and 34%, respectively, of its revenue from agencies of the United States Government, including approximately 29% and 11% respectively, of revenue from one significant customer.

Contract receivables from four significant partners comprised approximately 43%, 22%, 18%, and 11% of contract receivables at March 31, 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.

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 March 31, 2006 (in thousands).

	Facility Consolidation and Closure Related Costs	Contract Termination Costs	Other Costs	Total
Balance at December 31, 2005	$ 856	$ 765	$ 126	$ 1,747
Accrued and expensed	11	—	25	36
Charged against accrual	(143)	—	(32)	(175)
Balance at March 31, 2006	$ 724	$ 765	$ 119	$ 1,608

6. Stock-Based Compensation Plans

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 March 31, 2006, 2,631,145 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 3,990,000 shares of common stock to its employees, directors, and consultants. In May 2002, the Board of Directors increased the 2000 Plan by 2,000,000 shares, authorizing up to 5,990,000 shares of

common stock under the 2000 Plan for issuance to employees, directors, and consultants. Typically options expire 10 years from the date of grant. Options granted under this plan generally vest over a four-year period, with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted under this plan pursuant to the April 2003 stock option exchange program 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 March 31, 2006, 2,097,978 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"), and it had an aggregate of 600,000 shares of common stock authorized for issuance. Options under this plan expire 10 years from the date of grant. Options granted become exercisable in four equal annual installments beginning one year after the date of grant. As of March 31, 2006, 131,000 shares were available for future grant. 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.

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 March 31, 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 three months ended March 31, 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	1,710	$ 5.41		
Exercised	(450)	$ 8.07		
Cancelled/forfeited/expired	(341)	$ 8.55		
Outstanding at March 31, 2006	8,898	$ 7.46	5.52	$ 20,922
Exercisable at March 31, 2006	5,315	$ 8.66	4.73	$ 9,027

The following table summarizes information concerning outstanding and exercisable options as of March 31, 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
$2.8600 - $5.24	1,180	4.90	$ 4.83	717	$ 5.00
$5.2500 - $5.25	1,441	6.76	$ 5.25	3	$ 5.25
$5.3500 - $6.59	1,644	6.10	$ 5.91	603	$ 6.00
$6.6000 - $6.81	1,487	5.78	$ 6.81	1,131	$ 6.81
$6.8125 - $9.63	1,767	5.48	$ 7.92	1,488	$ 7.96
$9.7500 - $22.83	1,379	3.83	$ 14.00	1,373	$ 14.01
	8,898	5.52	$ 7.46	5,315	$ 8.66

The weighted average fair values of options granted were $3.13 and $3.79 for the three months ended March 31, 2006 and 2005, respectively. The total intrinsic value of options exercised during the three months ended March 31, 2006 was $1.0 million, determined as of the date of exercise and the amount of cash received from the exercise of stock options was $2.7 million. As of March 31, 2006, there was $8.8 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 1.5 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 months ended March 31, 2006 (in thousands, except per share data), which was allocated as follows:

	Three Months Ended March 31, 2006
Research and development	$ 1,153
General and administrative	$ 221
Non-cash compensation expense related to stock options included in operating expenses	$ 1,374
Basic and diluted net loss per share	$ 0.02

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 months ended March 31, 2005:

	Three Months Ended March 31, 2005
Net loss applicable to common stock—as reported	$ (29,658)
Net loss applicable to common stock—pro forma	$ (31,864)
Basic and diluted net loss per share—as reported	$ (0.52)
Basic and diluted net loss per share—pro forma	$ (0.55)

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:

	March 31, 2006	March 31, 2005
Risk-free interest rate	4.3%	4.2%
Dividend yield	0.0%	0.0%
Volatility	68.7%	82.7%
Expected Life	4.6 years	4.8 years

ESPP:

	March 31, 2006	March 31, 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.

7. Subsequent Events

On April 7, 2006, Isis entered into a series of related agreements in connection with a transaction with Symphony Capital Partners, L.P. 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 aggressively, 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 certain of its expenses, Isis paid a structuring fee of $3.75 million.

In accordance with FIN 46, Isis has determined that Symphony GenIsis is a variable interest entity for which Isis is the primary beneficiary. As a result, beginning in the second quarter of 2006, Isis will include the financial condition and results of operations of Symphony GenIsis in its consolidated financial statements.

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 and 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.

PART II — OTHER INFORMATION

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
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.

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/A 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/A 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, as amended for the period ended March 31, 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.