UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

Form 10-Q

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

For the Quarterly Period Ended March 31, 2007

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 7, 2007 was 82,534,511.

ISIS PHARMACEUTICALS, INC.
FORM 10-Q

INDEX

TRADEMARKS

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

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

	March 31, 2007 (Unaudited)	December 31, 2006
ASSETS		
Current assets:		
Cash and cash equivalents (including cash and cash equivalents held by Symphony GenIsis, Inc. of $49.6 million and $54.8 million at March 31, 2007 and December 31, 2006, respectively)	$ 183,423	$ 114,514
Short-term investments	102,131	78,819
Contracts receivable	2,057	2,395
Inventory	1,093	861
Other current assets	7,363	9,614
Total current assets	296,067	206,203
Property, plant and equipment, net	7,042	7,157
Licenses, net	20,851	21,435
Patents, net	17,037	16,836
Debt issuance costs	6,110	1,400
Deposits and other assets	2,797	2,876
Total assets	$ 349,904	$ 255,907

LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 3,274	$ 4,288
Accrued compensation	2,017	6,222
Accrued liabilities	7,300	6,071
Current portion of 5¹⁄₂% convertible subordinated notes	80,825	—
Current portion of long-term obligations	7,482	7,514
Current portion of deferred contract revenue	1,043	1,044
Total current liabilities	101,941	25,139
5¹⁄₂% convertible subordinated notes	—	125,000
2⅝% convertible subordinated notes	162,500	—
Long-term obligations, less current portion	5,889	7,822
Long-term deferred contract revenue	143	44
Total liabilities	270,473	158,005
Noncontrolling interest in Symphony GenIsis, Inc	22,533	29,339
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 82,497,982 and 82,283,693 shares issued and outstanding at March 31, 2007 and December 31, 2006, respectively	82	82
Additional paid-in capital	884,506	880,954
Accumulated other comprehensive income	2,081	4,278
Accumulated deficit	(829,771)	(816,751)
Total stockholders' equity	56,898	68,563
Total liabilities, noncontrolling interest and stockholders' equity	$ 349,904	$ 255,907

See accompanying notes

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

	Three Months Ended March 31,	
	2007	2006
Revenue:		
Research and development revenue under collaborative agreements	$ 2,002	$ 4,468
Licensing and royalty revenue	448	490
Total revenue	2,450	4,958
Expenses:		
Research and development	19,949	18,372
Selling, general and administrative	3,402	2,566
Restructuring activities	—	36
Total operating expenses	23,351	20,974
Loss from operations	(20,901)	(16,016)
Other income (expense):		
Investment income	3,401	811
Interest expense	(2,628)	(2,275)
Gain on investments	1,521	—
Loss on early retirement of debt	(1,219)	—
Net loss before noncontrolling interest in Symphony GenIsis, Inc.	(19,826)	(17,480)
Loss attributed to noncontrolling interest in Symphony GenIsis, Inc.	6,806	—
Net loss applicable to common stock	$ (13,020)	$ (17,480)
Basic and diluted net loss per share	$ (0.16)	$ (0.24)
Shares used in computing basic and diluted net loss per share	82,456	72,377

See accompanying notes.

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

	Three Months Ended March 31,	
	2007	2006
Net cash used in operating activities	$ (20,795)	$ (16,166)
Investing activities:		
Purchases of short-term investments	(47,493)	(19,270)
Proceeds from the sale of short-term investments	24,481	23,000
Purchases of property, plant and equipment	(539)	(117)
Acquisition of licenses and other assets	(354)	(514)
Proceeds from the sale of strategic investments	2,245	—
Net cash provided by (used in) investing activities	(21,660)	3,099
Financing activities:		
Net proceeds from issuance of equity	1,188	2,731
Proceeds from issuance of 2⅝% convertible subordinated notes, net of issuance costs	157,067	—
Principal and redemption premium payment on prepayment of the 5½% convertible subordinated notes	(44,926)	—
Principal payments on debt and capital lease obligations	(1,965)	(1,945)
Net cash provided by financing activities	111,364	786
Net increase (decrease) in cash and cash equivalents	68,909	(12,281)
Cash and cash equivalents (including cash and cash equivalents held by Symphony GenIsis, Inc. of $54.8 million and $0 at December 31, 2006 and 2005, respectively) at beginning of period	114,514	50,885
Cash and cash equivalents (including cash and cash equivalents held by Symphony GenIsis, Inc. of $49.6 million and $0 at March 31, 2007 and 2006, respectively) at end of period	$ 183,423	$ 38,604
Supplemental disclosures of cash flow information:		
Interest paid	$ 860	$ 409
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 443	$ 261

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
March 31, 2007
(Unaudited)

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three month periods ended March 31, 2007 and 2006 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2006. The financial statements include all normal recurring 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, 2006 included in Isis' Annual Report on Form 10-K filed with the Securities and Exchange Commission ("SEC").

The condensed consolidated financial statements include the accounts of Isis Pharmaceuticals, Inc. and its wholly owned subsidiaries, Ibis Biosciences, Inc. ("Ibis"), Isis Pharmaceuticals Singapore Pte Ltd., Isis USA Ltd. and Orasense, Ltd. On October 25, 2006, Isis dissolved the Orasense, Ltd. subsidiary. As part of its restructuring activities, Isis closed its Singapore operations in early 2005. 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") 46R (revised 2003), *Consolidation of Variable Interest Entities, an Interpretation of ARB 51*. All significant intercompany balances and transactions have been eliminated.

2. Significant Accounting Policies

Revenue recognition

Isis follows the provisions as set forth by Staff Accounting Bulletin ("SAB") 101, *Revenue Recognition in Financial Statements*, SAB 104, *Revenue Recognition*, and Financial Accounting Standards Board Emerging Issues Task Force ("EITF") 00-21, *Accounting for Revenue Arrangements with Multiple Deliverables*.

Isis generally recognizes revenue when it has satisfied all contractual obligations and is reasonably assured of collecting the resulting receivable. Isis is often entitled to bill its customers and receive payment from its customers in advance of recognizing the revenue under current accounting rules. In those instances where Isis has billed its customers or received payment from its customers in advance of recognizing revenue, the amounts are included in deferred revenue on the balance sheet.

Research and development revenue under collaborative agreements

Isis often enters into collaborations where it receives non-refundable upfront payments for prior or future expenditures. Isis recognizes revenue related to upfront payments ratably over the period of the contractual arrangements as it satisfies its performance obligations. Occasionally, Isis is required to estimate the period of a contractual arrangement or its performance obligations when the agreements it enters into do not clearly define such information. Should different estimates prevail, revenue recognized could be materially different. Isis has made estimates of its continuing obligations on several agreements.

Isis' collaborations often include contractual milestones. When it achieves these milestones, it is entitled to payment, as defined by the underlying agreements. Isis generally recognizes revenue related to milestone payments upon completion of the milestone's performance requirement, as long as it is reasonably assured of collecting the resulting receivable and it is not obligated for future performance related to the achievement of the milestone.

Isis generally recognizes revenue related to the sale of its drug inventory as it ships or delivers drugs to its partners. In several instances, Isis completed the manufacturing of drugs, but its partners asked it to deliver the drug on a later date. Under these circumstances, Isis ensured that its obligations were complete under the terms of the manufacturing agreement in place and title had transferred to the customer before it recognized the related revenue.

Isis often enters into revenue arrangements that contain multiple deliverables. In these cases, it recognizes revenue from each element of the arrangement as long as it is able to determine a separate value for each element, it has completed its obligation to deliver or perform on that element and it is reasonably assured of collecting the resulting receivable.

In the fourth quarter of 2006 and the first quarter of 2007, Isis delivered its first two commercial Ibis T5000 Biosensor Systems. The sale of each Ibis T5000 Biosensor System contains multiple elements. Since Isis had no previous experience of commercially selling the Ibis T5000 Biosensor System, it had no basis to determine the fair values of the various elements included in each system; therefore, it must account for the entire system as one deliverable and recognize revenue over the entire period of performance. For a one-year period following the sale, Isis has ongoing support obligations for the Ibis T5000 Biosensor System, therefore it is amortizing the revenue for the entire system over a one-year period. Once Isis obtains a sufficient number of sales to enable it to identify each element's fair value, it will be able to recognize revenue separately for each element.

Licensing and royalty revenue

Isis often enters into agreements to license its proprietary patent rights on an exclusive or non-exclusive basis in exchange for license fees and/or royalties. Isis generally recognizes as revenue immediately those licensing fees and royalties for which it has no future performance obligations and is reasonably assured of collecting the resulting receivable.

Short-term investments

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. Isis determined that there were no other-than-temporary declines in value of its investments during the three months ended March 31, 2007 and 2006. During the first quarter of 2007, Isis sold a portion of the equity securities of Alnylam Pharmaceuticals, Inc. that it owned resulting in a realized gain of $1.5 million. In April 2007, Isis sold the remaining equity securities of Alnylam resulting in a realized gain of $2.0 million, which will be reflected in the statement of operations in the second quarter of 2007.

Inventory valuation

Isis includes in inventory material costs for drugs that Isis manufactures for its partners under contractual terms and that Isis uses primarily in its clinical development activities and drug products. Isis expenses these costs when it delivers its drugs to partners, or as it provides these drugs for its own clinical trials. Also included in inventory are material costs and related manufacturing costs associated with the Ibis T5000 Biosensor System and related assay kits. 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 the 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 life 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 $1.1 million and $861,000 as of March 31, 2007 and December 31, 2006, respectively.

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 Isis is not actively pursuing 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. For the first three months of 2007 and 2006, Isis recorded a non-cash charge of $168,000 and $176,000, which was included in

research and development expenses and was related to the write-down of its patent costs to their estimated net realizable values.

Long-lived assets

Isis periodically evaluates carrying values of long-lived assets including property, plant and equipment and intangible assets, when events and circumstances indicate that these assets may have been impaired. Isis has adopted Statement of Financial Accounting Standards ("SFAS") 144, *Accounting for the Impairment of Long-Lived Assets*. Isis recorded a charge of $168,000 and $176,000 for the first quarter of 2007 and 2006, respectively, primarily related to the write-down of intangible assets to their estimated net realizable values.

Income taxes

In July 2006, the Financial Accounting Standards Board ("FASB") issued FIN 48, *Accounting for Uncertainty in Income Taxes*, which addressed the determination of how tax benefits claimed or expected to be claimed on a tax return should be recorded in the financial statements. Under FIN 48, Isis must recognize the tax benefit from an uncertain tax position only if it is more likely than not that the tax position will be sustained on examination by the taxing authorities, based on the technical merits of the position. The tax benefits recognized in the financial statements from such a position are measured based on the largest benefit that has a greater than fifty percent likelihood of being realized upon ultimate resolution. The accounting provisions of FIN 48 became effective for Isis beginning January 1, 2007.

At December 31, 2006, Isis had federal, foreign and California tax net operating loss ("NOL") carryfowards of approximately $560.0 million, $1.0 million and $179.5 million, respectively. The federal and California NOL carryforwards began expiring in 2007. The foreign NOL may be carried forward indefinitely and used to offset future taxable profits in the foreign jurisdiction in which this NOL arose, provided there is no substantial change in ownership. Isis also had federal and California research and development ("R&D") credit carryforwards of approximately $25.7 million and $18.5 million, respectively. The R&D tax credits began expiring in 2007. Because realization of such tax benefits is uncertain, Isis has provided a 100% valuation allowance. As a result of the adoption of FIN 48, Isis has not recorded any change to retained earnings at January 1, 2007 and it had no unrecognized tax benefits that, if recognized, would favorably affect Isis' effective income tax rate in future periods. At March 31, 2007, Isis had no unrecognized tax benefits. Isis' continuing practice is to recognize interest and/or penalties related to income tax matters in income tax expense. Isis had no accrued interest or penalties at January 1, 2007 and March 31, 2007.

Isis has not currently completed a study to assess whether a change in control has occurred or whether there have been multiple changes of control since Isis' formation due to the significant complexity and cost associated with such study and the possibility that there could be additional changes in the future. If Isis experienced a greater than 50% change or shift in ownership over a 3-year time frame since its formation, utilization of its NOL or R&D credit carryforwards would be subject to an annual limitation under Sections 382 and 383. The annual limitation generally is determined by multiplying the value of Isis' stock at the time of the ownership change (subject to certain adjustments) by the applicable long-term tax-exempt rate. Any limitation may result in expiration of a portion of the NOL or R&D credit carryforwards before utilization. Further, until a study is completed and any limitation known, no amounts are being presented as an uncertain tax position under FIN 48.

Isis is subject to taxation in the US and various state jurisdictions. Isis' tax years for 1989 and forward are subject to examination by the US and California tax authorities due to the carryforward of unutilized NOL's and R&D credits. Isis' tax years for 2001 and 2002 are currently being audited by California's Franchise Tax Board.

Use of estimates

The preparation of condensed 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 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 March 31, 2007, Isis had collaborative arrangements with six 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, ISIS 325568 and ISIS 377131. 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 included the financial condition and results of operations of Symphony GenIsis in its condensed consolidated financial statements. The creditors of Symphony GenIsis do not have recourse to the general credit of Isis.

As part of the collaboration between Isis and Atlantic Healthcare (UK) Limited, during March 2007, Isis licensed alicaforsen, its ICAM-1 antisense drug, to Atlantic, in exchange for $2.0 million of Atlantic's common stock. Isis has recognized a valuation allowance of $2.0 million to offset the equity instrument, as realization of this asset is uncertain. Isis is not required to consolidate Atlantic's results of operations under FIN 46R as Isis is not the primary beneficiary.

Comprehensive loss

SFAS 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,	
	2007	2006
Comprehensive loss:		
Unrealized holding gains (losses)	$ (780)	$ 2,561
Reclassification adjustment for realized gains included in net income	(1,417)	—
Net loss applicable to common stock	(13,020)	(17,480)
Comprehensive loss	$ (15,217)	$ (14,919)

Stock-based compensation expense

Isis accounts for its stock-based compensation expense related to employee stock options and employee stock purchases under SFAS 123R, *Share-Based Payment*. Isis estimates the fair value of each stock option grant and the employee stock purchase plan ("ESPP") purchase rights on the date of grant using the Black-Scholes model. The expected term of stock options granted represents the period of time that they are expected to be outstanding. For the stock options granted in the first quarter of 2007 and 2006, the estimated expected term is a derived output of the simplified method, as allowed under SAB 107.

For the quarter ended March 31, 2007 and 2006, Isis used the following weighted-average assumptions in its Black-Scholes calculations:

Employee Stock Option Plan:

	March 31,	
	2007	2006
Risk-free interest rate	4.7%	4.3%
Dividend yield	0.0%	0.0%
Volatility	63.8%	68.7%
Expected Life	4.6 years	4.6 years

ESPP:

	March 31,	
	2007	2006
Risk-free interest rate	5.1%	4.4%
Dividend yield	0.0%	0.0%
Volatility	56.1%	45.8%
Expected Life	6 months	6 months

Stock-based compensation expense for the three months ended March 31, 2007 and 2006 (in thousands, except per share data) was allocated as follows:

	Three Months Ended March 31, 2007	Three Months Ended March 31, 2006
Research and development	$ 1,926	$ 1,153
Selling, general and administrative	438	221
Non-cash compensation expense related to stock options included in operating expenses	$ 2,364	$ 1,374
Basic and diluted net loss per share	$ (0.03)	$ (0.02)

As of March 31, 2007, total unrecognized compensation cost related to non-vested stock-based compensation plans was $15.4 million. Total unrecognized compensation cost will be adjusted for future changes in estimated forfeitures. Isis expects to recognize this cost over a weighted average period of 1.5 years.

Impact of recently issued accounting standards

In September 2006, the FASB issued SFAS 157, *Fair Value Measurements.* This Statement defines fair value, establishes a framework for measuring fair value in generally accepted accounting principles and expands disclosures about fair value measurements. This Statement applies across a broad number of other accounting pronouncements that require or permit fair value measurements. This Statement is effective for all financial statements issued for fiscal years that begin after November 15, 2007. Isis is currently evaluating the impact of adopting SFAS 157 to determine the effects, if any, on its operating results and financial position.

In February 2007, the FASB issued SFAS 159, *The Fair Value Option for Financial Assets and Financial Liabilities*, which allows entities to account for most financial instruments at fair value rather than under other applicable generally accepted accounting principles ("GAAP"), such as historical cost. The accounting results in the instrument being marked to fair value every reporting period with the gain/loss from a change in fair value recorded in the

income statement. SFAS 159 is effective for all financial statements issued for fiscal years that begin after November 15, 2007. Isis does not expect a material impact on its financial statements.

3. Long-Term Obligations

In January 2007, Isis completed a $162.5 million convertible debt offering, which raised proceeds of approximately $157.1 million, net of $5.4 million in issuance costs. The $162.5 million convertible subordinated notes mature in 2027 and bear interest at 2⅝%, which is payable semi-annually. The 2⅝% notes are convertible, at the option of the note holders, into approximately 11.1 million shares of common stock at a conversion price of approximately $14.63 per share. Isis will be able to redeem the 2⅝% notes at a redemption price equal to 100.75% of the principal amount between February 15, 2012 and February 14, 2013; 100.375% of the principal amount between February 15, 2013 and February 14, 2014; and 100% of the principal amount thereafter. Holders of the 2⅝% notes will also be able to require Isis to repurchase these notes on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100% of the principal amount of the 2⅝% notes being repurchased plus accrued interest and unpaid interest.

Isis used the net proceeds from the issuance of the 2⅝% notes to repurchase its 5½% convertible subordinated notes due in 2009. In January 2007, Isis repurchased approximately $44.2 million aggregate principal amount of its 5½% notes at a redemption price of $44.9 million plus accrued but unpaid interest. In May 2007, Isis redeemed the remaining $80.8 million principal balance at a redemption price of $82.1 million plus accrued but unpaid interest. As a result of the repayment of these notes, Isis will recognize a $3.2 million loss on the early extinguishment of debt in 2007, which includes a $1.2 million write-off of unamortized debt issuance costs. Included in the first quarter 2007 Condensed Consolidated Statement of Operations was $1.2 million of that loss and the remainder will be recorded in the second quarter of 2007. As a result of the

May 2007 redemption, the $80.8 million principal is classified as a current liability at March 31, 2007 in the Condensed Consolidated Balance Sheet.

4. Collaborative Arrangements and Licensing Agreements

Bristol-Myers Squibb Company

In May 2007, Isis entered into a collaboration agreement with Bristol-Myers Squibb Company ("BMS") to discover, develop and commercialize novel therapeutic antisense drugs targeting proprotein convertase subtilisin/kexin type 9

("PCSK9"). Under the terms of the agreement, BMS will pay Isis a $15 million upfront licensing fee, and will provide Isis with at least $9 million in research funding over a period of three years. Isis will also receive up to $168 million for the achievement of pre-specified development and regulatory milestones for the first drug in the collaboration, as well as additional milestones associated with development of follow-on compounds. BMS will also pay Isis royalties on sales of products resulting from the collaboration.

5. Segment Information and Concentration of Business Risk

Segment information

The following is information for revenue and loss from operations by segment (in thousands):

	Drug Discovery and Development	Ibis	Corporate	Total
Three Months Ended March 31, 2007				
Revenue:				
Research and development	$ 426	$ 945	$ —	$ 1,371
Commercial revenue (1)	—	631	—	631
Licensing and royalty	448	—	—	448
Total segment revenue	$ 874	$ 1,576	$ —	$ 2,450
Loss from operations	$ (17,766)	$ (3,135)	$ —	$ (20,901)
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)

(1) Ibis' commercial revenue has been classified as research and development revenue under collaborative agreements on Isis' Condensed Consolidated Statements of Operations.

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

Concentrations of business risk

Isis has historically funded its operations in part from collaborations with corporate partners and as it relates to Ibis, from collaborations with various government agencies. Beginning in the second half of 2006, Ibis began selling commercial products and services. 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,	
	2007	2006
Partner A	37%	14%
Partner B	19%	18%
Partner C	13%	7%
Partner D	2%	29%
Partner E	0%	15%

For the three months ended March 31, 2007 and 2006, Isis derived approximately 64% and 65%, respectively, of its revenue from agencies of the United States Government. For both of the quarters ended March 31, 2007 and 2006, three of the five significant partners listed above represent revenue from agencies of the United States Government.

Contract receivables from three significant partners comprised approximately 49%, 24% and 22% of contract receivables at March 31, 2007. Contract receivables from four significant partners comprised approximately 25%, 20%, 19%, and 16% of contract receivables at December 31, 2006.

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

In this Report on Form 10-Q, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us," means Isis Pharmaceuticals, Inc. and its subsidiaries.

Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, this Report includes forward-looking statements regarding our business, the therapeutic and commercial potential of our technologies and products in development, and the financial position of Isis Pharmaceuticals, Inc. and our Ibis Biosciences subsidiary. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' goals and projections. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, in developing and commercializing systems to identify infectious organisms that are effective and commercially attractive, and in the endeavor of building a business around such products. 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, 2006, which is on file with the U.S. Securities and Exchange Commission, and those identified within this Item entitled "Risk Factors" beginning on page 26 of this Report.

Overview

We are a biopharmaceutical company that, since our inception in 1989, has pioneered the science of antisense for the development of a new class of drugs to treat important diseases. We are the leader in making drugs that target RNA, and we have a strong proprietary position in RNA-based drug discovery technologies. RNA, or ribonucleic acid, is a molecule that provides to a cell the information the cell needs to produce proteins, including those proteins associated with disease. Interference with RNA can keep the body from producing the proteins that are involved in disease. With our primary technology, antisense, we create inhibitors, called oligonucleotides, designed to hybridize, with a high degree of specificity to their RNA target and modulate the production of specific proteins associated with disease. Separately, within our Ibis Biosciences subsidiary, we have developed a revolutionary biosensor system, called the Ibis T5000 Biosensor System, that can simultaneously identify from a sample a broad range of infectious organisms without needing to know beforehand what might be present in the sample.

We have built a business dedicated to RNA-based drug discovery and development. This is our expertise, and we are fostering the innovations that enable creation of this entirely new class of drugs—antisense drugs. We successfully developed the first marketed antisense drug, Vitravene. The regulatory approval we received for Vitravene demonstrated our ability to meet Food and Drug Administration (FDA), and European regulatory requirements for safety and efficacy, and for the commercial manufacture of antisense drugs. With the pioneering work we have done in developing our technology platform, we can discover and validate many more drug candidates than we can advance ourselves. Our strategy is to apply our expertise to discover and develop drugs, advancing them to strategic points and then to license them to others to leverage their resources and existing infrastructures. Our key therapeutic areas are cardiovascular and metabolic diseases, and we develop drugs in these franchises internally to points where we believe we have established significant value before partnering them. In other therapeutic areas, our strategy is to work with partners sooner in the discovery and development process to take advantage of their therapeutic area of focus to build on our development pipeline. The strategy is working. It has allowed us to maintain internal focus while creating an expansive pipeline with multiple partnership franchises in cancer, inflammation, ocular, and other disease areas. Our pipeline has matured to consist almost entirely of drugs based on our proprietary second generation chemistry. Our second generation antisense drugs have the potential to be safer and more effective than our first generation drugs. In addition, because second generation drugs have a longer half-life, they have the potential to produce long-duration of therapeutic response and to support more convenient, less-frequent dosing.

We have a broad patent portfolio to protect our substantial innovation and investment in RNA-based technologies and products. We own or exclusively license more than 1,500 issued patents, which we believe represents the largest antisense and RNA-oriented patent estate in the pharmaceutical industry. In addition to protecting our key assets, 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 March 31, 2007, we had generated more than $92.5 million from our intellectual property licensing program that helps support our internal drug discovery and development programs.

Business Segments

We focus our business on two principal segments:

Drug Discovery and Development—Within our primary business segment, we are exploiting our expertise in RNA to discover and develop novel drugs for our product pipeline and for that of our partners. We have successfully commercialized the world's first antisense drug and, along with our partners, we currently have 17 drugs in development. Our partners are licensed to develop, with our support, eleven of these 17 drugs, which substantially reduces our development costs. We focus our internal drug development programs on drugs to treat cardiovascular, metabolic and inflammatory diseases. Our partners focus on disease areas such as ocular, viral, inflammatory and neurodegenerative diseases, and cancer.

Ibis Biosciences—Ibis Biosciences, Inc., formerly a division of Isis and now a wholly owned subsidiary of Isis, has developed a revolutionary biosensor system, called the Ibis T5000 Biosensor System, for rapid identification and characterization of infectious agents. The Ibis T5000 is capable of identifying virtually all bacteria, virus and fungi, and can provide information about drug resistance, virulence and strain type of these pathogens. We are commercializing the Ibis T5000 Biosensor System and related assay kits for use in biodefense, forensics, epidemiological surveillance, infectious disease research, hospital-associated infection control and plan to commercialize the Ibis T5000 Biosensor System for use in *in vitro* diagnostics.

Much of the development of the Ibis T5000 system and related applications has been funded through government contracts and grants. As of March 31, 2007, we had earned $59.0 million in revenue under our government contracts and grants, and we had an additional $5.6 million committed under our existing contracts and grants.

Recent Events

Issuance of 2⅝% Convertible Subordinated Notes; Repurchase of 5½% Convertible Subordinated Notes

In January 2007, we issued $162.5 million of 2⅝% Convertible Subordinated Notes due 2027. Using the net proceeds from the issuance of the 2⅝% notes, we repurchased our 5½% Convertible Subordinated Notes due 2009. The significantly lower interest rate of the 2⅝% notes reduces our annual cash interest payments by approximately $2.6 million. In addition, the extended maturity date of the 2⅝% notes further strengthens our financial position.

Clinical Data on ISIS 301012

In March 2007, we reported positive results from three studies of ISIS 301012. ISIS 301012 inhibits production of apoB-100 to reduce low-density lipoproteins (LDL-C) and other atherogenic lipids and triglycerides. We are developing ISIS 301012 to reduce LDL-C in the significant and growing number of patients who are unable to achieve recommended LDL-C levels. At the American College of Cardiology meeting at the end of March, Isis reported new data from three Phase 2 studies. Collectively, the key conclusions from the Phase 2 studies are that treatment with ISIS 301012:

- Resulted in highly consistent and predictable linear, dose-dependent, prolonged reductions of apoB and related atherogenic lipids including LDL-C and triglycerides in patients with polygenic hypercholesterolemia (routine high cholesterol) and in patients with homozygous familial hypercholesterolemia (FH).

- Was similarly effective when administered as a single agent, when coadministered with moderately-dosed statins and when added to maximally-tolerated lipid-lowering therapies.

- Was well-tolerated in all Phase 2 trials.

Development of ISIS 301012 is continuing in three ongoing studies in which it is being coadministered with statins for three months in polygenic hypercholesterolemic patients, and with maximally-tolerated lipid-lowering therapies in homozygous and heterozygous FH patients. Isis expects results from these studies later in the year. Additionally, Isis plans

to start its pivotal FH trials this year, as well as to initiate a longer-term dosing study in coadministration with statins in patients with routine high cholesterol.

Bristol-Myers Squibb Company

In May 2007, we entered into a collaboration agreement with BMS to discover, develop and commercialize novel therapeutic antisense drugs targeting PCSK9. Under the terms of the agreement, BMS will pay us a $15 million upfront licensing fee, and will provide us with at least $9 million in research funding over a period of three years. We will also receive up to $168 million for the achievement of pre-specified development and regulatory milestones for the first drug in the collaboration, as well as additional milestones associated with development of follow-on compounds. BMS will also pay us royalties on sales of products resulting from the collaboration.

Critical Accounting Policies

We prepare our condensed 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. Each quarter, our senior management discusses the development, selection and disclosure of such estimates with our audit committee of our Board of Directors. There are specific risks associated with these critical accounting policies and 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, the expected stock price volatility over the term of the expected life and estimated forfeitures.

There have been no material changes to our critical accounting policies and estimates from the information provided in Item 7, “Management’s Discussion and Analysis of Financial Condition and Results of Operations”, included in our Annual Report on Form 10-K for the year ended December 31, 2006.

Results of Operations

Revenue

Total revenue for the three months ended March 31, 2007 was $2.5 million compared to $5.0 million for the same period in 2006. Revenue was lower for the first quarter of 2007 compared to the same period in 2006 because of lower revenue from our collaborations and differences in the timing of Ibis Biosciences, Inc.s’ government contract revenue. Our revenue fluctuates based on the nature and timing of payments under agreements with our partners, including license fees, milestone-related payments and other payments, including those for drugs we manufacture for our partners. For example, in the first quarter of 2006, revenue included a one-time milestone of $750,000 that we received from Eli Lilly and Company. As a result of our recently announced collaboration with BMS, not including milestone or manufacturing revenue, we will recognize approximately $8 million in revenue annually for the three years of the collaboration since we will amortize the $15 million upfront payment, and receive research funding of approximately $3 million per year.

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

	Three Months Ended March 31,	
	2007	2006
Drug Discovery and Development:		
Research and development revenue	$ 426	$ 1,270
Licensing and royalty revenue	448	490
	$ 874	$ 1,760
Ibis Biosciences:		
Research and development revenue	$ 945	$ 3,198
Commercial revenue (1)	631	—
	$ 1,576	$ 3,198
Total revenue:		
Research and development revenue	$ 1,371	$ 4,468
Commercial revenue (1)	631	—
Licensing and royalty revenue	448	490
	$ 2,450	$ 4,958

(1) Ibis Biosciences’ commercial revenue has been classified as research and development revenue under collaborative agreements on Isis’ Condensed Consolidated Statements of Operations.

Drug Discovery & Development

Research and Development Revenue Under Collaborative Agreements

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 months ended March 31, 2007 was $426,000 compared to $1.3 million for the same period in 2006. The decrease was primarily a result of lower revenue from our research collaborations, including a decrease in revenue associated with our collaboration with Lilly. Our research and development revenue under collaborative agreements fluctuates based on the timing of activities under contract, and as a result, it frequently includes non-recurring items.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the three months ended March 31, 2007 was $448,000 compared to $490,000 for the same period in 2006.

Ibis Biosciences, Inc.

Ibis' revenue for the three months ended March 31, 2007 was $1.6 million compared to $3.2 million for the same period in 2006. Ibis earned commercial revenue of $631,000 for the three months ended March 31, 2007, which consisted of

the amortization of revenue for Ibis' first commercial instrument and assay kits, as well as revenue from Ibis' assay services business. Because Ibis provides a full year of support for each Ibis T5000 Biosensor System following installation, Ibis is amortizing the revenue for each instrument sold over the period of this support obligation. Additionally, Ibis generated revenue from its government contracts and grants of $945,000 for the three months ended March 31, 2007 compared to $3.2 million for the same period in 2006. As Ibis has matured from research and development to commercial stage, some of its large government contracts that supported technology development have been successfully completed. New contracts supporting application development are being initiated, resulting in this transient decline in contract revenue. Isis expects that revenue from government contracts will continue to provide a solid revenue base going forward.

From inception through March 31, 2007, Ibis has earned $59.0 million in revenue from various government agencies to further the development of our Ibis T5000 Biosensor System and related assay kits. An additional $5.6 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. 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

Even with our increased costs associated with the expansion of our clinical development programs and with building the manufacturing, marketing and sales infrastructure required to successfully commercialize the Ibis T5000 Biosensor System, careful control of expenses in other areas resulted in total operating expenses for the quarter ended March 31, 2007 of $23.4 million compared to $21.0 million for the same period in 2006. Included in our operating expenses is non-cash compensation expense related to stock options, which increased from $1.4 million for the first quarter of 2006 to $2.4 million for the same period in 2007, primarily reflecting the increase in our stock price from period to period.

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 them.

Research and Development Expenses

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

	Three Months Ended March 31,	
	2007	2006
Research and development expenses	$ 18,023	$ 17,218
Non-cash compensation expense related to stock options	1,926	1,153
Total research and development expenses	$ 19,949	$ 18,372

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

	Three Months Ended March 31,	
	2007	2006
Drug Discovery and Development	$ 16,227	$ 15,092
Ibis Biosciences	3,722	3,280
Total research and development expenses	$ 19,949	$ 18,372

For the three months ended March 31, 2007, we incurred total research and development expenses, excluding stock compensation, of $18.0 million compared to $17.2 million for the same period in 2006. The increase is attributed to the continued development of our key programs including the additional costs required for the initiation of larger Phase 2 studies of ISIS 301012.

Drug Discovery & Development

Antisense Drug Discovery

Using proprietary antisense oligonucleotides to identify what a gene does, called gene functionalization, and then determining whether a specific gene is a good target for drug discovery, called target validation, are the first steps in our drug discovery process. We use our proprietary antisense technology to generate information about the function of genes and to determine the value of genes as drug discovery targets. We use this information to direct our own antisense drug discovery research, and that of our antisense drug discovery partners. Antisense drug discovery is also the function within Isis that is responsible for advancing antisense core technology.

As we have advanced our antisense technology to a point where we and our partners now have extensive clinical and preclinical development pipelines that are full of product opportunities, we have far more drug assets than we can afford to develop on our own. As a result, we have significantly reduced our antisense drug discovery activities so that we can focus on our drugs in development. 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 discovery costs for the three months ended March 31, 2007 were $3.8 million compared to $3.4 million for the same period in 2006. The increase was primarily due to an increase in the use of lab supplies. Additionally, the price of lab supplies increased in the first quarter of 2007 compared to the same period in 2006.

Antisense Drug Development

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

	Three Months Ended March 31,	
	2007	2006
Alicaforsen for Crohn's disease	$ —	$ 2
Other antisense development products	4,341	4,454
Development overhead costs	1,340	770
Non-cash compensation expense related to stock options	650	358
Total antisense drug development	$ 6,331	$ 5,584

Antisense drug development expenditures were $5.7 million, excluding $650,000 of non-cash stock compensation expense, and $5.2 million, excluding $358,000 of non-cash stock compensation expense for the quarter ended March 31, 2007 and 2006, respectively. The increase of $455,000 was primarily attributed to the continued development of our key programs including additional costs incurred as we prepare to initiate larger Phase 2 studies of ISIS 301012. We expect our drug development expenses to fluctuate based on the timing and size of our clinical trials. We are currently conducting multiple Phase 2 trials for ISIS 301012. Development overhead costs were $1.3 million and $770,000 for the quarter ended March 31, 2007 and 2006, respectively. The increase of $570,000 was primarily due to increased personnel costs.

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 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, eleven of our 17 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. These costs for the three months ended March 31, 2007 were $1.6 million compared to $1.7 million for the same period in 2006. This function is responsible for providing drug supplies to antisense drug discovery and antisense drug development, including the analytical testing to satisfy good laboratory and good manufacturing practices requirements.

Ibis Biosciences, Inc.

Ibis' research and development expenses are primarily the result of its performance under government contracts in support of the ongoing development of the Ibis T5000 Biosensor System and related assay kits. Ibis' expenses include all contract-related costs it incurs on behalf of government agencies in connection with the performance of its obligations under the respective contracts, including costs for equipment to which the government retains title. Research and development expenditures in Ibis include costs for scientists, pass-through equipment costs, laboratory supplies, chemicals and highly specialized information technology consultants to advance the research and development of the Ibis T5000 Biosensor System. Further, we allocate a portion of R&D support costs and selling, general and administrative costs to Ibis Biosciences.

The following table sets forth information on Ibis' research and development expenses (in thousands):

	Three Months Ended March 31,	
	2007	2006
Research and development costs	$ 2,696	$ 2,381
R&D support costs	725	682
Non-cash compensation expense related to stock options	301	217
Total Ibis' research and development expenses	$ 3,722	$ 3,280

Ibis' research and development expenses, excluding R&D support costs and non-cash compensation expense related to stock options, for the three months ended March 31, 2007 and 2006 were $2.7 million and $2.4 million, respectively. The increase in expenses primarily reflects an increase in costs necessary to support commercialization of the Ibis T5000 Biosensor System. Ibis has delivered four systems to its government partners for use in biodefense and epidemiological surveillance and two systems under a commercial purchase order. The first commercial systems, one of which was delivered in the fourth quarter of 2006 and one that was delivered in the first quarter of 2007, were part of an order for two Ibis T5000 Biosensor Systems from a U.S. government agency for human forensics applications. We expect costs and expenses for Ibis 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 March 31,	
	2007	2006
Personnel costs	$ 1,536	$ 1,568
Occupancy	1,515	1,527
Depreciation and amortization	1,205	1,244
Insurance	237	256
Other	768	498
Total R&D support costs	$ 5,261	$ 5,093

R&D support costs for the three months ended March 31, 2007 were $5.3 million and were only slightly higher as compared to $5.1 million for the same period in 2006.

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

	Three Months Ended March 31,	
	2007	2006
Drug Discovery and Development	$ 4,536	$ 4,411
Ibis Biosciences	725	682
Total R&D support costs	$ 5,261	$ 5,093

Selling, General and Administrative Expenses

Selling, general and administrative expenses include corporate costs required to support our company, our employees and our stockholders. These costs include personnel and outside costs in the areas of business development, legal, human resources, investor relations, finance and Ibis sales and marketing. Additionally, we include in selling, general and administrative expenses such costs as rent, repair and maintenance of buildings and equipment, depreciation, utilities, information technology and procurement costs that we need to support the corporate functions listed above. Beginning in the second quarter of 2006, as a result of the consolidation of Symphony GenIsis, selling, general and administrative expenses also include Symphony GenIsis' general and administrative expenses.

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

	Three Months Ended March 31,	
	2007	2006
Selling, general and administrative expenses	$ 2,964	$ 2,345
Non-cash compensation expense related to stock options	438	221
Total selling, general and administrative expenses	$ 3,402	$ 2,566

Selling, general and administrative expenses, excluding non-cash compensation expense related to stock options, for the three months ended March 31, 2007 were $3.0 million compared to $2.3 million for the same period in 2006. The increase is a result of increased selling, general and administrative expenses associated with the commercialization of the Ibis T5000 Biosensor System and the addition of general and administrative expenses that are consolidated from Symphony GenIsis. As Ibis continues to execute its commercialization plan, we expect selling, general and administrative expense for Ibis to continue to increase.

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

	Three Months Ended March 31,	
	2007	2006
Drug Discovery and Development	$ 2,414	$ 2,117
Ibis Biosciences	988	449
Total selling, general and administrative expenses	$ 3,402	$ 2,566

Restructuring Activities

During the three months ended March 31, 2006, we recorded a charge of $36,000 for restructuring activities resulting from our decision to focus our resources on key programs.

Investment Income

Investment income for the three months ended March 31, 2007 totaled $3.4 million compared to $811,000 for the same period in 2006. The increase in investment income was primarily due to a higher average cash balance during the first three months of 2007 compared to the same period in 2006 as a result of the funds held by Symphony GenIsis, the proceeds we received from the Azimuth equity financing and the proceeds we received from the issuance of our 2⅝% convertible subordinated notes in January 2007.

Interest Expense

Interest expense for the three months ended March 31, 2007 totaled $2.6 million compared to $2.3 million for the same period in 2006. This increase was due to the effect of a higher debt balance for the first quarter of 2007 compared to 2006 primarily related to the issuance of our 2⅝% convertible subordinated notes in January 2007.

Gain on Investments

Gain on investments for the three months ended March 31, 2007 and 2006 was $1.5 million and $0, respectively. The gain on investments reflected a gain realized on the sale of a portion of the equity securities of Alnylam that we owned. In April 2007, we sold our remaining equity securities of Alnylam resulting in a realized gain of $2.0 million, which will be reflected in the statement of operations in the second quarter of 2007.

Loss on Early Retirement of Debt

Loss on early retirement of debt for the three months ended March 31, 2007 and 2006 was $1.2 million and $0, respectively. The loss on early retirement of debt reflected the early extinguishment of a portion of our 5½% convertible subordinated notes in January 2007. In May 2007, we redeemed the remaining balance of the 5½% convertible subordinated notes. As a result of the May 2007 redemption, we incurred an additional loss on the early retirement of debt of $2.0 million, which will be reflected in the statement of operations in the second quarter of 2007.

Net Loss Applicable to Common Stock

Net loss applicable to common stock for the three months ended March 31, 2007 was $13.0 million compared with a net loss applicable to common stock of $17.5 million for the same period in 2006. We recognized a benefit of $6.8 million for the three months ended March 31, 2007 in the loss attributed to noncontrolling interest in Symphony GenIsis, Inc. This benefit was a significant reason for the improvement in our net loss applicable to common stock in the first quarter of 2007 compared to the same period in 2006 offset by the increase in the loss from operations. As further discussed below under “Liquidity and Capital Resources,” in January 2007, we issued new convertible subordinated notes which increased our average cash and debt balances resulting in additional interest income and interest expense in the first quarter of 2007 compared to the same period in 2006. Additionally, in conjunction with the issuance of these new notes, during the first quarter of 2007, we repaid a portion of our existing 5½% convertible subordinated notes, and as a result recognized a $1.2 million loss on the early extinguishment of debt as discussed above under “Loss on Early Retirement of Debt.” The decrease in the net loss applicable to common stock was also impacted by the gain on investments.

Net Loss Per Share

Net loss per share for the three months ended March 31, 2007 was $0.16 per share compared to a net loss per share for the same period in 2006 of $0.24 per share. In the second half of 2006, we issued approximately 8 million shares of our common stock to Azimuth under an equity financing that raised $75 million and approximately 1.4 million shares of our common stock in connection with the exercise of stock options and warrants, and the purchase of shares under our employee stock purchase plan. These additional shares, combined with the substantial decrease in net loss applicable to common stock, resulted in the significant decrease in our net loss per share for the first quarter of 2007 compared 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 March 31, 2007, we have earned approximately $510.2 million in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through March 31, 2007, we have raised net proceeds of approximately $730.0 million from the sale of our equity securities and we have borrowed approximately $543.8 million under long-term debt arrangements to finance a portion of our operations.

At March 31, 2007, we had cash, cash equivalents and short-term investments of $285.6 million, which included $49.6 million of cash and cash equivalents held by Symphony GenIsis, consolidated working capital of $194.1 million and stockholders' equity of $56.9 million. In comparison, we had cash, cash equivalents and short-term investments of $193.3 million, which included $54.8 million of cash and cash equivalents held by Symphony GenIsis, consolidated working capital of $181.1 million and stockholders' equity of $68.6 million as of December 31, 2006. The increase in our cash, cash equivalents and short-term investments was due primarily to the net proceeds received from the issuance of our 2⅝% convertible subordinated notes in January 2007, along with proceeds of $2.2 million that we received from the sale of a portion of our Alnylam equity securities, offset by cash used in operations and to repurchase the 5 ½% notes. The significantly lower interest rate of the 2⅝% convertible subordinated notes reduces our annual cash interest payments by approximately $2.6 million. In addition, the extended maturity date of the 2⅝% notes further strengthens our balance sheet.

As of March 31, 2007, our debt and other obligations totaled $256.7 million, compared to $140.3 million at December 31, 2006. The increase in our debt and other obligations was primarily due to the issuance of our 2⅝% convertible subordinated notes offset by the January 2007 partial repayment of our 5 ½ % convertible subordinated notes and the declining balance on our Silicon Valley Bank term loan. In May 2007, we redeemed the $80.8 million remaining principal balance of our 5½% convertible subordinated notes, which will be reflected in the balance sheet for the second quarter of 2007 as a reduction in cash and current liabilities. We will continue to use lease financing as long as the terms remain commercially attractive.

Based on our current operating plan with reasonable assumptions for new sources of revenue and cash, we believe our resources will be sufficient to meet our anticipated requirements through at least the middle of 2010.

The following table summarizes our contractual obligations as of March 31, 2007. 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**
5½% Convertible Subordinated Notes	$ 80.8	$ 80.8	$ —	$ —	$ —
2⅝% Convertible Subordinated Notes	162.5	—	—	—	162.5
Silicon Valley Bank Term Loan	12.3	6.8	5.5	—	—
Capital Lease and Other Obligations	1.1	0.7	—	—	0.4
Operating Leases	21.9	2.8	5.5	4.0	9.6

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 debt from two partners. We amortize the term loan over sixty months. The term loan requires 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 8.0% at March 31, 2007. 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 March 31, 2007 was $12.3 million.

In January 2007, we completed a $162.5 million convertible debt offering, which raised proceeds of approximately $157.1 million, net of $5.4 million in issuance costs. The $162.5 million convertible subordinated notes bear interest at 2⅝%, which is payable semi-annually, and mature in 2027. Using the net proceeds from the issuance of the 2⅝% notes, we repaid the entire $125 million of our 5½% convertible subordinated notes due 2009. The 2⅝% notes are convertible, at the option of the note holders, into approximately 11.1 million shares of common stock at a conversion price of $14.63 per share. We will be able to redeem these notes at a redemption price equal to 100.75% of the principal amount between February 15, 2012 and February 14, 2013; 100.375% of the principal amount between February 15, 2013 and February 14, 2014; and 100% of the principal amount thereafter. Holders of the 2⅝% notes are also able to require us to repurchase the 2⅝% notes on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100% of the principal amount of the 2⅝% notes being repurchased plus accrued interest and unpaid interest.

In addition to contractual obligations, we had outstanding purchase orders as of March 31, 2007 for the purchase of services, capital equipment and materials as part of our normal course of business.

We plan to continue to enter into collaborations with partners to provide for additional revenue 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. We have marked with an asterisk those risk factors that reflect substantive changes from the risk factors included in our Annual Report on Form 10-K for the year ended December 31, 2006.

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 March 31, 2007, we had accumulated losses of approximately $829.8 million and stockholders' equity of approximately $56.9 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from research grants and the sale or licensing of patents as well as interest income. We currently have only one product, Vitravene, approved for commercial use. This product has limited sales potential, and Novartis, our exclusive distribution partner for this product no longer markets it. We expect to incur additional operating losses over the next several years, and

these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or services, or achieve or sustain future profitability.

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

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

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

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and their price, as well as the price of our other securities, may decline. If adequate funds are not available or not available on acceptable terms, we may have to cut back on one or more of our research, drug discovery or development programs. For example, in January 2005 we decided to terminate the development of two lower priority drugs, ISIS 14803 and ISIS 104838. Alternatively, as in our transaction with Symphony GenIsis, we may obtain funds through arrangements with collaborative partners or others, which could require us to give up rights to certain of our technologies, drugs or products.

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

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

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

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

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

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

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

· conduct clinical trials;

· seek and obtain regulatory approvals; and

· manufacture, market and sell existing and future products.

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

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

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

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

· choose to devote fewer resources to our drugs than it does for drugs of its own development.

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

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

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

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

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

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

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

For example, in December 2006, the European Patent Office (EPO) Technical Board of Appeal reinstated with amended claims our Patent EP0618925 which claims a class of antisense compounds, any of which is designed to have a

sequence of phosphorothioate-linked nucleotides having two regions of chemically modified RNA flanking a region of DNA. Prior to its reinstatement, this patent was originally opposed by several parties and revoked by an EPO Opposition Division in December of 2003. We intend to fully exercise our rights under this patent by pursuing licensing arrangements, but if licensing efforts are unsuccessful we may choose to assert our rights through litigation.

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

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

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

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

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

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding March 31, 2007, the market price of our common stock ranged from $5.57 to $14.00 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial results, technological innovations or new products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

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

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

- interruption of our research, development and manufacturing efforts;
- injury to our employees and others;
- environmental damage resulting in costly clean up; and

- liabilities under federal, state and local laws and regulations governing health and human safety, as well as the use, storage, handling and disposal of these materials and resultant waste products.

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

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

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

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

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

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

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

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

Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. We have granted registration rights to Lilly, which cover approximately 2.5 million shares of our common stock, which we issued to Lilly upon the conversion of outstanding convertible securities. We also registered for resale 12,000,000 shares of our common stock and 2,999,998 shares of our common stock issuable upon the exercise of the warrants we issued as part of our August 2005 private placement as well as 4.25 million shares of our common stock issuable upon the exercise of the warrant we issued to Symphony GenIsis Holdings. In addition, on December 22, 2005, we filed a Form S-3 shelf registration statement with the SEC to register up to $200,000,000 worth of our common stock for possible issuance. Finally, we have registered for resale our 2¾% convertible subordinated notes, including the approximately 11,111,116 shares issuable upon conversion of the notes. The addition of any of these shares into the market may have an adverse effect on the price of our securities.

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

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

Risks Associated with our Drug Discovery and Development Business

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

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

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

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

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

In the past, we have invested in clinical studies of drugs that have not met the primary clinical end points in their Phase 3 studies. In March 2003, we reported the results of a Phase 3 clinical trial of Affinitak in patients with late-stage non-small cell lung cancer and in October 2004, we reported the results of a second similar Phase 3 clinical trial. In each case, Affinitak failed to demonstrate improved survival sufficient to support an NDA filing. In December 2004, we reported the results of our Phase 3 clinical trials of alicaforsen in patients with active Crohn's disease, in which alicaforsen did not demonstrate statistically significant induction of clinical remissions compared to placebo. Similar results could occur with the clinical trials for our other drugs ISIS 301012 and ISIS 113715. If any of our drugs in clinical studies ISIS 301012 and ISIS 113715 do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for this and other drugs and our stock price could decline.

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

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

· the clinical trial may produce negative or inconclusive results;

· regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;

- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical trial due to adverse side effects of a drug on subjects or patients in the trial;

- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical trials;

- enrollment in our clinical trials may be slower than we currently anticipate;

- the cost of our clinical trials may be greater than we anticipate; and

- the supply or quality of our drugs or other materials necessary to conduct our clinical trials may be insufficient, inadequate or delayed.

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

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

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

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

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

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

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

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

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

- the receipt and scope of regulatory approvals;

- the establishment and demonstration in the medical and patient community of the efficacy and safety of our drugs and their potential advantages over competing products;

- the cost and effectiveness of our drugs compared to other available therapies;

- the patient convenience of the dosing regimen for our drugs; and

- reimbursement policies of government and third-party payors.

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

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

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

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

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

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

· priced lower than our drugs;

· safer than our drugs; or

· more effective than our drugs.

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

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

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

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

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

Risks Associated With Our Ibis Biosciences Business

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

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

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

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

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

In July 2006, we entered into a strategic alliance with Bruker Daltonics to manufacture and distribute the Ibis T5000 Biosensor System. Bruker Daltonics will be the exclusive, worldwide manufacturer of the Ibis T5000 Biosensor System and will also be responsible for order processing, system

installations and service in North America, Europe and the Middle East. In Europe and the Middle East, Bruker Daltonics will have exclusive rights to sell Ibis T5000 Biosensor Systems and Ibis assay kits for various government applications, and non-exclusive rights to sell to customers for all other applications except diagnostics. As such, we rely heavily on Bruker Daltonics to successfully manufacture and distribute our Ibis T5000

Biosensor System, but do not control many aspects of Bruker Daltonics activities. If Bruker Daltonics fails to carry out its obligations under our alliance, such failure could harm or delay the commercialization of our Ibis T5000 Biosensor System.

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

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

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

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

For the three months ended March 31, 2007 and 2006, we derived approximately 64% and 65%, respectively, of our revenue from agencies of the U.S. government. Because of the concentration of our contracts, we are vulnerable to adverse changes in our revenues and cash flows if a significant number of our U.S. government contracts and subcontracts are simultaneously delayed or canceled for budgetary, performance or other reasons.

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

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

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

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

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

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

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

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

delay our commercialization efforts and lengthen our sales cycle.

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

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

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

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

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

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

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

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

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

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

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

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

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

The sales cycles for Ibis T5000 Biosensor Systems are typically lengthy. Our sales and licensing efforts, and those of our partners, will require the effective demonstration of the benefits, value, and differentiation and validation of our products and services, and significant training of multiple personnel and departments within a potential customer organization. We or our partners may be required to negotiate agreements containing terms unique to each prospective customer or licensee, which would lengthen the sales cycle. We may expend substantial funds and management effort with no assurance that we

will sell our products. In addition, this lengthy sales cycle makes it more difficult for us to accurately forecast revenue in future periods and may cause revenues and operating results to vary significantly in future periods.

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

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

potential products based on changes in regulatory policy for product approval during the period of product development and regulatory agency review. If our Ibis T5000 Biosensor System is considered a medical device, after gaining market approval from the FDA, our Ibis T5000 Biosensor System may be subject to ongoing FDA requirements governing the labeling, packaging, storage, advertising, promotion, recordkeeping and reporting of safety and other post-market information.

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

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

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 March 31, 2007. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 2007.

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

Not applicable

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

Issuer Purchases of 5¹¤₂% Convertible Subordinated Notes due 2009

Period	Total principal amount purchased(1)	Average price paid per $1,000 principal amount	Total principal amount purchased as part of publicly announced plans or programs	Maximum number of principal amount that may yet be purchased under the plans or programs
January 1, 2007 to January 31, 2007	$ 44,175,000	$ 1,017	—	—(2)
February 1, 2007 to February 28, 2007	—	—	—	—
March 1, 2007 to March 31, 2007	—	—	—	—
Total	$ 44,175,000			

(1) In January 2007, through privately negotiated transactions, we repurchased $44,175,000 aggregate principal amount of our 5 ¹¤₂% convertible subordinated notes due 2009. The average price paid per $1,000 principal amount reflected above does not include the interest on the notes that was accrued but unpaid as of the repurchase date.
(2) In May 2007, we voluntarily redeemed all of the remaining outstanding 5 ¹¤₂% convertible subordinated notes due 2009, pursuant to Isis' optional redemption under paragraph 6 of the convertible subordinated notes. The redemption price was $1,015.71 per $1,000 principal amount outstanding, plus $1.375 in accrued but unpaid interest per $1,000 principal amount outstanding.

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

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

Not applicable

ITEM 5. OTHER INFORMATION

Not applicable

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	License Agreement between the Registrant and Atlantic Healthcare (UK) Limited dated March 7, 2007 (with certain confidential information deleted).
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)	May 10, 2007
/s/ B. Lynne Parshall B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary	

	(Principal financial and accounting officer)	May 10, 2007

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R §§ 200.80(b)4, AND 240.24b-2

LICENSE AGREEMENT

THIS LICENSE AGREEMENT is made and entered into effective as of March 7, 2007 (the "Effective Date"), by and between **Atlantic Healthcare (UK) Limited** (registered number 6025726), whose registered office is MoFo Notices Limited, 7th Floor, City Point, One Ropemaker Street, London EC2Y 9AW (proposed to be renamed [***] Limited) ("Atlantic") and **Isis Pharmaceuticals, Inc.**, having principal offices at 1896 Rutherford Road, Carlsbad, CA 92008 ("Isis"). Atlantic and Isis each may be referred to herein individually as a "Party," or collectively as the "Parties."

WHEREAS, Isis wishes to license to Atlantic the drug known as Alicaforsen (also known as ISIS 2302) so that Atlantic may develop and commercialize Alicaforsen Products, on the terms set forth below;

WHEREAS, Isis wishes to collaborate with Atlantic to discover, develop, and commercialize Second Generation ICAM-1 Products (as defined below);

WHEREAS, Isis is willing to grant Atlantic a license to develop and commercialize Second Generation ICAM-1 Products on the terms set out below;

NOW, THEREFORE, the Parties do hereby agree as follows:

ARTICLE 1 - - DEFINITIONS

Capitalized terms used in this Agreement and not otherwise defined herein have the meanings set forth in Appendix 1.

ARTICLE 2 - -
ALICAFORSEN GRANT OF RIGHTS

Section 2.1 **Alicaforsen License Grant.**

2.1.1 Subject to the terms and conditions of this Agreement, Isis hereby grants to Atlantic:

(i) an exclusive, worldwide license under the Alicaforsen Patents and the ICAM-1 Specific Patents solely to develop, make, have made, use, sell, offer for sale, have sold and import Alicaforsen API and Alicaforsen Products. The license granted to Atlantic under this Section 2.1.1(i) is sublicensable only in connection with a license of rights to an Alicaforsen Product to a Third Party for the continued development, manufacture and commercialization of that Alicaforsen Product in accordance with the terms of this Agreement; and

(ii) a non-exclusive, worldwide license under the Excluded Manufacturing IP solely to make and have made Alicaforsen API. The license granted to Atlantic under this Section 2.1.1(ii) is sublicensable to a Third Party for the manufacture of Alicaforsen API in accordance with the terms of this Agreement.

*** CONFIDENTIAL TREATMENT REQUESTED

2.1.2 The Parties agree that Atlantic shall have no right to exercise the license right granted to it under Section 2.1.1(ii) to make and have made Alicaforsen API unless and until it is permitted to do so under the terms of the Manufacturing Agreement.

Section 2.2 **Data Transfer**.

2.2.1 Promptly after the Effective Date, Isis will transfer and assign to Atlantic all of Isis' right, title and interest in and to (i) the Regulatory Documentation, data, results and information related to testing and studies of Alicaforsen (including clinical data, analytical test results and non-clinical pharmacology and safety data) in the possession of Isis on the Effective Date to the extent such data, results and/or information is necessary for the continued development and commercialization of Alicaforsen Products ("Isis Data"), and (ii) the know how which is owned by or licensed to Isis at the Effective Date that relates to the formulation of Alicaforsen Product from Alicaforsen API, *but excluding* the Excluded Manufacturing IP (the "Isis Manufacturing Know How").

ARTICLE 3 -
ALICAFORSEN PRODUCT DEVELOPMENT

Section 3.1 **Development/Commercialization/Regulatory Responsibilities.** Unless Isis exercises its reversion rights under Section 11.2, Atlantic is fully responsible for the continued development and commercialization of Products and undertakes to Isis to use Commercially Reasonable Efforts to develop Products for all commercially reasonable indications, including Alicaforsen Products for the treatment of pouchitis and to make its First Commercial Sale of an Alicaforsen Product for the treatment of pouchitis in the USA as soon as practicable. Atlantic hereby assumes all regulatory responsibilities in connection with Products, including sole responsibility for all Regulatory Documentation and for obtaining all Regulatory Approvals. Atlantic will comply with all Applicable Laws in connection with the development and commercialization of Products.

Section 3.2 **Joint Development Committee.**

3.2.1 To promote the successful development of the Products, the Parties will establish a Joint Development Committee (the "JDC") which will be comprised of one Isis representative and one or more representatives of Atlantic ("Committee Members"). A Party may replace any of its Committee Member(s) by notice to the other Party. Each Committee Member shall be appropriately qualified and experienced in order to make a meaningful contribution to JDC meetings. The purpose of the JDC is to provide a forum for the Parties to share information and knowledge on the on-going research and development of the Alicaforsen Products, including sharing scientific direction and data, discussing the current development and regulatory status of Alicaforsen Products, discussing regulatory or quality assurance issues in relation to the Alicaforsen API and coordinating the conduct of the Second Generation ICAM-1 Research Program in accordance with the Agreement. The JDC shall conduct its discussions in good faith with a view to operating to the mutual benefit of the and in furtherance of the successful marketing of Alicaforsen Products. The JDC shall meet at Isis' corporate offices located in Carlsbad, California, USA where such meeting is not held by video-conference or telephone conference, as often as the Committee Members may determine but in any event not

less than once per calendar quarter. Each JDC meeting shall be chaired by a Committee Member nominated by Atlantic.

3.2.2 The JDC will continue in existence for three years after the Effective Date or until completion of the Second Generation ICAM-1 Research Program, which ever is the later, subject to extension by mutual agreement of the Parties.

Section 3.3 **Safety Database**.

3.3.1 Isis maintains a database that includes information regarding the tolerability of its drug compounds, individually and as a class, including information discovered during pre-clinical and clinical development (the "Isis Database"). In an effort to maximize understanding of the safety profile and pharmacokinetics of Isis compounds, Atlantic will cooperate in connection with populating the Isis Database. Atlantic will promptly provide Isis with copies of toxicology, pharmacokinetic and serious adverse event reports related to each Alicaforsen Product. In addition, in connection with any reported serious adverse event, Atlantic will provide Isis (promptly following such event and prior to any communication with a Regulatory Authority or ethics committee) in a mutually acceptable format, the following patient data where it is reasonably available to Atlantic once informed of a serious adverse event and any other data Atlantic reasonably deems relevant to the Isis Database: (a) basic statistics (including age, race, gender, weight, height); (b) medical history; (c) concurrent medication usage; (d) particulars of the event (verbatim term, MedDRA term & system organ class, onset date, resolution date, relation to Alicaforsen Product, severity/seriousness, outcome); (e) dosing history (dates, quantity of Alicaforsen Product administered, method of administration); (f) chemistry and hematology lab tests; and (g) ocular pressure. For clarity, Atlantic shall be responsible for all safety and/or pharmacovigilance matters relating to or arising from the development and commercialization of the Alicaforsen Products and for making all adverse event reports to the relevant Regulatory Authorities at the times and in the manner it deems appropriate to comply with all Applicable Laws.

Section 3.4 **Reports.** Atlantic agrees to keep Isis informed with respect to activities and progress with the further development and commercialization of Alicaforsen Products, and agrees to provide to the JDC every six months a summary of such activities and progress.

Section 3.5 **Supply of Existing Alicaforsen API.**

3.5.1 Isis agrees to supply Atlantic with a quantity of Alicaforsen API that is in Isis' possession as of the Effective Date, reasonably sufficient to obtain Regulatory Approval for an Alicaforsen Product for pouchitis (but not to exceed [***] kg) in the USA [***], in accordance with a clinical trial program designed by Atlantic and discussed by the JDC.

3.5.2 Atlantic and Isis agree that, to the extent available from the stocks of Alicaforsen API in Isis' possession as of the Effective Date, any other quantities of Alicaforsen API required by Atlantic for the development of Alicaforsen Product may be purchased from Isis in a minimum order size of [***] kg at a cost of [***] Dollars ($[***]) per gram until such stocks have been exhausted; once such existing stocks of Alicaforsen API with greater than [***]

*** CONFIDENTIAL TREATMENT REQUESTED

months of shelf life have been exhausted, additional quantities of Alicaforsen API may be acquired from Isis on the terms of Section 3.6.

3.5.3 All Alicaforsen API ordered by Atlantic pursuant to Section 3.5 will be shipped by Isis to Atlantic, EXW (Incoterms 2000) Isis' premises, to the destination specified in writing by Atlantic. All transportation and insurance costs are the sole responsibility of Atlantic. Isis warrants that each such amount of Alicaforsen API supplied by Isis pursuant to Section 3.5; (i) will have been manufactured in accordance with cGMP, (ii) meets the specification for Alicaforsen API set out in the Regulatory Documentation existing at the Effective Date, (iii) have at least [***] months shelf life remaining when delivered, and will be accompanied by a certificate of analysis.

3.5.4 The Parties agree that any supply of Alicaforsen API under this Section 3.5 will be subject to and in accordance with the terms of the Manufacturing Agreement (as defined below).

Section 3.6 **Commercial Supply and Manufacturing of Alicaforsen API.**

3.6.1 Following the Effective Date, at Atlantic's election, Isis and Atlantic will negotiate in good faith, agree and execute a separate written agreement for the commercial supply and manufacture of Alicaforsen API by Isis for Atlantic (the "Manufacturing Agreement") such Manufacturing Agreement to be entered into within [***] of the Effective Date. Such Alicaforsen API will be manufactured in accordance with cGMP, applicable Alicaforsen API specifications, and the terms and conditions of the Manufacturing Agreement, which will include, among other standard commercial terms, Isis' agreement to maintain a drug master file for Alicaforsen API ("DMF") and Atlantic's right to reference the DMF in its Regulatory Documentation.

Should: (a) a Regulatory Authority in a particular jurisdiction in which Isis has not filed a DMF, or (b) a Regulatory Authority which does not allow cross-referencing to an existing DMF, request information regarding Alicaforsen API and its manufacture contained in a DMF somewhere in the world, Isis undertakes to (i) provide such information directly on behalf of Atlantic to the applicable Regulatory Authority, or if not legally possible (ii) consult with Atlantic in good faith regarding the appropriate response to such inquiry and to give Atlantic (and its relevant sub-licensee(s)) reasonable assistance with answering that Regulatory Authority's questions, save that should a Regulatory Authority request Isis's proprietary information relating to the Alicaforsen API or its manufacture outside of the definition of Isis Manufacturing Know-How Isis shall not be obliged to share such information with Atlantic (or its relevant sub-licensee(s)) and shall respond directly to the Regulatory Authority on Atlantic's or the relevant sublicensee's behalf. Notwithstanding Section 2.1.1 and 2.2.1 above, while Isis is manufacturing Alicaforsen API for Atlantic under the Manufacturing Agreement, Isis will transfer, at Atlantic's written request and subject to the confidentiality obligations under Article 8, analytical methods within Excluded Manufacturing IP necessary to properly characterize and release the Alicaforsen API.

3.6.2 Atlantic agrees that a minimum order size of [***] kg at a price of [***] Dollars ($[***]) per gram will apply to all purchases of Alicaforsen API under the Manufacturing Agreement.

*** CONFIDENTIAL TREATMENT REQUESTED

3.6.3 Isis and Atlantic agree that Atlantic shall only be permitted to exercise its license rights under Section 2.1.1(ii) to manufacture Alicaforsen API in the event either that Isis is unable to supply Atlantic with its requirements of Alicaforsen API for [***] successive calendar quarters or that Isis fails to supply Atlantic with Alicaforsen API that meets the agreed specification therefor for [***] successive calendar quarters or because Atlantic is otherwise entitled to terminate the Manufacturing Agreement for cause and there is not another available supplier who can produce Alicaforsen API without access to the Excluded Manufacturing IP. For clarity such permission shall not arise simply by virtue of expiration of either this Agreement or the Manufacturing Agreement.

Section 3.7 **Product Manufacturing Responsibility.** Except as otherwise provided in this Agreement, Atlantic acknowledges and agrees that it is solely responsible for the manufacturing of Alicaforsen Product, including management of the overall manufacturing strategy and tactics, formulation, contract manufacturer selection for finished Product, associated audits, and stability testing.

ARTICLE 4 - - SECOND GENERATION ICAM-1 PRODUCTS

Section 4.1 **Second Generation ICAM-1 ASO Drug Candidate License.**

4.1.1 Candidate Pool. Immediately following receipt of a notice from Atlantic requesting Isis to commence the work (such notice to be given within [***] of the grant of Regulatory Approval in the USA of an Alicaforsen Product for the treatment of pouchitis, *but* in no event will such notice be given later than [***] after the Effective Date), Isis agrees to, at its sole cost and expense, commence *in vitro* screening in accordance with a written work plan to be mutually agreed upon by both Parties (the "Work Plan"), to attempt to discover between [***] and [***] Second Generation ICAM-1 ASO Drug Candidates (the "Candidate Pool") (the "Second Generation ICAM-1 Research Program"). Isis agrees to use Commercially Reasonable Efforts and the Quality Standard when discharging any of its obligations under the Work Plan and will keep or cause to be kept written laboratory notebooks and other records and reports of its progress with the Work Plan and its activities under the Work Plan in sufficient detail and in a good scientific manner for all purposes including patent purposes. Isis will report its progress with the Second Generation ICAM-1 Research Program to the JDC.

4.1.2 Candidate Selection. Isis will provide Atlantic with written notice and any supporting *in vitro* data at such time as the Candidate Pool is available for consideration by Atlantic (the "Notice"). Atlantic must notify Isis, in writing within [***] following the Notice, that (i) it has elected to develop a Second Generation ICAM-1 Product and nominate one of the candidates from the Candidate Pool as the lead Second Generation ICAM-1 ASO Drug Candidate, and (ii) it agrees to promptly establish, in good faith, a significant development program pursuant to a written development plan to be set by Atlantic (the "Second Generation Development Plan"). If Atlantic fails to elect to develop a Second Generation ICAM-1 Product using the Second Generation ICAM-1 ASO Drug Candidates under this Article 4 neither Isis nor Atlantic will have any further obligations under this Agreement with regard to the Candidate Pool, any Second Generation ICAM-1 ASO Drug Candidate or any Second Generation ICAM-1 Product. If, despite Isis' Commercially Reasonable Efforts, Isis fails to produce a Candidate

*** CONFIDENTIAL TREATMENT REQUESTED

Pool that is reasonably acceptable to Atlantic, neither Isis nor Atlantic will, for a period of three years following the date of the Notice, take any steps to research another anti-sense oligonucleotide drug candidate designed to directly inhibit ICAM-1 without the prior consent of the other Party.

4.1.3 License Grant. If Atlantic so informs Isis of such election and agreement under Section 4.1.2 above, then Isis will grant to Atlantic, subject to and upon the same terms and conditions of this Agreement:

(x) an exclusive license under the ICAM-1 Specific Patents solely to develop, make, have made, use, sell, offer for sale, have sold and import Second Generation ICAM-1 ASO Drug Candidates and Second Generation ICAM-1 Products;

(y) an exclusive license under the Second Generation ICAM-1 Product-Specific Patents solely to develop, make, have made, use, sell, offer for sale, have sold and import Second Generation ICAM-1 ASO Drug Candidates and Second Generation ICAM-1 Products; and

(z) a non-exclusive worldwide license under the Isis Core Technology Patents solely to develop, make, have made, use, sell, offer for sale, have sold and import Second Generation ICAM-1 ASO Drug Candidates and Second Generation ICAM-1 Products.

The licenses granted to Atlantic under this Section 4.1.3 are sublicensable only in connection with a license of a Second Generation ICAM-1 Product to a Third Party for the continued development and commercialization of Second Generation ICAM-1 Products in accordance with the terms of this Agreement.

4.1.4 Data Transfer. In addition, promptly following Isis' license grants to Atlantic under Section 4.1.3 above, Isis will transfer and assign to Atlantic all of Isis' right, title and interest in and to all data, results, and information related to testing and studies of the Second Generation ICAM-1 ASO Drug Candidates (including analytical test results and non-clinical pharmacology and safety data) in the possession of Isis (the "Second Generation Isis Data") to the extent such data, results and/or information is necessary for the continued development and commercialization of Second Generation ICAM-1 Products; *but excluding* any Excluded Isis IP.

4.1.5 Should Atlantic elect to develop Second Generation ICAM-1 Products pursuant to Section 4.1.2, Atlantic shall be fully responsible for the development and commercialization of Second Generation ICAM-1 Products and undertakes to use Commercially Reasonable Efforts to develop a Second Generation ICAM-1 Product and to make its First Commercial Sale of a Second Generation ICAM-1 Product in a Major Market as soon as practicable following its election, in accordance with Section 3.1 above. Atlantic will develop such Products on the terms set out in Section 3.3 and Section 3.4. Should Atlantic elect to have Second Generation ICAM-1 ASO Drug Candidate manufactured by Isis, Isis and Atlantic will conduct a negotiation in good faith, agree and execute a separate written agreement for the supply of Second Generation ICAM-1 ASO Drug Candidates for use in the development and

commercialization of Second Generation ICAM-1 Products within [***] of Atlantic notifying Isis that it wishes Isis to so supply.

Section 4.2 **Exclusive Partner.**

4.2.1 For a period of [***] following the Effective Date or until the [***] period following the delivery of the Notice set out in Section 4.1.2 has expired (which ever is the later) (the "Period"), and thereafter during the Term of this Agreement if Atlantic elects to develop a Second Generation ICAM-1 Product under Section 4.1.2 within the Period, Isis will not develop or commercialize itself, and will not permit or grant any license under the Alicaforsen Patents, ICAM-1 Specific Patents, Second Generation ICAM-1 Product-Specific or Isis Core Technology Patents to a Third Party to develop or commercialize, any antisense drug compound designed to directly inhibit ICAM-1. Notwithstanding the foregoing, Isis retains the right to use antisense compounds modulating ICAM-1 or to transfer such antisense compounds to Third Parties for non-commercial target validation purposes, and such activities will not be interpreted as a breach of this Agreement. Isis' obligations under this Section 4.2.1 will automatically terminate in the event of a Discontinuance.

4.2.2 To avoid confusion in the marketplace, during the term of this Agreement, Atlantic agrees not to develop or commercialize any product designed to directly inhibit ICAM-1 other than the Product(s), and will not permit or grant any license under the Alicaforsen Patents, ICAM-1 Specific Patents, or Second Generation ICAM-1 Product-Specific Patents to a Third Party to develop or commercialize any such product other than the Product(s).

ARTICLE 5 - - BONA FIDE THIRD PARTY LICENSE OFFERS

Section 5.1 **Bona Fide Third Party License Offers.**

5.1.1 If, following the earlier to occur of a [***] or [***], a Third Party makes an offer to Atlantic to take a Sublicense under the Alicaforsen Patents, ICAM-1 Specific Patents, Second Generation ICAM-1 Product-Specific Patents and/or the Isis Core Technology Patents in order to develop and commercialize a Product in [***] that Atlantic is developing for an alternative indication, for an indication for which Atlantic is not then developing a Product, Atlantic will promptly inform Isis of its receipt of this offer and whether it considers this offer to be a bona fide offer on commercial terms which are reasonably acceptable to Atlantic. If Atlantic considers the offer to be a bona fide offer on commercial terms which are reasonably acceptable to Atlantic, Atlantic will, in good faith, consider such offer and within [***] from receipt of such a bona fide offer Atlantic will either:

(i) notify Isis that it reasonably believes that it is unlikely that Atlantic will, within the period of [***] from the date of receipt of such offer, initiate development of a Product for the indication in question itself; in which case it will then promptly commence good faith negotiation of a definitive written license agreement with such Third Party pursuant to which the Third Party will be granted the rights under the Alicaforsen Patents, ICAM-1 Specific Patents, Second Generation ICAM-1 Product-Specific Patents and/or the Isis Core

*** CONFIDENTIAL TREATMENT REQUESTED

Technology Patents (as applicable) to develop, make and commercialize a Product in [***] for the indication in question; or

(ii) notify Isis that it reasonably believes that it is likely that Atlantic will, within the period of [***] from the date of receipt of such offer, initiate development of a Product for the indication in question itself; in which case it may decline such Third Party licensing offer and, if it declines such offer, will use its Commercially Reasonable Efforts to initiate development of a Product in [***] for the indication in question within [***] of the date of this notice.

5.1.2 If a Third Party makes an offer to Atlantic to take a Sublicense under the Alicaforsen Patents, ICAM-1 Specific Patents, Second Generation ICAM-1 Product-Specific Patents and/or the Isis Core Technology Patents in order to develop and commercialize a Product in [***] for an indication for which Atlantic is not then developing a Product Atlantic will promptly inform Isis of its receipt of this offer and whether it considers this offer to be a bona fide offer on commercial terms which are reasonably acceptable to Atlantic. If Atlantic considers the offer to be a bona fide offer on commercial terms which are reasonably acceptable to Atlantic, Atlantic will, in good faith, consider such offer and within [***] from receipt of such a bona fide offer Atlantic will either:

(i) notify Isis that it reasonably believes that it is unlikely that Atlantic will, within the period of [***] from the date of receipt of such offer, initiate [***]; in which case it will promptly commence good faith negotiation of a definitive written license agreement with such Third Party pursuant to which the Third Party will be granted the rights under the Alicaforsen Patents, ICAM-1 Specific Patents, Second Generation ICAM-1 Product-Specific Patents and/or the Isis Core Technology Patents (as applicable) to develop, make and commercialize a Product in [***] for the indication in question; or

(ii) notify Isis that it reasonably believes that it is likely that Atlantic will, within the period of [***] from the date of receipt of such offer, initiate [***]; in which case it may decline such Third Party licensing offer and if it declines such offer will [***] of the date of this notice.

ARTICLE 6 - - FINANCIAL PROVISIONS

Section 6.1 **Up-Front Payment by Atlantic.**

6.1.1 Upon the execution of the Subscription and Share Exchange Agreement (defined below), Atlantic will pay an up-front license fee of $[***] to Isis which shall be satisfied (in full) by the issue to Isis of [***] ordinary shares in Atlantic's share capital, which shall then be immediately exchanged for [***] ordinary shares in Atlantic Healthcare's share capital pursuant to the terms of the subscription and share exchange agreement (the "**Subscription and Share Exchange Agreement**"), which will be executed by and between Isis,

*** CONFIDENTIAL TREATMENT REQUESTED

Atlantic, and Atlantic Healthcare on or before March 16, 2007 (the "SSEA Execution Date"); *provided, however,*

(a) if at any time during the Anti-Dilution Protection Period (to be defined in the Subscription and Share Exchange Agreement) Atlantic Healthcare issues any shares in the capital of Atlantic Healthcare to current shareholders (determined by reference to the date of this Agreement) at a subscription price per share of less than £[***], then Isis shall have the right to subscribe for additional AH Shares (to be defined in the Subscription and Share Exchange Agreement) at [***] in the share capital of Atlantic Healthcare (for which purpose all shares in Atlantic Healthcare previously issued to Isis pursuant to this Agreement shall be deemed held by Isis, irrespective of whether Isis remains the registered holder thereof) had such new shares so issued to existing shareholders [***], as further provided for in the Subscription and Share Exchange Agreement; and

(b) if at any time during the Anti-Dilution Protection Period Atlantic Healthcare issues any shares in the capital of Atlantic Healthcare to [***] (to be defined in the Subscription and Share Exchange Agreement) and/or [***] (to be defined in the Subscription and Share Exchange Agreement) beyond [***] shares on terms not offered to other shareholders (including Isis), then Isis will have the right to participate on the same terms as [***] (as the case may be) so as to maintain its pro-rata shareholding in Atlantic Healthcare (for which purpose all shares in Atlantic Healthcare previously issued to Isis pursuant to this Agreement shall be deemed held by Isis, irrespective of whether Isis remains the registered holder thereof) as further provided for in the Subscription and Share Exchange Agreement.

6.1.2 In no event will Atlantic issue shares to Isis that exceed the Equity Cap.

6.1.3 If the Subscription and Share Exchange Agreement is not executed by Isis, Atlantic, and Atlantic Healthcare on or before [***], this Agreement will automatically terminate without any liability to either Party.

Section 6.2 **Milestone Payments by Atlantic.**

6.2.1 Atlantic will pay to Isis the relevant milestone payment in cash or in an equivalent amount of Atlantic Equity Securities (subject to the written consent of Atlantic Healthcare Limited and in accordance with the terms of the Subscription and Share Exchange Agreement), at Atlantic's sole discretion, not more than 60 days after achievement by Atlantic, its Affiliates or a sublicensee, of each of the applicable events, as follows:

Event	Payment
[***]	US $[***]
[***]	US $[***]

*** CONFIDENTIAL TREATMENT REQUESTED

6.2.2 Notwithstanding the foregoing, in no event will Atlantic issue Atlantic Equity Securities to Isis that exceed the Equity Cap. To the extent any milestone payment of Atlantic Equity Securities will cause Isis' aggregate equity ownership in Atlantic to exceed the Equity Cap, Atlantic will issue to Isis only the number of shares that will maintain such Equity Cap, and will pay Isis the remainder of such milestone payment in cash. For purposes

of this Section 6.2, the term "Atlantic Equity Securities" means (a) if Atlantic has a class of stock (x) registered under Section 12(b) or 12(g) of the Securities Exchange Act of 1934 and that is publicly traded on a major US exchange such as the NYSE or NASDAQ, or (y) traded on a major European exchange such as Deutsche Börse or the London Stock Exchange, such publicly traded common stock of Atlantic, the value of which will be determined [***] by the average closing price for the 15 trading days immediately preceding the date the particular milestone event referenced in this Section 6.2 is achieved; or (b) if Atlantic does not have a class of publicly traded stock, the equity securities of Atlantic issued in its most recent venture capital financing occurring prior to the date the particular milestone event referenced in this Section 6.2 is achieved, which will be issued to Isis at the same price per share and with the same rights, preferences and privileges as provided to the other investors in such financing.

Section 6.3 **Sublicense Revenue.**

6.3.1 In the event that Atlantic enters into a Sublicense Atlantic will pay Isis [***]% of the Sublicense Revenue (which does not include royalties on Net Sales) from such sublicensing of any Product by Atlantic and its Affiliates.

6.3.2 Any payment to Isis for its portion of Sublicensing Revenue due under this Section 6.3 will be due within 30 days of Atlantic receiving such Sublicensing Revenue.

Section 6.4 **Royalty Payments by Atlantic.**

6.4.1 For any Product sold by Atlantic or its Affiliates, in consideration of Isis' collaborative efforts and the licenses granted hereunder, Atlantic will pay Isis royalties on Net Sales of each Product in accordance with the following table.

Cumulative Net Sales	Royalty Rate (Alicaforsen Products)	Royalty Rate (Second Generation ICAM-1 Products)
Less than US $[***]	[***]%	[***]%
US $[***] to US $[***]	[***]%	[***]%
Above US $[***]	[***]%	[***]%

*** CONFIDENTIAL TREATMENT REQUESTED

6.4.2 For any Products sold pursuant to a Sublicense, in consideration of Isis' collaborative efforts and the licenses granted hereunder, Atlantic will pay Isis royalties on Net Sales as follows:

6.4.2.1 For Alicaforsen Products sold for [***] indication, Atlantic will pay Isis royalties on Net Sales of each Product equal to the greater of (i) [***]% of the royalty Atlantic is entitled to receive under such Sublicense, or (ii) [***]% of Net Sales; and

6.4.2.2 For Products sold pursuant to a Sublicense of (i) a Second Generation ICAM-1 Product, or (ii) an Alicaforsen Product that is not indicated for [***], Atlantic will pay Isis royalties on Net Sales of each Product as follows:

(a) If the royalty to Atlantic is less than or equal to [***]% of Net Sales, then Isis receives [***]% of Net Sales of each Product;

(b) If the royalty to Atlantic is greater than [***]% but less than [***]% of Net Sales, then Isis receives [***]% of Net Sales of each Product; or

(c) If the royalty to Atlantic is equal to or greater than [***]% of Net Sales, then Isis receives [***]% of Net Sales of each Product.

6.4.3 Isis will be responsible for payment of any Third Party royalty obligations related to Product that exist as of the Effective Date ("Existing Royalties"), including (i) with respect to the Alicaforsen Product, Existing Royalties due under the agreement with [***] dated [***], and (ii) with respect to Second Generation ICAM-1 Products, Existing Royalties due under the agreement with [***] dated [***] and the agreement with [***] dated [***]. Atlantic will be responsible for all other Third Party royalties, fees and milestones that may arise related to the development or commercialization of Products.

Section 6.5 **Term; Timing of Royalty Payments.** Atlantic's obligation to pay royalties on each Product will expire on a county-by-country basis as follows:

6.5.1 With respect to Alicaforsen Products, Atlantic's obligation to pay royalties on each Product will expire on a county-by-country basis upon the later of: (i) [***] years from the date of First Commercial Sale of such Product in such country of sale, or (ii) the expiration of the last to expire Valid Claim of Alicaforsen Patents and ICAM-1 Specific Patents covering the making, using, or selling of such Alicaforsen Product in the country of sale, or (iii) the expiration of the last to expire Valid Composition of Matter Claim within Alicaforsen Patents or ICAM-1 Specific Patents in the country of manufacture of that Alicaforsen Product.

6.5.2 With respect to Second Generation ICAM-1 Products, Atlantic's obligation to pay royalties on each Second Generation ICAM-1 Product will expire on a county-by-country basis upon the later of: (i) [***] years from the date of First Commercial Sale of such Second Generation ICAM-1 Product in such country of sale, or (ii) the expiration of the last to expire Valid Claim of ICAM-1 Specific Patents and Second Generation ICAM-1 Product Specific Patents covering the making, using, or selling of such Second Generation ICAM-1

*** CONFIDENTIAL TREATMENT REQUESTED

Product in the country of sale, or (iii) the expiration of the last to expire Valid Composition of Matter Claim within ICAM-1 Specific Patents and Second Generation ICAM-1 Product Specific Patents in the country of manufacture of that Second Generation ICAM-1 Product.

6.5.3 The royalties due under Section 6.4 will become due and payable: (i) within 30 days of each respective Royalty Due Date with respect to Net Sales received by Atlantic or its Affiliates, and (ii) with respect to royalties due under Sublicenses, within 30 days of Atlantic itself receiving the royalty payments due from its sublicensees. In each case royalties will be calculated in respect of the Net Sales in the calendar quarter immediately preceding the applicable Royalty Due Date.

Section 6.6 **Payment Method.** Any amounts due to Isis under this Agreement will be paid in U.S. dollars, by wire transfer in immediately available funds to an account designated by Isis. Any payments or portions thereof due hereunder which are not paid on the date such payments are due under this Agreement and the payment is not in dispute between the Parties, or if disputed the dispute has not been resolved, will bear interest at a rate equal to the prime rate as published in *The Wall Street Journal*, Eastern Edition, on the first day of each calendar quarter in which such payments are overdue, plus 1% calculated on the number of days such payment is delinquent, compounded monthly.

Section 6.7 **Currency; Foreign Payments.** If any currency conversion will be required in connection with any payment hereunder, such conversion will be made by using the exchange rate for the purchase of U.S. dollars as published in *The Wall Street Journal*, Eastern Edition, on the last business day of the calendar quarter to which such payments relate. If at any time legal restrictions prevent the prompt remittance of any payments in any jurisdiction, Atlantic may notify Isis and make such payments by depositing the amount thereof in local currency in a bank account or other depository in such country in the name of Isis or its designee, and Atlantic will have no further obligations under this Agreement with respect thereto. All payments under this Agreement shall be made free and clear and without any set off, deduction, withholding or deferment in respect of any taxes unless required by law or practice of any relevant governmental authority. The Parties shall co-operate to minimize any deduction or withholding in relation to any payments pursuant to this Agreement.

Section 6.8 **Records Retention; Audit.**

6.8.1 **Record Retention.** Atlantic will maintain (and will ensure that its Affiliates and sublicensees will maintain) complete and accurate books, records and accounts that fairly reflect Net Sales with respect to each Product, in each case in sufficient detail to confirm the accuracy of any payments required hereunder and in accordance with IFRS, which books, records and accounts will be retained by Atlantic, its Affiliates or sublicensees (as applicable) for the later of (i) 5 years after the end of the period to which such books, records and accounts pertain, and (ii) the expiration of the applicable tax statute of limitations (or any extensions thereof), or for such longer period as may be required by Applicable Law.

6.8.2 **Audit.** Isis will have the right to have an independent certified public accounting firm of nationally recognized standing, reasonably acceptable to Atlantic, have access during normal business hours, and upon reasonable prior written notice, to Atlantic's records

(and its Affiliates and sublicensees) as may be reasonably necessary to verify the accuracy of Net Sales, Sublicense Revenue, as applicable, for any calendar quarter or calendar year ending not more than [***] months prior to the date of such request; *provided, however*, that Isis will not have the right to conduct more than one such audit in any Calendar Year except as provided below. The accounting firm will enter into appropriate obligations with Atlantic to treat all information it receives during its inspection as confidential. The accounting firm shall disclose to Isis only whether the reported Net Sales and Sublicense Revenue are correct and details of any discrepancies but no other information shall be disclosed to Isis. Isis will bear the cost of such audit unless the audit reveals a variance of more than [***]% from the reported results, in which case Atlantic will bear the cost of the audit.

6.8.3 **Payment of Additional Amounts.** If, based on the results of such audit, additional payments are owed by either party to the other under this Agreement, the party due to make a payment will make such additional payments, with interest as set forth in Section 6.6, within 30 days after the date on which such accounting firm's written report is delivered to such Party.

6.8.4 **Confidentiality.** Isis will treat the financial information reported to it under Section 6.8.2 in accordance with the confidentiality provisions of Article 8; *provided, however,* that Isis may provide Third Parties to which Isis owes Existing Royalties on Products such information if it exercises its audit rights concerning the Products against Isis and provided such Third Party is bound to keep such information confidential.

ARTICLE 7 - -
PRESS RELEASES & PUBLICATIONS

Section 7.1 Press Releases

7.1.1 Press Releases - Generally. Each provision of this Section 7.1.1 is subject to Section 7.1.2 below. Press releases or other similar public communication by either Party relating to this Agreement, will be approved in advance by the other Party, which approval will not be unreasonably withheld or delayed, except for those communications required by Applicable Law, which are Authorized Disclosures or disclosures of information for which consent has previously been obtained, and information of a similar nature to that which has been previously disclosed publicly with respect to this Agreement, each of which will not require advance approval, but will be provided to the other Party as soon as practicable after the release or communication thereof.

*** CONFIDENTIAL TREATMENT REQUESTED

7.1.2 Press Releases – Product Safety/Efficacy. Each Party will immediately notify (and, if possible, provide as much advance notice as possible to) the other of any event materially related to Products (including any regulatory approval) so that the Parties may analyze the need to or desirability of publicly disclosing or reporting such event. Notwithstanding Section 7.1.1 above, any press release or other similar public communication by either Party related a Product's efficacy or safety data and/or results, will be submitted to the other Party for review and approval at least 72 hours in advance of such proposed public disclosure, which approval will not be unreasonably withheld or delayed.

Section 7.2 **Publications.** Each provision of this Section 7.2 is subject to Section 7.1.2 above. At least [***] days prior to a Party's submission of any material related to the research or development activities hereunder for publication or presentation, the publishing Party will provide to the other Party with a draft of such material for its review and comment. The non-publishing Party will provide any comments to the publishing Party within [***] days of receipt of such materials. No publication or presentation with respect to the research or development activities hereunder will be made unless and until the non-publishing Party's comments on the proposed publication or presentation have been discussed by the Parties. If requested in writing by the non-publishing Party, the publishing Party will withhold material from submission for publication or presentation for a reasonable time to allow for the filing of a patent application.

ARTICLE 8 - - CONFIDENTIALITY

Section 8.1 **Disclosure and Use Restriction.** Except pursuant to an Authorized Disclosure, the Parties agree that, for the Term and for five years thereafter, each Party will keep completely confidential and will not publish, submit for publication or otherwise disclose, and will not use for any purpose except for the purposes contemplated by this Agreement, any Confidential Information received from the other Party.

ARTICLE 9 - - INTELLECTUAL PROPERTY

Section 9.1 **Prosecution of Patents.**

9.1.1 Solely Owned Patents. With the exception of the Alicaforsen Patents, the ICAM-1 Specific Patents, and the Second Generation ICAM-1 Product-Specific Patents, which are addressed in Sections 9.1.2 and 9.1.3 below, each Party will have the sole right, at its cost and expense and at its sole discretion, to obtain, prosecute, maintain and enforce throughout the world any Patents solely owned or Controlled by such Party, including with respect to Isis, the Isis Core Technology Patents.

9.1.2 Alicaforsen Patents and ICAM-1 Specific Patents. Subject to Section 9.1.4 below, Isis will have the sole obligation at its expense, to obtain, prosecute and maintain the Alicaforsen Patents and the ICAM-1 Specific Patents in such countries as Isis is prosecuting such Patents on the Effective Date using Commercially Reasonable Efforts. For clarity, Atlantic will not have the right to review or comment on any applications or registrations to be filed by

*** CONFIDENTIAL TREATMENT REQUESTED

Isis under this Section 9.1.2, and Isis may cease prosecuting or maintaining particular applications or patents in the Alicaforsen Patents and ICAM-1 Specific Patents in selected jurisdictions, if Isis determines that it is not commercially reasonable to continue such efforts (in which case the terms of Section 9.1.4 will apply).

9.1.3 Second Generation ICAM-1 Product-Specific Patents. Subject to Section 9.1.4 below, Atlantic will have the sole obligation, at Atlantic's expense, to obtain, prosecute and maintain in such countries as are commercially appropriate the Second Generation ICAM-1 Product-Specific Patents using Commercially Reasonable Efforts. Atlantic will keep Isis informed of all Second Generation ICAM-1 Product-Specific Patent applications and registrations to be filed by Atlantic, and Isis will have the right to review and comment on such applications within the timeframes of the patent filing process and deadlines. For clarity, Atlantic may cease prosecuting or maintaining particular applications or patents in the Second Generation ICAM-1 Product-Specific Patents in selected jurisdictions, if Atlantic determines that it is not commercially reasonable to continue such efforts (in which case the terms of Section 9.1.4 will apply). Isis' review and comment rights in this Section 9.1.3 will continue so long as there is the possibility of a Discontinuance.

9.1.4 Discontinued Patents. If under Section 9.1.2 or Section 9.1.3 a Party elects to discontinue prosecution or maintenance of any particular applications or patents in the Alicaforsen Patents, the ICAM-1 Specific Patents (if applicable), or the Second Generation ICAM-1 Product-Specific Patents, as the case may be, in a selected jurisdiction, such Party will give thirty (30) days advance written notice to the other Party of any decision to cease preparation, filing, prosecution and maintenance of that Patent right (a ***"Discontinued Patent"***). In such case, the other Party may elect at its sole discretion to continue preparation, filing, prosecution or maintenance of the Discontinued Patent in the select jurisdiction at its sole expense, and thereafter such Party will own any such patent application and patents maturing therefrom and be solely responsible for all costs. In the event of a Discontinued Patent caused by Atlantic, Atlantic's exclusive licenses under Article 2 and Article 4 (if applicable) with respect to such Discontinued Patent in such jurisdiction will automatically convert into nonexclusive licenses with the financial terms set forth in Article 6 remaining intact, and Isis' obligations under Section 4.2 will terminate in such select jurisdiction solely with respect to such Discontinued Patent. The Party electing to cause a Discontinued Patent will execute such documents and perform such acts as may be reasonably necessary for the other Party to continue prosecution or maintenance of the applicable Discontinued Patent, including assigning ownership of such Patent or application. Should Atlantic elect to continue preparation, filing, prosecution and maintenance of Discontinued Patents which are Alicaforsen Patents or ICAM-1 Specific Patents, such Patents will no longer be deemed to be Alicaforsen Patents or ICAM-1 Specific Patents for the purposes of this Agreement. Notwithstanding the foregoing, Atlantic's right to continue the preparation, filing, prosecution and maintenance of a Discontinued Patent that is an ICAM-Specific Patent is limited solely to the extent such Patent claims ICAM-1.

9.1.5 Cooperation. Each Party will cooperate reasonably in the preparation, filing, prosecution, and maintenance of the Alicaforsen Patents, the ICAM-1 Specific Patents (if applicable), the Second Generation ICAM-1 Product-Specific Patents, and the other Party's Patents which cover a Product. Such cooperation includes (a) promptly executing all papers and instruments and requiring employees to execute such papers and instruments as reasonable and

appropriate so as to enable such other Party, to file, prosecute, and maintain its Patents in any country; and (b) promptly informing such other Party of matters that may affect the preparation, filing, prosecution, or maintenance of any such Patents.

9.1.6 Patent Term Extensions. The Parties agree to cooperate in an effort to avoid loss of any of the Patents forming part of Alicaforsen Patents, ICAM-1 Specific Patents or Second Generation ICAM-1 Product-Specific Patents including by executing any documents as may be reasonably required. In particular, the Parties shall cooperate with each other in obtaining patent term extension or restoration or supplemental protection certificate ("Patent Term Extensions") or their equivalents in any country and region where applicable. In particular but without limiting the foregoing Isis shall provide reasonable assistance to Atlantic, including by executing any required documents and providing any relevant patent information to Atlantic, so that Atlantic, as Regulatory Approval applicant, may deal with the applicable Regulatory Authority in connection with obtaining such Patent Term Extension.

Section 9.2 **Enforcement of Patents**

9.2.1 Rights and Procedures. If Isis or Atlantic determines that any Patent licensed hereunder is being infringed by a Third Party's activities and that such infringement could affect the exercise by the Parties of their respective rights and obligations under this Agreement, it will promptly notify the other Party in writing. Except for the Alicaforsen Patents, the ICAM-1 Specific Patents, and the Second Generation ICAM-1 Product-Specific Patents, which are discussed below, the Party controlling the Patent(s) which are allegedly being infringed will have the sole right and obligation to remove such infringement.

9.2.2 Alicaforsen Patents; ICAM-1 Specific Patents; and Second Generation ICAM-1 Product-Specific Patents. With respect to the Alicaforsen Patents, the ICAM-1 Specific Patents (if applicable and solely to the extent infringed by a Third Party with a product targeting ICAM-1), and the Second Generation ICAM-1 Product-Specific Patents, Atlantic will have the first right, but not the obligation, at Atlantic's expense, to remove such infringement. In the event that Atlantic fails to take commercially appropriate steps to remove any such infringement within 90 days following notice of such infringement, or earlier notifies Isis in writing of its intent not to take such steps, and such infringement is likely to have a material adverse effect on the Product, (i) so long as the infringement is not taking place in a Major Market and so long as Atlantic does not inform Isis that Atlantic considers, in good faith, that to take such proceeds would (x) be prejudicial to its litigation strategy in a Major Market and (y) be commercially unreasonable under the circumstances, Isis will have the right to do so at its expense, (ii) Atlantic will have the right, at its own expense, to be represented in any such action, and (iii) the exclusive license(s) granted under Article 2 and Article 4 (if applicable) that pertain to such Alicaforsen Patent, ICAM-1 Specific Patent (if applicable), or Second Generation ICAM-1 Product-Specific Patent, will automatically convert into nonexclusive licenses. Isis will have the right, at Isis's own expense, to remove infringement of the Alicaforsen Patents, ICAM-1 Specific Patents (if applicable), or Second Generation ICAM-1 Product-Specific Patents if (i) Isis is unilaterally developing and commercializing a Product pursuant to Section 11.2, or (ii) if a Third Party is infringing the ICAM-1 Specific Patents with any product that does not target ICAM-1.

(a) Cooperation. The Party not enforcing the applicable Patent will provide reasonable assistance to the other Party (at the enforcing Party's expense), including providing access to relevant documents and other evidence, making its employees available at reasonable business hours, and joining the action to the extent necessary to allow the enforcing Party to maintain the action. If Isis requests that Atlantic take action to remove infringement of an Alicaforsen Patent, ICAM-1 Specific Patent (if applicable) to the extent infringed by a Third Party with a product targeting ICAM-1, or a Second Generation ICAM-1 Product-Specific Patent, and Atlantic believes it is not commercially appropriate to take such actions, the Parties will meet and discuss in good faith such circumstances and seek to reach agreement on what appropriate steps to take to cause such infringement to end in a commercially appropriate manner.

9.2.3 Recovery. Any amounts recovered by Atlantic in connection with or as a result of any action contemplated by Section 9.2.1(a), whether by settlement or judgment, will be used to reimburse the Parties for their reasonable costs and expenses in making such recovery (which amounts will be allocated pro rata if insufficient to cover the totality of such expenses), with any remainder in excess of the reasonable costs and expenses in making such recovery will be treated as Net Sales of an Alicaforsen Product and royalties will be due in respect of such Net Sales pursuant to this Agreement. Isis will retain all amounts it recovers enforcing the Alicaforsen Patents, the ICAM-1 Specific Patents, the Second Generation ICAM-1 Product-Specific Patents, and the Isis Core Technology Patents.

ARTICLE 10 - TERM AND TERMINATION

Section 10.1 **Term.** The term of this Agreement (the "Term") commences upon the Effective Date and, unless earlier terminated in accordance with the provisions of this Article 10, will continue until the expiration of all obligations to pay royalties on all Products to Isis.

Section 10.2 **Rights in Bankruptcy or Insolvency** If either Party becomes insolvent, files a petition in bankruptcy, has such a petition filed against it, determines to file a petition in bankruptcy, or receives notice of a Third Party's intention to file an involuntary petition in bankruptcy, such Party immediately shall notify the other Party in writing. In addition to any other remedies available at law or in equity, the other Party (i.e., the non-bankrupt Party) may immediately terminate this Agreement, in whole or in part as the terminating Party may determine, upon learning of any of the foregoing events; *provided, however*, that the financial terms set forth in Article 6 above will remain in tact and will survive any such termination. The terminating Party shall provide to the other Party a written notice regarding the extent of termination. If Isis seeks to be or is involuntarily placed under the protection of the "Bankruptcy Code" (i.e., Title 11, U.S. Code) or its equivalent outside the USA, and the trustee in bankruptcy, or Isis as a debtor-in-possession, rejects this Agreement, then Atlantic hereby elects, under Section 365(n) of the Bankruptcy Code, to retain all licenses of rights to "intellectual property" (as defined under such Bankruptcy Code) granted to it under this Agreement, to the extent permitted by law. As of the commencement of a bankruptcy proceeding by or against Isis, Atlantic is entitled to a complete duplicate of all embodiments of "intellectual property" licensed to it hereunder. To the extent such embodiments are not already in Atlantic's possession as of

the commencement of a bankruptcy, Isis (or the trustee in bankruptcy) shall deliver such embodiments to Atlantic (i) upon any such commencement of a bankruptcy proceeding, unless Isis elects to continue to perform all of its obligations under this Agreement, or (ii) if not delivered under (i), then upon a rejection of this Agreement (or the equivalent) by or on behalf of Isis.

Section 10.3 **Material Breach.** Failure by a Party to comply with any of its material obligations contained herein will entitle the Party not in default to give to the defaulting Party notice specifying the nature of the material breach, requiring the defaulting Party to make good or otherwise cure such default, and stating its intention to invoke the provisions of Section 14.4 if such default is not cured. If such default is not cured within 90 days after the receipt of such notice (or, if such default cannot be cured within such 90-day period, if the Party in default does not commence actions to cure such default within such period and thereafter diligently continue such actions), the Party not in default will be entitled, without prejudice to any of its other rights conferred on it by this Agreement, to invoke the provisions of Section 14.4; provided, however, that in the event of a good faith dispute with respect to the existence of a material breach, the 90-day cure period will be stayed until such time as the dispute is resolved pursuant to Section 14.4 hereof.

Section 10.4 **Consequences of Expiration or Termination.**

10.4.1 Licenses. Upon expiration of the Term or upon termination of this Agreement in its entirety by either Party pursuant to Section 10.3, or by Isis pursuant to Section 10.2 and upon payment of all amounts owed pursuant to this Agreement, the licenses granted by Isis to Atlantic hereunder will terminate.

10.4.2 Return of Information and Materials. Upon early termination of this Agreement in its entirety by either Party pursuant to Section 10.3, or by Isis pursuant to Section 10.2, Atlantic will return all data, files, records and other materials in its possession or control relating to the Second Generation ICAM-1 Product Specific Patents or containing or comprising Isis' Confidential Information and, in each case (except one copy of which may be retained for archival purposes).

Section 10.5 **Accrued Rights; Surviving Obligations.**

10.5.1 Accrued Rights. Termination or expiration of this Agreement for any reason will be without prejudice to any rights or financial compensation that will have accrued to the benefit of a Party prior to such termination or expiration. Such termination or expiration will not relieve a Party from obligations that are expressly indicated to survive the termination or expiration of this Agreement.

10.5.2 Survival. Articles 7, 8, 9.1, 10, 11, 12, and 14, and Section 6.8 of this Agreement will survive expiration or termination of this Agreement for any reason.

ARTICLE 11
DISCONTINUED DEVELOPMENT BY ATLANTIC

Section 11.1 **Discontinuances.** In the event of a Discontinuance, Isis will have a reversion right as further described in Section 11.2.

Section 11.2 **Reversion Rights.** Following the occurrence of a Discontinuance, Isis may elect to continue to develop Product by notice in writing to Atlantic (an "Election Notice") that Isis is exercising its rights under this Section 11.2, in which case this Agreement will terminate (subject to the survival provisions set forth in Section 10.5.2). Upon receipt of an Election Notice, Atlantic will (i) grant to Isis a sublicensable, worldwide license or sublicense, as the case may be, to all Patents controlled by Atlantic solely as they are necessary to make, have made, use, sell, offer for sale, have sold and import the Product and (ii) transfer to Isis, for Isis' unlimited use, any data, results, regulatory information and files in the possession of Atlantic as of the date of the Election Notice that relate to the Product, subject to the negotiation in good faith of a reasonable royalty payable to Atlantic that represents the value of the items transferred to Isis.

ARTICLE 12 -
INDEMNIFICATION AND INSURANCE

Section 12.1 **Indemnification of Isis.** Atlantic will indemnify Isis and its Affiliates, and each of their respective directors, officers, employees and agents, and defend and hold each of them harmless, from and against any and all losses, damages, liabilities, costs and expenses (including reasonable attorneys' fees and expenses) to the extent arising from or occurring as a result of any and all liability suits, investigations, claims or demands by a Third Party (collectively, "Losses") arising from or occurring as a result of or in connection with (a) the breach of any of Atlantic's representations, warranties, or covenants contained in Article 13 below, or (b) whether or not negligence is found or alleged, the manufacture (except to the extent attributable to Isis' negligence), use, handling, storage, sale or other disposition of a Product or other compound that is developed or sold by Atlantic, its Affiliates, agents or sublicensees, except to the extent Isis has an obligation to indemnify Atlantic under Section 12.2 below.

Section 12.2 **Indemnification of Atlantic.** Isis will indemnify Atlantic, its Affiliates, and its sublicensees, and each of their respective directors, officers, employees and agents, and defend and hold each of them harmless, from and against any and all Losses arising from or occurring as a result of or in connection with the breach of any of Isis' representations, warranties, or covenants contained in Article 13 below, except to the extent Atlantic has an obligation to indemnify Isis under Section 12.1 above.

Section 12.3 **Insurance.** Each Party will have and maintain such types and amounts of liability insurance as is reasonable and customary in the industry generally for parties similarly situated, and will upon request provide the other with a certificate of insurance. Each

Party will promptly notify the other of any material change in insurance coverage or lapse in coverage in that regard.

Section 12.4 **Liability.** Neither Party shall be liable to the other in contract, tort, negligence, breach of statutory duty or otherwise for any loss, damage, costs or expenses of any nature whatsoever incurred or suffered by the other or its Affiliates:

12.4.1 of a direct nature where the same is a loss of turnover, profits, business or goodwill; or

12.4.2 of an indirect or consequential or punitive nature, including any indirect or consequential economic loss or other indirect or consequential loss of turnover, profits, loss of enterprise value, business or goodwill or otherwise.

ARTICLE 13 -
REPRESENTATIONS AND WARRANTIES

Section 13.1 **Representations, Warranties and Covenants.** Each Party hereby represents, warrants and covenants to the other Party as of the Effective Date as follows:

Section 13.2 **Corporate Authority.** Such Party (a) has the power and authority and the legal right to enter into this Agreement and perform its obligations hereunder, and (b) has taken all necessary action on its part required to authorize the execution and delivery of this Agreement and the performance of its obligations hereunder. This Agreement has been duly executed and delivered on behalf of such Party and constitutes a legal, valid and binding obligation of such Party and is enforceable against it in accordance with its terms subject to the effects of bankruptcy, insolvency or other laws of general application affecting the enforcement of creditor rights and judicial principles affecting the availability of specific performance and general principles of equity, whether enforceability is considered a proceeding at law or equity.

Section 13.3 **Consents, Approvals, etc.** All necessary consents, approvals and authorizations of all Regulatory Authorities and other parties required to be obtained by such Party in connection with the execution and delivery of this Agreement and the performance of its obligations hereunder have been obtained.

Section 13.4 **Conflicts.** The execution and delivery of this Agreement and the performance of such Party's obligations hereunder (a) do not conflict with or violate any requirement of Applicable Law or any provision of the articles of incorporation, bylaws or any similar instrument of such Party, as applicable, in any material way, and (b) do not conflict with, violate, or breach or constitute a default or require any consent not already obtained under, any contractual obligation or court or administrative order by which such Party is bound.

Section 13.5 **Intellectual Property**. To each Party's knowledge, as of the Effective Date, no additional Third Party licenses are required to develop, use and sell the enema formulation of Alicaforsen.

Section 13.6 **Isis Representations, Warranties, and Covenants**. Isis hereby represents, warrants and covenants to Atlantic as of the Effective Date as follows:

13.6.1 **IP Ownership**. Isis has the sufficient legal and/or beneficial title and ownership of the Alicaforsen Patents, the ICAM-1 Specific Patents, and the Isis Core Technology Patents as is necessary to fulfill its obligations under this Agreement and to grant the licenses (or sublicenses as the case may be) to Atlantic pursuant to this Agreement; Isis has not previously entered into any agreement, whether written or oral, with respect to, or otherwise assigned, licensed, transferred, conveyed or otherwise encumbered its right, title or interest in or to the Isis Data ("Isis Background Know How") or the Alicaforsen Patents and ICAM-1 Specific Patents licensed hereunder (including by granting any covenant not to sue with respect thereto) (the Isis Background Know How and such Alicaforsen Patents and ICAM-1 Specific Patents licensed hereunder together being the "Isis Background IP"). To the best of Isis' knowledge, the conception, development and reduction to practice of the Isis Background IP existing as of the Effective Date have not constituted or involved the misappropriation of trade secrets or other rights or property of any Third Party; and

13.6.2 **Patent Maintenance.** True, complete and correct copies of the complete file wrapper and other material correspondence with any patent office relating to the prosecution, validity and enforceability of the Patents within the Alicaforsen Patents and the ICAM-1 Specific Patents existing at the Effective Date have been provided to or made available to Atlantic prior to the Effective Date and, to the best of Isis' knowledge, there is no material reason why any of such Patents are invalid. In respect of the pending patent applications included within such Patents, Isis has presented all relevant prior art of which it and the inventors are aware to the relevant patent examiners at the relevant patent offices; and

13.6.3 **Patent Prosecution.** The Alicaforsen Patents and ICAM-1 Specific Patents licensed hereunder that are applications at the Effective Date are being diligently procured from the respective patent offices and the Patents within such Patents licensed hereunder that are granted at the Effective Date have been maintained properly and correctly and all applicable fees have been paid on or before the due date for payment; and

13.6.4 **Third Party Actions.** To the best of Isis' knowledge, no actions, suits, claims, disputes, or proceedings concerning the Alicaforsen Patents, the ICAM-1 Specific Patents, or the Isis Core Technology Patents licensed hereunder or the Alicaforsen Product are currently pending or are threatened in writing, that if determined adversely to Isis would have a material adverse effect on the Alicaforsen Product or would impair Isis' ability to perform its obligations under this Agreement.

13.6.5 **Alicaforsen.** As of the Effective Date, Isis does not Control any Patents other than the Alicaforsen Patents and the ICAM-1 Specific Patents that would be necessary to develop or commercialize Alicaforsen Products or to manufacture Alicaforsen Product or Alicaforsen API other than the Patents within Excluded Isis IP.

Section 13.7 **Atlantic Representations, Warranties, and Covenants.** Atlantic hereby represents, warrants and covenants to Isis that:

13.7.1 Capabilities. Atlantic has the requisite personnel, expertise, experience and skill to perform its obligations under this Agreement; Atlantic's sales representatives will

perform in a professional, timely, competent and efficient manner; and Atlantic, its Affiliates, and its sublicensees will at all times comply with all Applicable Laws.

13.7.2 Capitalization. Appendix 6 contains a complete and correct table showing the capitalization of Atlantic as of the Effective Date, on a fully-diluted basis. Except as set forth in Appendix 6, there are no outstanding shares of capital stock of Atlantic or warrants, options, agreements, convertible securities or other commitments pursuant to which Atlantic is or may become obligated to issue any shares of its capital stock or other securities. Atlantic understands and agrees that Isis is relying upon these representations and warranties when accepting the issuance of Atlantic Equity Securities under Section 6.1 above.

Section 13.8 **DISCLAIMER OF WARRANTY.** EXCEPT FOR THE EXPRESS WARRANTIES SET FORTH IN THIS ARTICLE 13, ATLANTIC AND ISIS MAKE NO REPRESENTATIONS AND GRANT NO WARRANTIES, EXPRESS OR IMPLIED, EITHER IN FACT OR BY OPERATION OF LAW, BY STATUTE OR OTHERWISE, AND ATLANTIC AND ISIS EACH SPECIFICALLY DISCLAIM ANY OTHER WARRANTIES, WHETHER WRITTEN OR ORAL, OR EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF QUALITY, MERCHANTABILITY OR FITNESS FOR A PARTICULAR USE OR PURPOSE OR ANY WARRANTY AS TO THE VALIDITY OF ANY PATENTS OR THE NON-INFRINGEMENT OF ANY INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES.

ARTICLE 14 - MISCELLANEOUS

Section 14.1 **Assignment.** Without the prior written consent of the other Party hereto, neither Party will sell, transfer, assign, delegate, pledge or otherwise dispose of, whether voluntarily, involuntarily, by operation of law or otherwise, this Agreement or any of its rights or duties hereunder; *provided, however,* that (i) either Party hereto may assign or transfer this Agreement or any of its rights or obligations hereunder without the consent of the other Party to (a) any of its Affiliates, or (b) any Third Party with which it has merged or consolidated, or to which it has transferred all or substantially all of its assets to which this Agreement relates provided always in the case where Isis is the assigning Party it also transfers title to the Alicaforsen Patents, the ICAM-1 Specific Patents, the Second Generation ICAM-1 Product-Specific Patents and the Isis Core Technology Patents to such Third Party, and if in any such event the Third Party assignee or surviving entity assumes in writing all of the assigning Party's obligations under this Agreement, (ii) Atlantic may assign or transfer this Agreement, without Isis' consent, to Atlantic Healthcare, or (iii) Isis may assign or transfer its rights under Article 6.4 (but no liabilities) to a Third Party in connection with a royalty factoring transaction. Any purported assignment or transfer in violation of this Section 14.1 will be void *ab initio* and of no force or effect.

Section 14.2 **Severability.** If any provision of this Agreement is held to be illegal, invalid or unenforceable by a court of competent jurisdiction, such adjudication will not affect or impair, in whole or in part, the validity, enforceability, or legality of any remaining portions of this Agreement. All remaining portions will remain in full force and effect as if the original Agreement had been executed without the invalidated, unenforceable or illegal part.

Section 14.3 **Governing Law.** This Agreement will be governed by and construed in accordance with the laws of New York, USA without reference to any rules of conflicts of laws.

Section 14.4 **Dispute Resolution.**

14.4.1 General. Any dispute, controversy or claim arising from or related to this Agreement or the breach thereof will first be referred to the attention of the Chief Executive Officer of Atlantic and the Executive Vice President of Isis (the "Executive Officers") by notice in writing in accordance with the terms of this Agreement. The Executive Officers (or their respective designees) will meet as soon as reasonably possible thereafter, and use their good faith efforts to mutually agree upon the resolution of the dispute, controversy or claim. If any dispute, controversy or claim is not resolved by the designated officers of the Parties (or their designees) within 30 days after such dispute is referred to them, then the Parties agree that such dispute will be referred to mediation, and if the dispute remains unresolved after mediation, either Party will have the right to arbitrate such dispute in accordance with Section 14.4.3; *provided, however*, that any dispute relating to the construction or validity of any Patent will not be subject to arbitration.

14.4.2 Mediation. If the Parties pursue mediation proceedings the Parties will attempt to resolve such dispute in accordance with the Commercial Mediation Procedures of the American Arbitration Association ("AAA"), before resorting to arbitration in accordance with Section 14.4.3 below. The mediation will be conducted by a single mediator experienced in the business and technology that is the subject of this Agreement. The place of mediation will be in New York, NY, USA. Either Party may apply to the mediator or to a court for interim injunctive relief until the mediation decision is rendered or the dispute, controversy or claim is otherwise resolved.

14.4.3 Arbitration. If the Parties do not fully settle any dispute, controversy or claim pursuant to Section 14.4.1 or 14.4.2 and a Party wishes to pursue the matter further, each such dispute, controversy or claim will be finally resolved by binding arbitration in accordance with the Commercial Arbitration Rules of the AAA, and judgment on the arbitration award may be entered in any court having jurisdiction thereof. The arbitration will be conducted by a single arbitrator agreeable by the Parties, if the Parties cannot agree upon an arbitrator, the arbitrator will be appointed by the AAA. No individual will be appointed to arbitrate a dispute pursuant to this Agreement unless he or she agrees in writing to be bound by the provisions of this Section 14.4. The place of arbitration will be New York, NY, USA. Either Party may apply to the arbitrator for interim injunctive relief until the arbitration award is rendered or the controversy is otherwise resolved.

14.4.4 Disputes Regarding Material Breach. If the Parties are in dispute as to whether one party is in material breach of this Agreement, then the mediator or arbitrators will first determine if material breach has in fact occurred, and if so, will grant the defaulting Party the cure period provided pursuant to Section 10.3. If the material breach is not cured within the time period provided pursuant to Section 10.3, the mediation or arbitration will continue and the mediator or arbitrators will, as part of the same mediation or arbitration, award actual direct damages to the non-defaulting Party.

14.4.5 Costs and Expenses. Except as expressly provided herein, each Party will bear its own costs and expenses and attorneys' fees and an equal share of the mediator's and/or arbitrators' and any administrative fees of mediation and arbitration. Notwithstanding the foregoing, in the case of arbitration, if a Party has been found to be in material breach of this Agreement, the defaulting Party will be responsible for both Parties' Third Party costs and expenses (including the costs of the arbitrators and any administrative fees of arbitration) and the reasonable attorneys' fees of the non-defaulting Party; *provided, however*, that the total amount of such fees and expenses the defaulting Party is required to reimburse the non-defaulting Party cannot exceed the total amount of monetary damages awarded to the non-defaulting Party as a result of such material breach.

14.4.6 Procedure. Except to the extent necessary to confirm an award or as may be required by law, neither a Party, a mediator, nor an arbitrator may disclose the existence, content, or results of a mediation or an arbitration without the prior written consent of both Parties. In no event will arbitration be initiated after the date when commencement of a legal or equitable proceeding based on the dispute, controversy or claim would be barred by the applicable New York statute of limitations.

14.4.7 Speedy Resolution. The Parties intend, and will take all reasonable action as is necessary or desirable to ensure, that there be a speedy resolution to any dispute which becomes the subject of mediation or arbitration, and the mediator and arbitrators will conduct the mediation or arbitration so as to resolve the dispute as expeditiously as possible.

14.4.8 Awards. In any mediation, a decision or opinion issued by the mediator regarding the dispute between the Parties is non-binding. The arbitrators may award monetary damages and injunctive relief, but may not order the granting or termination of licenses or assign rights to a Product to either of the Parties. Monetary damages will be in the form of off-set royalties or otherwise, to account for the damages to the non-defaulting Party from the breach, and to account for the defaulting Party's contribution to the Product in view of the breach. All awards will be in writing and will state reasons. Executed copies of all awards will be delivered by the arbitrators to the Parties as soon as is reasonably possible. All awards of the arbitrators will be final and binding on the Parties, and there will be no appeal of any such award whatsoever. The Parties undertake to satisfy any award without delay.

Section 14.5 **Notices.** All notices or other communications that are required or permitted hereunder will be in writing and delivered personally with acknowledgement of receipt, sent by facsimile (and promptly confirmed by personal delivery, registered or certified mail or overnight courier as provided herein), sent by nationally-recognized overnight courier or sent by registered or certified mail, postage prepaid, return receipt requested, addressed as follows:

If to Atlantic, to:

Atlantic Healthcare (UK) Limited
MoFo Notices Limited
7th Floor
CityPoint
One Ropemaker Street
London EC2Y 9AW
Attention: Chief Executive Officer
Facsimile: +44 (0) 20 7496 8500

If to Isis, to:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, California 92008
Attention: Executive Vice President and CFO
Facsimile: +1 (760) 603-4650

with a copy to:

Attention: General Counsel
Facsimile: +1 (760) 268-4922

or to such other address as the Party to whom notice is to be given may have furnished to the other Party in writing in accordance herewith. Any such communication will be deemed to have been given (i) when delivered, if personally delivered or sent by facsimile on a Business Day, (ii) on the Business Day after dispatch, if sent by nationally-recognized overnight courier, and (iii) on the third business day following the date of mailing, if sent by mail. It is understood and agreed that this Section 14.5 is not intended to govern the day-to-day business communications necessary between the Parties in performing their duties, in due course, under the terms of this Agreement.

Section 14.6 **Entire Agreement; Modifications.** This Agreement sets forth and constitutes the entire agreement and understanding between the Parties with respect to the subject matter hereof and all prior agreements, understanding, promises and representations, whether written or oral, with respect thereto are superseded hereby. Each Party confirms that it is not relying on any representations or warranties of the other Party except as specifically set forth herein. No amendment, modification, release or discharge will be binding upon the Parties unless in writing and duly executed by authorized representatives of both Parties.

Section 14.7 **Relationship of the Parties.** It is expressly agreed that the Parties will be independent contractors of one another and that the relationship between the Parties will not constitute a partnership, joint venture or agency.

Section 14.8 **Waiver.** Any term or condition of this Agreement may be waived at any time by the Party that is entitled to the benefit thereof, but no such waiver will be effective unless set forth in a written instrument duly executed by or on behalf of the Party waiving such term or condition. Any such waiver will not be deemed a waiver of any other right or breach hereunder.

Section 14.9 **Counterparts.** This Agreement may be executed in two or more counterparts, each of which will be deemed an original, but all of which together will constitute one and the same instrument.

Section 14.10 **No Benefit to Third Parties.** The provisions of this Agreement are for the sole benefit of the Parties and their successors and permitted assigns. This Agreement shall not confer any rights or remedies upon any person other than Isis and Atlantic and their respective successors and permitted assigns except as otherwise expressly provided in Section 12. Except as expressly provided in Section 12, no person who is not a party to this Agreement (including any employee, officer, agent, representative or subcontractor of either Party) shall have the right to enforce any terms of this Agreement which expressly or by implication confers a benefit on that person without the prior written agreement of the Parties which agreement must refer to this Section 14.10.

Section 14.11 **Further Assurance.** Each Party will duly execute and deliver, or cause to be duly executed and delivered, such further instruments and do and cause to be done such further acts and things, including the filing of such assignments, agreements, documents and instruments, as may be necessary to carry out the provisions and purposes of this Agreement.

Section 14.12 **Force Majeure.** Neither Party shall be responsible to the other for any failure or delay in performing any of its obligations under this Agreement or for other non-performance hereunder if such delay or non-performance is caused by strike, stoppage of labor, lockout or other labor trouble, fire, flood, accident, war, act of terrorism, act of God or of the government of any country or of any local government, or by cause unavoidable or beyond the control of any Party hereto. In such event, the Party affected will use Commercially Reasonable Efforts to resume performance of its obligations.

[SIGNATURES ON FOLLOWING PAGE]

IN WITNESS WHEREOF, the Parties hereto have caused this Agreement to be executed by their duly authorized representatives as of the date first above written.

Atlantic Healthcare (UK) Limited	**Isis Pharmaceuticals, Inc.**
Per: /s/ Toby Wilson Waterworth	*Per: /s/ Stanley T. Crooke, M.D., Ph.D.*
Toby Wilson Waterworth Director	Stanley T. Crooke, M.D., Ph.D. Chief Executive Officer

APPENDIX 1

Definitions

"Affiliate" of a Party means any other party that, directly or indirectly, through one or more intermediaries, controls, is controlled by, or is under common control with such Party. For purposes of this definition only, "control" and, with correlative meanings, the terms "controlled by" and "under common control with" will mean the possession, directly or indirectly, of the power to direct the management or policies of a party, whether through the ownership of voting securities or by contract relating to voting rights or corporate governance.

"**Agreement**" means this document including any and all schedules, appendices and other addendum to it as may be added and/or amended from time to time in accordance with the provisions of this document.

"Alicaforsen" means the compound known by the USAN name "Alicaforsen," which is also known as ISIS 2302.

"Alicaforsen API" means Alicaforsen in bulk form manufactured in accordance with cGMP.

Alicaforsen Patents" means (i) the Patents listed on Appendix 2, and (ii) all Patents issuing from the Patents in (i), and (iii) any other Patent Controlled by Isis during the term of this Agreement which covers the composition, formulation or use of Alicaforsen *but excluding always* the Patents within Excluded Isis IP and the ICAM-1 Specific Patents.

"Alicaforsen Product" means a pharmaceutical preparation in any formulation comprising Alicaforsen.

"Applicable Law" means all applicable laws, rules, and regulations, including any rules, regulations, guidelines, or other requirements of the Regulatory Authorities that may be in effect from time to time.

"Atlantic Equity Securities" has the meaning set forth in Section 6.2.2.

"Atlantic Healthcare" means that company incorporated in England and Wales with company registration no. 5878612 whose registered address is Maple House, Birdbrook, Halstead, Essex CO9 4BB.

"Authorized Disclosure" means a disclosure of Confidential Information by the receiving Party to the extent that such disclosure is:

(i) made in response to a valid order of a court of competent jurisdiction; *provided, however*, that such receiving Party will first have given notice to such other Party and given such other Party a reasonable opportunity to quash such order and to

---

obtain a protective order requiring that the Confidential Information and documents that are the subject of such order be held in confidence by such court or agency or, if disclosed, be used only for the purposes for which the order was issued; and *provided further* that if a disclosure order is not quashed or a protective order is not obtained, the Confidential Information disclosed in response to such court or governmental order will be limited to that information which is legally required to be disclosed in response to such court or governmental order;

(ii) otherwise required to comply with Applicable Laws, including to the extent such disclosure is required in publicly filed financial statements or other public statements under rules governing a stock exchange (e.g., the rules of the United States Securities and Exchange Commission, NASDAQ, NYSE, UKLA or any other stock exchange or which securities of either Party may be listed) *provided, however*, to the extent possible bearing in mind such Applicable Laws and subject to the next subsequent sentence of this paragraph, the receiving Party shall provide the other Party with a copy of the proposed text of such statements or disclosure five (5) Business Days in advance of the date on which the disclosure is to be made to enable the other Party to review and provide comments, unless a shorter review time is agreed. If the compliance with an Applicable Law requires filing of this Agreement, the filing Party shall to the extent possible seek confidential treatment of portions of this Agreement from the relevant competent authority and shall provide the other Party with a copy of the proposed filings at least ten (10) Business Days prior to filing for the other Party to review any such proposed filing. Each Party agrees that it will obtain its own legal advice with regard to its compliance with Applicable Laws and will not rely on any statements made by the other receiving Party relating to such laws;

(iii) made by such receiving Party to the Regulatory Authorities as necessary for (a) the development or commercialization of a Product in a particular country, or (b) as required in connection with any filing, application or request for Regulatory Approval in a particular country and in either case to the extent consistent with the licenses granted under the terms of this Agreement;

(iv) made by the receiving Party, in connection with the performance of this Agreement, to Affiliates sublicensees, licensors, licensees, directors, officers, employees, consultants, representatives or agents, each of whom prior to disclosure must be bound by obligations of confidentiality and non-use at least equivalent in scope to those set forth in this Agreement;

(v) made by the receiving Party to existing or potential acquirers; existing or potential pharmaceutical collaborators (to the extent contemplated hereunder); investment bankers; existing or potential investors, merger candidates, partners, venture capital firms or other financial institutions or investors for purposes of obtaining financing; or, bona fide strategic potential partners; each of whom prior to disclosure must be bound by obligations of confidentiality and non-use at least equivalent in scope to those set forth in this Agreement; or

---

(vi) made by the receiving Party to its legal advisers for the purpose of seeking advice.

"Business Day" means 9.00am to 5.00pm local time on any day, other than Saturday, Sunday or any statutory holiday or public holiday in the United States or England and Wales.

"Calendar Year" means each successive period of 12 months commencing on January 1 and ending on December 31.

"**cGMP**" means current Good Manufacturing Practices as specified in ICH Guideline Q7A, the United States Code of Federal Regulations, or equivalent laws, rules, or regulations of an applicable Regulatory Authority at the time of manufacture.

"**Commercially Reasonable Efforts**" (i) in respect of Atlantic means efforts and resources commonly used in the biotechnology industry by companies at a similar stage of development for products of similar commercial potential to develop and commercialize a product owned by such a company or to which it has rights, which product is at a similar stage in its development or product life and is of similar market potential to the Product in question and taking into account the patent and other proprietary position of the product; and (ii) in respect of Isis means efforts and resources commonly used by biotechnology companies of a similar size to Isis based on market capitalization to develop a product owned by such a company or to which it has rights, which product is at a similar stage in its development or product life and is of similar market potential to the Product in question and taking into account the patent and other proprietary position of the product. Promptly following the meeting with the FDA to discuss the registration strategy for a pouchitis indication, Atlantic and Isis will agree on the Development Timeline to be included in Appendix 5. Atlantic's meeting of such Development Timeline in Appendix 5 and Isis' provision of the Candidate Pool to Atlantic in accordance with the Work Plan will be deemed to be examples of using Commercially Reasonable Efforts; *provided, however*, that a failure to meet such Development Timeline will not be dispositive of a failure to use Commercially Reasonable Efforts.

"Committee Members" has the meaning set forth in Section 3.2.

"Candidate Pool" has the meaning set forth in Section 4.1.1.

"Confidential Information" means all information and know-how and any tangible embodiments thereof provided by or on behalf of one Party to the other Party either in connection with the discussions and negotiations pertaining to this Agreement or in the course of performing this Agreement, including data; knowledge; practices; processes; ideas; research plans; engineering designs and drawings; research data; manufacturing processes and techniques; scientific, manufacturing, marketing and business plans; and financial and personnel matters relating to the disclosing Party or to its present or future products, sales, suppliers, customers, employees, investors or business.

Exceptions. Notwithstanding the foregoing, information or know-how of a Party will not be deemed Confidential Information for purposes of this Agreement if such information or know-how:

(a) was already known to the receiving Party, other than under an obligation of confidentiality or non-use, at the time of disclosure to such receiving Party;

(b) was generally available or known to parties reasonably skilled in the field to which such information or know-how pertains, or was otherwise part of the public domain, at the time of its disclosure to, or, with respect to know-how, discovery or development by, such receiving Party;

(c) became generally available or known to parties reasonably skilled in the field to which such information or know-how pertains, or otherwise became part of the public domain, after its disclosure to such receiving Party through no fault of the receiving Party;

(d) was disclosed to such receiving Party, other than under an obligation of confidentiality or non-use, by a Third Party who had no obligation to the disclosing Party not to disclose such information or know-how to others; or

(e) was independently discovered or developed prior to disclosure by such receiving Party, as evidenced by their written records, without the use of Confidential Information belonging to the disclosing Party.

"Control" means, with respect to any Patent or other intellectual property right, possession of the right (whether by ownership, license or otherwise), to assign, or grant a license, sublicense or other right to or under, such Patent or right as provided for herein without violating the terms of any agreement or other arrangement with any Third Party or incurring any additional financial or other obligation to a Third Party except the obligations specifically described in Section 6.7.

"Cumulative Net Sales" means the total cumulative amount of Net Sales calculated separately for each of the Alicaforsen Products and each of the Second Generation ICAM-1 Products, from the first date that each respective Product was approved for commercialization by a Regulatory Authority. For purposes of clarity, the Net Sales for any Second Generation ICAM-1 Products will not be taken into consideration when calculating Cumulative Net Sales for Alicaforsen Products, and *vice versa*.

"Discontinuance" means the occurrence of any one of the following:

1. Atlantic voluntarily elects to abandon researching, developing and/or commercializing all Products, as evidenced by a written communication from an authorized officer of Atlantic to Isis; or

---

2. Atlantic fails to use Commercially Reasonable Efforts and the Quality Standard to develop and commercialize at least one Product.

"Discontinued Patent" has the meaning set forth in Section 9.1.4.

"DMF" has the meaning set forth in Section 3.6.1.

"EMEA" means the European Regulatory Authority known as the European Medicines Agency and any successor agency thereto.

"Equity Cap" means [***]% of the issued and outstanding share capital of Atlantic (on an as-issued, post financing basis).

"Excluded Isis IP" means all know how and Patents Controlled by Isis on the Effective Date and at any time during the term of the Agreement other than (A) Alicaforsen Patents, (B) ICAM-1 Specific Patents, (C) Isis Core Technology Patents, (D) Second Generation ICAM-1 Product-Specific Patents, (E) Isis Data, (F) Isis Manufacturing Know How, and (G) Second Generation Isis Data. For clarity, Excluded Isis IP include any know how and Patents Controlled by Isis which cover Isis' (i) formulation and delivery technology (save as expressly claimed in the Alicaforsen Patents, ICAM-1 Specific Patents, Second Generation ICAM-1 Product-Specific Patents and Isis Manufacturing Know How), (ii) RNAi technologies, (iii) microRNA technologies, and (iv) chemical modifications and motifs other than Isis MOE Gapmer Chemistry, and (v) the Excluded Manufacturing IP.

"Excluded Manufacturing IP" means all Patents and know how (including any and all information directly relating to manufacturing methods (including related analytical methods) of Alicaforsen API) Controlled by Isis on the Effective Date and at any time during the term of the Agreement which claim the manufacturing process by which Isis manufactures Alicaforsen API.

"Existing Royalties" has the meaning set forth in Section 6.4.3.

"FDA" means the United States Food and Drug Administration and any successor agency thereto.

"First Commercial Sale" means the first sale of a Product by Atlantic, its Affiliates or a sublicensee to a Third Party in a particular country after Regulatory Approval has been obtained.

"[***]" means a chronic disorder of the [***], including without limitation, [***] or [***].

"ICAM-1" means intercellular adhesion molecule-1 (also called CD54).

"ICAM-1 Specific Patents" means (i) the Patents listed on Appendix 3 (ii) all Patents issuing therefrom, and (iii) any other Patents Controlled by Isis during the term of this Agreement which cover the composition, formulation or use of Alicaforsen Products

or Second Generation ICAM-1 Products, *but excluding always* the Alicaforsen Patents, the Second Generation ICAM-1 Product-Specific Patents and the Patents within Excluded Isis IP.

"IFRS" means International Financial Reporting Standards established by the International Accounting Standards Board, as amended from time to time.

"[***]" means a formulation and excipient system and technologies that delivers a drug compound into the human body by [***] directly into the [***] to achieve a local or systemic therapeutic effect.

"**Initiation of Phase I Clinical Trial"** means the first visit by the first human patient in a Phase I Clinical Trial during which dosing of Product or placebo occurs.

"Initiation of Pivotal Quality Clinical Trial" means the first visit by the first patient in a Pivotal Quality Clinical Trial during which dosing of Product or placebo occurs.

"Isis Background IP" has the meaning set forth in Section 13.6.1.

"Isis Background Know How" has the meaning set forth in Section 13.6.1.

"**Isis Core Technology Patents**" means Patents Controlled by Isis on the Effective Date that are necessary for the development and commercialization of the Product, but does not include (A) Alicaforsen Patents, (B) ICAM-1 Specific Patents, (C) Second Generation ICAM-1 Product-Specific Patents, or (D) Patents Controlled by Isis that claim, and only to the extent that they claim, Excluded Isis IP.

"Isis Data" has the meaning set forth in Section 2.2.1.

"Isis Database" has the meaning set forth in Section 3.3.1.

"Isis Manufacturing Know How" has the meaning set forth in Section 2.2.1.

"JDC" has the meaning set forth in Section 3.2.

"Losses" has the meaning set forth in Section 12.1.

"Major Market" means the [***], [***], [***], [***], [***], [***], [***] and [***].

"Manufacturing Agreement" has the meaning set forth in Section 3.6.1.

"MOE Gapmer" means a single stranded antisense Phosphorothioate oligonucleotide of 15-30 nucleotides wherein all of the backbone linkages are modified by adding a sulfur at the non-bridging oxygen (Phosphorothioate) and a stretch of at least 10 consecutive nucleotides remain unmodified (deoxy sugars) and the remaining nucleotides contain an O' – methyl O' – ethyl substitution at the 2' position.

"NDA" means a New Drug Application filed with the FDA after completion of clinical trials to obtain Regulatory Approval for commercial product in the United States or an equivalent application for regulatory approval in other Major Market countries.

"Net Sales" means the gross invoiced price charged by Atlantic or its Affiliates or sublicensees, as appropriate, for the sale of a Product to a Third Party by Atlantic, its Affiliates or its sublicensees, as appropriate, less the following deductions:

(i) Trade and quantity discounts actually granted;

(ii) Credits for returns or allowances;

(iii) Actual uncollectible amounts for Product where collectibility is determined in accordance with IFRS consistently applied to all of Atlantic's products;

(iv) Freight, shipping insurance and other transportation expenses directly related to the sale of the Product (if actually borne by Atlantic, its Affiliates or sublicensees without reimbursement from any Third Party);

(v) The amount of any sales tax or other taxes assessed directly on the sale of such Product which is not refunded; and

(vi) Charge back payments or rebates granted to managed health care organizations or federal, state and local governments, their agencies, purchasers and reimburses.

The transfer of Product by Atlantic or one of its Affiliates to another Affiliate shall not be considered a sale. Upon the sale or other disposal of Product for other than monetary consideration , which sales price is either customary or is reasonably expected in the country in which such sale is made, such sale or other disposal shall be deemed to be a sale with the consideration for such sale constituting Net Sales hereunder at the average sales price during the applicable reporting period generally achieved (or as achieved by similar products) for such Product in the country in which such sale or other disposal occurred when such Product is sold alone and not with other products. Disposal of Product for or use of Product in clinical trials or as free samples shall not be deemed a sale under this Section. Such amounts shall be determined from the books and records of Atlantic maintained in accordance with IFRS, consistently applied.

Where Product contains Alicaforsen API or a Second Generation ICAM-1 ASO Drug Candidate and is sold in combination with one or more other active ingredient(s) that are sold either as a fixed dose or as separate doses in a single package for a single price (a "Combination Product"), Net Sales will be determined as follows:

(X divided by Y) multiplied by Z

where X is the average sales price during the applicable reporting period generally achieved for the Product in the country in which such sale or other disposal occurred when such Product is sold alone and not as a Combination Product; Y is the sum of the

---

average sales price during the applicable reporting period generally achieved in that country, when sold alone, by each product (including the Product) included in the Combination Product that is sold for the single price; and Z equals the single price at which the Combination Product represented in Y was actually sold. In the event one or more of the products in the Combination Product are not sold separately, the Parties shall confer in good faith to determine a fair market price that shall be equitable for the value of the Product within the Combination Product.

"Notice" has the meaning set forth in Section 4.1.2.

"[***]" means a formulation and excipient system and technologies to deliver a drug compound to the [***] to achieve a local or systemic therapeutic effect.

"Patents" will include (x) all U.S. patents and patent applications, (y) any substitutions, divisions, continuations, reissues, renewals, registrations, confirmations, re-examinations, extensions, supplementary protection certificates and the like, and any provisional applications, of any such patents or patent applications, and (z) any foreign or international equivalent of any of the foregoing.

"Patent Term Extensions" has the meaning set forth in Section 9.1.6.

"**Phase I Clinical Trial"** means the initial clinical testing of a Product in humans (first-in-humans study).

"Pivotal Quality Clinical Trial" means a human clinical trial of a Product designed to be of a size and statistical power to support an NDA filing alone or in combination with other studies. If it is unclear whether or not a study design will be sufficient to support an NDA filing (other than by virtue of the uncertainty of safety and efficacy data from that trial) the study will be deemed to be a Pivotal Quality Clinical Trial on the initiation of activities to support an NDA filing. A Phase III clinical study will be deemed to be a Pivotal Quality Clinical Trial.

"Positive Pouchitis Clinical Trial" means a clinical study of Alicaforsen Product in humans conducted by Atlantic in accordance with this Agreement that is directed to the treatment of pouchitis, which meets the study's primary endpoint(s).

"Product" means (i) an Alicaforsen Product and, (ii) at such time as Isis grants to Atlantic the licenses in Section 4.1.3 of the Agreement, a Second Generation ICAM-1 Product, or (iii) both, which Atlantic or its Affiliates are developing or commercializing under this Agreement or that is being developed or commercialized under a Sublicense.

"Quality Standard" means, with respect to research, development, manufacture or commercialization of the Candidate Pool, the Second Generation ICAM-1 ASO Drug Candidate or a Product, the standard of care, quality, and professional competence commonly used in the biotechnology industry for products of similar commercial potential at a similar stage in its lifecycle.

"Regulatory Approval" means (a) in the United States, approval by the FDA of an NDA, or similar application for marketing approval, and satisfaction of any related applicable FDA registration and notification requirements (if any), and (b) in a Major Market other than the United States, approval by Regulatory Authorities having jurisdiction over such country of a single application or set of applications comparable to an NDA and satisfaction of any related applicable regulatory and notification requirements (if any).

"Regulatory Authority" means any applicable government entities regulating or otherwise exercising authority with respect to the development and commercialization of the Product.

"Regulatory Documentation" means all applications, registrations, licenses, authorizations and approvals (including all Regulatory Approvals), all correspondence submitted to or received from Regulatory Authorities (including minutes and official contact reports relating to any communications with any Regulatory Authority), all supporting documents and all clinical studies and tests, including the manufacturing batch records, relating to the Product, and all data contained in any of the foregoing, including all regulatory drug lists, advertising and promotion documents, adverse event files and complaint files.

"Royalty Due Dates" means the last working days of March, June, September and December of each and every year during which this Agreement remains in full force and effect.

"**Second Generation Development Plan"** has the meaning set forth in Section 4.1.2.

"**Second Generation ICAM-1 ASO Drug Candidate**" means a MOE Gapmer targeted to ICAM-1 that is selected by Atlantic under Section 4.1.2 of the Agreement.

"Second Generation ICAM-1 Products" means pharmaceutical preparation(s) comprising the Second Generation ICAM-1 ASO Drug Candidate.

"Second Generation ICAM-1 Product-Specific Patents" means any Patent that is Controlled by Isis on, before or after Atlantic makes its election under Section 4.1.2 of this Agreement, that (i) claims the specific composition of matter of a Second Generation ICAM-1 ASO Drug Candidate, or (ii) methods of using such Second Generation ICAM-1 ASO Drug Candidate as a therapeutic.

"Second Generation ICAM-1 Research Program" has the meaning set forth in Section 4.1.1.

"**Second Generation Isis Data"** has the meaning set forth in Section 4.1.4.

"SSEA Execution Date" has the meaning set forth in Section 6.1.1.

"Sublicense" means a sublicense from Atlantic to a Third Party under the Alicaforsen Patents or the ICAM-1 Patents or the Second Generation ICAM-1 Product-Specific Patents to develop, use, sell, offer for sale, have sold and/or import any Product.

"Sublicense Revenue" means any consideration that Atlantic receives from a sublicensee in consideration for a grant of any Sublicense, including, but not limited to, license fees, milestone payments, and license maintenance fees, but excluding: (i) royalties on Net Sales of Products, (ii) payments made in consideration of equity or debt securities of Atlantic at fair market value and (iii) payments specifically committed to reimburse Atlantic for the direct cost of research and development. If Atlantic receives any non-cash Sublicense Revenue, Atlantic will pay Isis, at Isis' election, either (x) a cash payment equal to the fair market value of Isis' appropriate portion of the Sublicense Revenue or (y) the in-kind portion, if practicable, of the Sublicense Revenue. For purposes of calculating Sublicense Revenue, a series of Sublicenses to the same sublicensee or related sublicensees will be aggregated to constitute a single Sublicense.

"**Subscription and Share Exchange Agreement**" has the meaning set forth in Section 6.1.1.

"Term" has the meaning set forth in Section 10.1.

"Third Party" means any party other than Isis or Atlantic or their respective Affiliates.

"Valid Claim" means a claim of a Patent which (i) in the case of any granted, unexpired United States or foreign Patent, shall not have been donated to the public, disclaimed or held invalid or unenforceable by a court of competent jurisdiction in an unappealed or unappealable decision, or (ii) in the case of any United States or foreign patent application, is being prosecuted in good faith and shall not have been permanently cancelled, withdrawn, or abandoned provided that no more than eight (8) years have passed since the earliest priority date for such application.

"Valid Composition of Matter Claim" means a Valid Claim of a Patent in a given country that covers the structure of the compound comprising the active pharmaceutical ingredient in the Product (be it Alicaforsen API or Second Generation ICAM-1 ASO Candidate Drug) as opposed to its process of manufacture, use or method of treatment.

"Work Plan" has the meaning set forth in Section 4.1.1.

APPENDIX 2

ALICAFORSEN PATENTS

[***]

*** CONFIDENTIAL TREATMENT REQUESTED

APPENDIX 3

ICAM-1 SPECIFIC PATENTS

[***]

*** CONFIDENTIAL TREATMENT REQUESTED

APPENDIX 4

ISIS CORE TECHNOLOGY PATENTS

[***]

*** CONFIDENTIAL TREATMENT REQUESTED

APPENDIX 5

DEVELOPMENT TIMELINE

[***]

*** CONFIDENTIAL TREATMENT REQUESTED

APPENDIX 6

ATLANTIC EQUITY SECURITIES CAPITALIZATION TABLE

[***]

*** CONFIDENTIAL TREATMENT REQUESTED

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 condensed consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, condensed consolidated results of operations and condensed 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: May 10, 2007

/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 condensed consolidated financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, condensed consolidated results of operations and condensed 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: May 10, 2007

/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 March 31, 2007, 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: May 10, 2007

/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.