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 June 30, 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 August 6, 2007 was 82,790,658.

ISIS PHARMACEUTICALS, INC.
FORM 10-Q

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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)

	June 30, 2007 (Unaudited)	December 31, 2006
ASSETS		
Current assets:		
Cash and cash equivalents (including cash and cash equivalents held by Symphony GenIsis, Inc. of $43.0 million and $54.8 million at June 30, 2007 and December 31, 2006, respectively)	$ 132,964	$ 114,514
Short-term investments	69,769	78,819
Contracts receivable	2,296	2,395
Inventories	1,510	861
Other current assets	4,238	9,614
Total current assets	210,777	206,203
Property, plant and equipment, net	6,890	7,157
Licenses, net	20,267	21,435
Patents, net	17,376	16,836
Debt issuance costs	5,136	1,400
Deposits and other assets	2,809	2,876
Total assets	$ 263,255	$ 255,907
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 4,161	$ 4,288
Accrued compensation	2,379	6,222

Accrued liabilities	5,094	6,071
Current portion of long-term obligations	7,474	7,514
Current portion of deferred contract revenue	6,070	1,044
Total current liabilities	25,178	25,139
5 1/2% convertible subordinated notes	—	125,000
2 5/8% convertible subordinated notes	162,500	—
Long-term obligations, less current portion	4,053	7,822
Long-term deferred contract revenue	9,310	44
Total liabilities	201,041	158,005
Noncontrolling interest in Symphony GenIsis, Inc	14,930	29,339
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 82,594,096 and 82,283,693 shares issued and outstanding at June 30, 2007 and December 31, 2006, respectively	82	82
Additional paid-in capital	887,579	880,954
Accumulated other comprehensive income	418	4,278
Accumulated deficit	(840,795)	(816,751)
Total stockholders' equity	47,284	68,563
Total liabilities, noncontrolling interest and stockholders' equity	$ 263,255	$ 255,907

See accompanying notes

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2007	2006	2007	2006
Revenue:				
Research and development revenue under collaborative agreements	$ 3,482	$ 4,322	$ 5,484	$ 8,791
Licensing and royalty revenue	331	53	779	543
Total revenue	3,813	4,375	6,263	9,334
Expenses:				
Research and development	20,384	18,982	40,333	37,354
Selling, general and administrative	3,089	2,710	6,491	5,276
Restructuring activities	—	(215)	—	(178)
Total operating expenses	23,473	21,477	46,824	42,452
Loss from operations	(19,660)	(17,102)	(40,561)	(33,118)
Other income (expense):				
Investment income	3,053	1,344	6,454	2,155
Interest expense	(2,016)	(2,285)	(4,644)	(4,560)
Gain on investments, net	1,989	2,263	3,510	2,263
Loss on early retirement of debt	(1,993)	—	(3,212)	—
Net loss before noncontrolling interest in Symphony GenIsis, Inc.	(18,627)	(15,780)	(38,453)	(33,260)
Loss attributed to noncontrolling interest in Symphony GenIsis, Inc.	7,603	13,608	14,409	13,608
Net loss applicable to common stock	$ (11,024)	$ (2,172)	$ (24,044)	$ (19,652)
Basic and diluted net loss per share	$ (0.13)	$ (0.03)	$ (0.29)	$ (0.27)
Shares used in computing basic and diluted net loss per share	82,548	72,822	82,502	72,601

See accompanying notes.

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

(Unaudited)

	Six Months Ended June 30,	
	2007	2006
Net cash used in operating activities	$ (22,166)	$ (30,396)
Investing activities:		
Purchases of short-term investments	(59,578)	(28,611)
Proceeds from the sale of short-term investments	69,098	39,950
Purchases of property, plant and equipment	(967)	(438)
Acquisition of licenses and other assets	(1,216)	(943)
Proceeds from the sale of strategic investments	5,181	4,397
Net cash provided by investing activities	12,518	14,355
Financing activities:		
Net proceeds from issuance of equity	1,872	3,401
Proceeds from issuance of $2^5/_8$% convertible subordinated notes, net of issuance costs	157,056	—
Principal and redemption premium payment on prepayment of the $5^1/_2$% convertible subordinated notes	(127,021)	—
Principal payments on debt and capital lease obligations	(3,809)	(3,836)
Proceeds from purchase of noncontrolling interest in Symphony GenIsis, Inc, net of fees	—	70,950
Net cash provided by financing activities	28,098	70,515
Net increase in cash and cash equivalents	18,450	54,474
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 $43.0 million and $64.4 million at June 30, 2007 and 2006, respectively) at end of period	$ 132,964	$ 105,359
Supplemental disclosures of cash flow information:		
Interest paid	$ 3,381	$ 4,272
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 544	$ 209
Warrant issued in conjunction with Symphony GenIsis, Inc. transaction	$ —	$ 18,590

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
June 30, 2007
(Unaudited)

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three and six month periods ended June 30, 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 its period of performance relating to the term of the contractual arrangements. Occasionally, Isis is required to estimate its period of performance when the agreements it enters into do not clearly define such information. Should different estimates prevail, revenue recognized could be materially different. To date Isis' estimates have not required material adjustments. Isis has made estimates of its continuing obligations on several agreements. Isis' collaborative agreements typically include a research and/or development project plan that includes activities to be performed in the collaboration and the party responsible for performing them. Isis estimates the period of time over which it will complete the activities for which it is responsible and uses that period of time as its period of performance for purposes of revenue recognition and amortizes revenue over such period. When Isis' collaborators have asked Isis to continue performing work in a collaboration beyond the initial period of performance, Isis has extended its amortization period to correspond to the new extended period of performance. In no case have adjustments to performance periods and related adjustments to revenue amortization periods had a material impact on Isis' revenue.

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 the provisions in SAB 104 were met 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, Isis started to sell the Ibis T5000 Biosensor System commercially. The sale of each Ibis T5000 Biosensor System contains multiple elements. Since Isis had no previous experience 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 accounts for the entire system as one deliverable and recognizes revenue over the period of performance. The assay kits, which are sold separately from the instrument, are considered part of the system from an accounting perspective because the assay kits and the instrument are dependent on each other. 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 including related assay kits, 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. During the first half of 2007, Isis sold the remainder of its equity securities of Alnylam Pharmaceuticals, Inc. that it owned resulting in a realized gain of $3.5 million compared to a net gain on investments of $2.3 million during the same period in 2006. The net gain on investments during the first half of 2006 represented a gain of $2.7 million realized on the sale of a portion of the equity securities of Alnylam that Isis owned, offset by a non-cash loss on investment of $465,000 related to the impairment of Isis' equity in Antisense Therapeutics Ltd. Since the impairment in the second quarter of 2006, Isis has recorded a net unrealized gain of $486,000 related to its equity investment in ATL as a separate component of stockholders' equity, reflecting the increase in the market value of the investment since the impairment. Isis determined that there were no other-than-temporary declines in value of investments in the first half of 2007.

Inventory valuation

In accordance with Statement of Financial Accounting Standards ("SFAS") 2, *Accounting for Research and Development Costs*, Isis capitalizes the costs of raw materials that it purchases for use in producing its drugs because until Isis uses these raw materials they have alternative future uses. Isis includes in inventory raw material costs and related manufacturing 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. Each of Isis' raw materials can be used in multiple products and, as a result, has future economic value independent of the development status of any single drug. For example, if one of Isis' drugs failed, the raw materials allocated for that drug could be used to manufacture its other drugs. 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 $1.5 million and $861,000 as of June 30, 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 half of 2007 and 2006, Isis recorded a non-cash charge of $337,000 and $463,000, respectively, 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 or when events and circumstances indicate that these assets may have been impaired. Isis has adopted SFAS 144, *Accounting for the Impairment of Long-Lived Assets*. Isis recorded a charge of $337,000 and $463,000 for the first half 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, California and foreign tax net operating loss ("NOL") carryfowards of approximately $560.0 million, $179.5 million and $1.0 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 tax benefits related to NOL carryforwards and R&D credits 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 June 30, 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 June 30, 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 a 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. Historically, Isis' estimates have been accurate as it has not experienced any material differences between its estimates and its actual results.

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 June 30, 2007, Isis had collaborative arrangements with six entities that it considers to be variable interest entities ("VIE") under FIN 46R. Described below is Isis' relationship with Symphony GenIsis, Inc., which is the only VIE Isis is consolidating, and the collaborative arrangements entered into in 2007 that Isis considers to be VIE's.

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 June 30,		Six Months Ended June 30,	
	2007	2006	2007	2006
Comprehensive loss:				
Unrealized gains (losses)	$ 67	$ (3,634)	$ (713)	$ (1,073)
Reclassification adjustment for realized gains included in net income	(1,730)	—	(3,147)	—
Net loss applicable to common stock	(11,024)	(2,172)	(24,044)	(19,652)
Comprehensive loss	$ (12,687)	$ (5,806)	$ (27,904)	$ (20,725)

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 half of 2007 and 2006, the estimated expected term is a derived output of the simplified method, as allowed under SAB 107, *Share-Based Payment*.

For the six months ended June 30, 2007 and 2006, Isis used the following weighted-average assumptions in its Black-Scholes calculations:

Employee Stock Option Plan:

	June 30,	
	2007	2006
Risk-free interest rate	4.7%	4.9%
Dividend yield	0.0%	0.0%
Volatility	63.7%	68.7%
Expected Life	4.6 years	4.6 years

ESPP:

	June 30,	
	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 and six months ended June 30, 2007 and 2006 (in thousands, except per share data) was allocated as follows:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2007	2006	2007	2006
Research and development	$ 1,952	$ 1,103	$ 3,878	$ 2,256
Selling, general and administrative	437	295	875	516
Non-cash compensation expense related to stock options included in operating expenses	$ 2,389	$ 1,398	$ 4,753	$ 2,772
Basic and diluted net loss per share	$ (0.03)	$ (0.02)	$ (0.06)	$ (0.04)

As of June 30, 2007, total unrecognized compensation cost related to non-vested stock-based compensation plans was $13.1 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 1.4 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. Under SFAS 159, a financial instrument is 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 $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 recognized a $3.2 million loss on the early extinguishment of debt in the first half of 2007, which included a $1.2 million non-cash write-off of unamortized debt issuance costs.

4. Collaborative Arrangements and Licensing Agreements

Antisense Drug Discovery and Development Collaborations

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, Isis received a $15 million upfront licensing fee and is amortizing this amount over the three year period of Isis' performance based on the research plan included in the agreement. BMS will also provide Isis with at least $9 million in research funding over a period of three years. As of June 30, 2007, Isis has recognized revenue of $1.3 million related to the upfront licensing fee and the research funding. Isis' balance sheet at June 30, 2007 includes deferred revenue of $14.2 million related to the upfront licensing fee. 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.

Symphony GenIsis, Inc.

In April 2006, Isis entered into a series of related agreements in connection with a transaction with Symphony Capital and a group of co-investors to provide $75 million to fund the development of Isis' cholesterol-lowering drug, ISIS 301012, and two novel drugs from Isis' metabolic disease program ISIS 325568, targeting glucagon receptor ("GCGR"), and ISIS 377131, targeting glucocorticoid receptor ("GCCR"). The financing supports ISIS 301012 through the completion of registration-supporting clinical studies in patients with familial hypercholesterolemia and the completion of Phase 2b clinical trials in patients with high cholesterol. The financing also supports the development of ISIS 325568 and ISIS 377131 through initial proof-of-concept in human clinical trials. In addition to providing the financial support to move these three drugs forward, the transaction allows Isis to continue to control and manage the development of these drugs through key development milestones.

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

In exchange for the purchase option, Isis granted to Symphony GenIsis Holdings LLC a five-year warrant to purchase 4.25 million shares of common stock at an exercise price of $8.93 per share, a 25% premium over Isis' prior 60-day

average trading price, which was $7.14. To compensate Symphony Capital for structuring the transaction and to pay a portion of its expenses, Isis paid structuring and legal fees of $4.1 million. Using a Black-Scholes option-pricing model, Isis estimated the fair value of the warrant, at the grant date, to be $18.6 million. Isis' determination of the fair value of the warrant on the date of grant using an option-pricing model is affected by Isis' stock price as well as assumptions regarding a number of highly complex and subjective variables. These variables include, but are not limited to, Isis' expected stock price volatility over the term of the warrant. Option-pricing models were developed for use in estimating the value of traded options that have no vesting or hedging restrictions and are fully transferable. Because the warrant has certain characteristics that are significantly different from traded options, and because changes in the subjective assumptions can materially affect the estimated value, in management's opinion, the existing valuation models may not provide an accurate

measure of the fair value of the warrant, specifically the value determined may not be indicative of the fair value observed in a willing buyer/willing seller market transaction.

In accordance with FIN 46R, Isis has determined that Symphony GenIsis is a variable interest entity for which Isis is the primary beneficiary. As a result, Isis includes the financial condition and results of operations of Symphony GenIsis in Isis' condensed consolidated financial statements. Isis' condensed consolidated financial statements include the cash and cash equivalents held by Symphony GenIsis. Additionally, the condensed consolidated financial statements include line items called "Noncontrolling interest in Symphony GenIsis." On the Condensed Consolidated Balance Sheets, this line item initially reflected the $75 million proceeds contributed into Symphony GenIsis less $4.1 million of structuring and legal fees and the $18.6 million fair value of the warrant issued by Isis to Symphony Capital. As Isis and Symphony GenIsis progress through their collaboration, this line item is being reduced by Symphony GenIsis' expenditures, which were $37.4 million from the inception of the collaboration to June 30, 2007, until the balance becomes zero. The reductions to the "Noncontrolling Interest in Symphony GenIsis" on the Condensed Consolidated Balance Sheets are also recognized in Isis' Condensed Consolidated Statements of Operations using a similar caption and reduce Isis' net loss applicable to common stock. For the three and six months ended June 30, 2007, Isis' net loss was reduced by $7.6 million and $14.4 million, respectively, compared to $13.6 million for the same periods in 2006.

The Ludwig Institute; Center for Neurological Studies

In October 2005, Isis entered a collaboration agreement with the Ludwig Institute, the Center for Neurologic Study (CNS) and researchers from these institutions to discover and develop antisense drugs in the areas of amyotrophic lateral sclerosis (ALS) and other neurodegenerative diseases. Under this agreement, Isis agreed to pay the Ludwig Institute and CNS royalties and modest milestones on any antisense drugs discovered and developed within the collaboration. The researchers from the Ludwig Institute and CNS, through funding from the ALS Association, will conduct preclinical safety and efficacy studies of ISIS 333611.

Pfizer, Inc.

In May 2005, Isis entered into a multi-year drug discovery collaboration with Pfizer to identify second generation antisense drugs for the treatment of ophthalmic disease. Under the terms of the agreement, Isis received an upfront technology access fee of $1.0 million and amortized this amount over the one year period of Isis' performance based on the research plan included in the agreement, which ended in April 2006. There were no changes in Isis' period of performance. There was no deferred revenue as of June 30, 2007 and December 31, 2006. As of June 30, 2007, Isis has earned milestone payments totaling $1.2 million under the collaboration. Pfizer will also pay Isis additional milestone payments if key research, clinical, regulatory and sales milestones are achieved, and provide research funding. Assuming that Pfizer successfully develops and commercializes the first drug for the first indication, Isis will earn milestone payments totaling up to $26.1 million. In addition, Isis will receive royalties on the sale of drugs resulting from the collaboration. For the three and six months ended June 30, 2007, Isis recognized revenue of $65,000 and $385,000, respectively, related to this collaboration compared to $203,000 and $533,000 for the same periods in 2006.

Eli Lilly and Company

In August 2001, Isis entered into a broad strategic relationship with Lilly, which included a joint antisense research collaboration in the areas of cancer, metabolic and imflammatory diseases and a $100 million loan that Lilly provided to Isis to fund its obligations under the research collaboration.

In August 2005, Isis extended the research collaboration with Lilly for approximately 24 months to focus on a select number of targets. During the extension, Isis and Lilly continue to advance antisense drugs identified during the initial collaboration, and continue their efforts to develop and refine antisense technologies. During the extension, Isis is using collaboration funds to support its scientists and Lilly is supporting Lilly scientists. The extended collaboration provides Lilly

access to Isis' patents to support Lilly's internal antisense drug discovery and development program for a limited number of targets. As part of the extension, Isis and Lilly will continue to characterize and develop RNase H, siRNA, and splicing modulating inhibitors for the treatment of cancer using advanced generation chemistries. In connection with the extension, Isis converted the $100 million loan that Lilly previously provided to it into 2.5 million shares of Isis common stock.

As part of the collaboration, Lilly licensed LY2181308, Isis' antisense inhibitor of survivin and LY2275796, an antisense inhibitor of eIF-4E. As of June 30, 2007, Isis has earned $4.1 million and $1.5 million in license fees and milestone payments related to the continued development of LY2181308 and LY2275796, respectively. Isis amortized the $1.1 million license fee related to LY2181308 over a two-year period, which ended in June 2004. The two-year period corresponded to Isis' period of performance for LY2181308 and there were no changes to the period of performance. In September 2004, Isis recognized $750,000 associated with the license fee it received for LY2275796. Lilly is responsible for the preclinical and clinical development of LY2275796 and Isis has no performance obligations for this drug. There was no deferred revenue as of June 30, 2007 and December 31, 2006. Isis will receive additional milestone payments aggregating up to $25.0 million and $19.5 million if LY2181308 and LY2275796, respectively, achieve specified regulatory and commercial milestones, and royalties on future product sales of these drugs.

As part of the collaboration extension, Isis is exploring with Lilly antisense drugs targeting Signal Transducer and Activator of Transcription 3 (STAT-3), a protein that regulates cell division and growth, and prevents cell death. Isis is working closely with Lilly to advance an improved STAT-3 candidate into development.

During the three and six months ended June 30, 2007, Isis generated revenue from its relationship with Lilly totaling $102,000 compared to $405,000 and $1.2 million for the same periods in 2006.

Merck & Co., Inc.

In June 1998, Isis entered into a multi-year research collaboration and license agreement with Merck to discover small molecule drug candidates to treat patients infected with HCV. The research collaboration ended in May 2003 in accordance with its terms. However, in December 2006, Merck advanced a drug discovered in this collaboration into Phase 1 clinical trials for which Isis received a $1 million milestone payment. In addition, Merck will pay Isis

aggregate milestone payments of up to $16 million upon the achievement of key clinical and regulatory milestones, and royalties on future product sales. During the first half of 2007 and 2006, Isis did not recognize any revenue from its relationship with Merck.

Satellite Company Drug Discovery and Development Collaborations

Achaogen, Inc.

In January 2006, Isis licensed its proprietary aminoglycosides program to Achaogen, a biotechnology company pursuing unique strategies to combat drug-resistant pathogens. Aminoglycosides are a group of antibiotics that inhibit bacterial protein synthesis and are used to treat serious bacterial infections. In exchange for the exclusive, worldwide license to Isis' aminoglycoside program, Achaogen issued to Isis $1.5 million of Achaogen Series A Preferred stock. Isis has recognized a valuation allowance of $1.5 million to offset this asset as realization of this asset is uncertain. In addition, assuming Achaogen successfully develops and commercializes the first drug in the first major market, Isis will receive milestone payments totaling up to $34.5 million for the achievement of key clinical, regulatory and sales milestones. Isis will also receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of the aminoglycoside program and products. During the first half of 2007 and 2006, Isis did not recognize any revenue from its relationship with Achaogen.

Antisense Therapeutics Limited

In December 2001, Isis licensed ATL1102 to ATL, an Australian company publicly-traded on the Australian Stock Exchange. Isis was responsible for completing the required preclinical studies for ATL1102 and for manufacturing the drug for human clinical trials at ATL's expense. ATL agreed to undertake the future clinical development and commercialization of the drug.

In addition to ATL1102, ATL is currently developing ATL1103 for growth and site disorders. ATL1103 is a product of Isis' joint antisense drug discovery and development collaboration, which Isis recently extended for an additional two years. ATL pays Isis for access to its antisense expertise and for research and manufacturing services Isis may provide to

ATL during the collaboration. Additionally, ATL will pay Isis royalties on any antisense drugs discovered and developed within the partnership.

In connection with this collaboration, Isis received 30.0 million shares of ATL common stock upon completion of ATL's initial public offering ("IPO"), representing an initial ownership percentage of approximately 14%, and options to purchase an additional 20.0 million shares of ATL common stock, which expired in 2006. The initial ATL common stock Isis received had a value of $2.8 million, and Isis recognized this amount into revenue ratably over the five-year period of performance under the collaboration, which ended in November 2006. There were no changes in Isis' period of performance. There was no deferred revenue as of June 30, 2007 and December 31, 2006. For the three and six months ended June 30, 2007, Isis recorded revenue of $44,000 and $55,000, respectively, related to this collaboration compared to $179,000 and $355,000 for the same periods in 2006. As of June 30, 2007, Isis' ownership percentage in ATL, including 10.3 million shares Isis purchased subsequent to shares it acquired in the IPO, was less than 10%. Isis' balance sheets at June 30, 2007 and December 31, 2006 included a short-term investment at fair market value of $1.4 million and $1.3 million, respectively, related to this equity investment.

Atlantic Healthcare (UK) Limited

In March 2007, Isis licensed alicaforsen to Atlantic Healthcare (UK) Limited, a UK-based company that was founded in 2006 by gastrointestinal drug developers to develop alicaforsen for the treatment of ulcerative colitis and other inflammatory diseases. Atlantic Healthcare plans to initially develop alicaforsen for pouchitis, an ulcerative colitis indication, followed by ulcerative colitis and other inflammatory diseases. In exchange for the exclusive, worldwide license to alicaforsen, Isis received an upfront payment from Atlantic Healthcare in the form of equity valued at $2 million. Isis has recognized a valuation allowance of $2 million to offset this asset as realization of this asset is uncertain. In addition, assuming Atlantic Healthcare successfully develops and commercializes alicaforsen, Isis will receive milestone payments and royalties on future product sales of alicaforsen. If Atlantic Healthcare meets certain of these milestones, at Atlantic Healthcare's request, Isis will attempt to identify a second generation lead drug candidate for Atlantic Healthcare. Atlantic Healthcare may take an exclusive worldwide license to the lead candidate under the terms and conditions of the agreement. Atlantic Healthcare is solely responsible for the continued development of alicaforsen, and, if selected, the second generation lead drug candidate. During the first half of 2007, Isis did not recognize any revenue from its relationship with Atlantic Healthcare.

iCo Therapeutics, Inc.

In August 2005, Isis granted a license to iCo for the development and commercialization of iCo 007, a second generation antisense drug. iCo is initially developing iCo 007 for the treatment of various eye diseases caused by the formation and leakage of new blood vessels, such as diabetic macular edema and diabetic retinopathy. iCo paid Isis a $500,000 upfront fee consisting of $250,000 in cash and a $250,000 convertible note. Isis has recognized a valuation allowance of $250,000 to offset the convertible note and the resulting common stock of iCo as the realization of this asset is uncertain. iCo will also pay Isis milestone payments totaling up to $23.0 million for the achievement of clinical and regulatory milestones. In addition, Isis will receive royalties on any product sales of this drug. Under the terms of the agreement, iCo is solely responsible for the clinical development and commercialization of the drug. In December 2006, iCo filed an IND application with the FDA for iCo 007 for which Isis earned a $200,000 milestone payment.

In December 2005, Isis entered into a manufacturing and supply agreement with iCo. Under the agreement, iCo purchased drug manufactured by Isis for $700,000. iCo made a $525,000 prepayment to Isis consisting of $175,000 in cash and a $350,000 convertible note. Isis has recognized a valuation allowance of $350,000 to offset the convertible note and the resulting common stock of iCo as the realization of this asset is uncertain. In December 2006, Isis' obligations under the manufacturing and supply agreement were completed and title of the product transferred to iCo. As a result, in January 2007, iCo paid Isis the remaining balance of $175,000. In May 2006, Isis received 869,025 shares of iCo common stock for the conversion of both convertible notes. There was no deferred revenue as of June 30, 2007 and December 31, 2006. During the first half of 2007 and 2006, Isis did not recognize any revenue from its relationship with iCo.

ImQuest Pharmaceuticals, Inc.

In April 2006, Isis granted an exclusive worldwide license to ImQuest for the development and commercialization of ISIS 5320, a compound that has been shown to be a potent and specific inhibitor of HIV, the virus that causes AIDS. ImQuest plans to develop ISIS 5320 as a topical microbicide therapy to prevent the sexual transmission of HIV throughout the world, but especially in developing countries. In exchange for the exclusive worldwide license, Isis will receive royalties on sales of drugs resulting from ISIS 5320. In addition, if ImQuest sublicenses ISIS 5320, Isis is entitled to a portion of the consideration received. During the first half of 2007 and 2006, Isis did not recognize any revenue from its relationship with ImQuest.

OncoGenex Technologies Inc.

In November 2001, Isis established a drug development collaboration with OncoGenex, a biotechnology company committed to the development of cancer therapeutics for patients with drug resistant and metastatic cancers, to co-develop and commercialize OGX-011, an anti-cancer antisense drug. Isis funds 35% of the costs of developing OGX-011. In exchange, Isis receives 35% of any revenue generated by OncoGenex for OGX-011. OGX-011 combines OncoGenex's proprietary antisense position in inhibitors to the target clusterin, with Isis' proprietary second generation antisense chemistry. Isis conducted preclinical toxicology and pharmacokinetic studies of OGX-011 during 2002. Isis also manufactured OGX-011 for preclinical and Phase 1/2 studies. OncoGenex's Phase 1 clinical trials to assess the safety of OGX-011 in combination with hormone ablation therapy in men with localized prostate cancer and in combination with standard chemotherapy in patients with solid tumors known to express clusterin formed the basis for OncoGenex's broad Phase 2 program for OGX-011. OncoGenex currently has five ongoing Phase 2 studies of OGX-011 for the treatment of prostate, non-small cell lung and breast cancers.

In September 2003, the companies expanded their antisense drug development partnership to include the development of the second generation antisense anti-cancer drug, OGX-225. OncoGenex is responsible for the preclinical and clinical development of the drug and Isis has no performance obligations. OncoGenex issued to Isis $750,000 of OncoGenex securities as payment for an upfront fee. In addition, OncoGenex will pay Isis milestone payments totaling up to $3.5 million for the achievement of clinical and regulatory milestones, and pay Isis royalties on product sales. As of June 30, 2007, OncoGenex had not triggered any of the milestone payments related to OGX-225.

In January 2005, Isis further broadened its antisense drug development partnership with OncoGenex to allow for the development of two additional second generation antisense anti-cancer drugs. Under the terms of the agreement, OncoGenex is responsible for the preclinical and clinical development of the drugs and Isis has no performance obligations. In April 2005, OncoGenex selected its first drug under this expansion, OGX-427. OGX-427 targets heat shock protein 27, or Hsp27, which is over-expressed in numerous tumor types and is associated with treatment resistance through its ability to help cancer cells survive stress-induced injury. OncoGenex paid Isis an upfront fee of $750,000 with a convertible note, which, in August 2005, converted into 244,300 shares of OncoGenex's preferred stock. OncoGenex will also pay Isis milestone payments totaling up to $5 million for the achievement of key clinical and regulatory milestones, and royalties on future product sales of these drugs. As of June 30, 2007, OncoGenex had not triggered any of the milestone payments related to OGX-427.

For the three and six months ended June 30, 2007, Isis earned revenue of $4,000 related to its collaboration with OncoGenex compared to $1.1 million for the same periods in 2006. Isis' balance sheets at June 30, 2007 and December 31, 2006 include a long-term investment of $1.5 million related to Isis' equity investment in OncoGenex. While there is no readily determinable market value for these securities, there has been no indication that Isis' investment in OncoGenex has been impaired; accordingly, Isis believes that the carrying value of this investment is equal to or below its current fair market value.

Sarissa, Inc.

In February 2005, Isis licensed an anti-cancer antisense drug to Sarissa, Inc., a biotechnology company emerging from the University of Western Ontario. The drug is an antisense inhibitor of thymidylate synthase, or TS, a drug target that protects cancer cells from the effects of several chemotherapy treatments. In preclinical studies, antisense inhibition of TS suppressed human tumor cell growth and overcame tumor cell resistance to marketed TS-targeted drugs.

Under the terms of the agreement, Sarissa paid Isis a $1.0 million upfront fee in exchange for the exclusive, worldwide license to the TS antisense drug. Sarissa paid the upfront fee with a convertible note, which will convert into Sarissa stock upon Sarissa's successful completion of a venture capital financing. Isis has recognized a valuation allowance of $1.0 million to offset the note as realization of this asset is uncertain. Sarissa will also pay Isis milestone payments totaling up to $5.5 million for the achievement of clinical and regulatory milestones. In addition, Isis will receive royalties on any sales of the TS antisense drug. Sarissa is solely responsible for preclinical and clinical development of the drug. During the first half of 2007 and 2006, Isis did not recognize any revenue from its relationship with Sarissa.

Satellite Company Technology Research Collaborations

Alnylam Pharmaceuticals, Inc.

In March 2004, Isis entered into a strategic alliance with Alnylam to develop and commercialize RNAi therapeutics. Under the terms of the agreement, Isis exclusively licensed to Alnylam its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5.0 million technology access fee, participation in fees for Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. For each drug developed by Alnylam under this alliance, the potential milestone payments from Alnylam total $3.4 million and are payable to Isis upon the occurrence of specified development and regulatory events. Isis retained rights to a limited number of double-stranded RNAi therapeutic targets and all rights to single-stranded RNAi therapeutics. Isis also made a $10 million equity investment in Alnylam.

In turn, Alnylam nonexclusively licensed to Isis Alnylam patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded RNAi therapeutics and to research double-stranded RNAi compounds. Isis also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on either an exclusive or co-exclusive basis depending on the target. If Isis develops or commercializes an RNAi-based drug using Alnylam's technology, Isis will pay Alnylam milestones and royalties. For each drug, the potential milestone payments to Alnylam total $3.4 million and are payable by Isis upon the occurrence of specified development and regulatory events. As of June 30, 2007, Isis did not have an RNAi-based drug in clinical development. As part of the collaboration, each party granted the other party a nonexclusive cross license to its respective patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for microRNA therapeutics.

Isis' Alnylam alliance provides it with an opportunity to realize substantial value from its pioneering work in antisense mechanism and oligonucleotide chemistry and is an example of Isis' strategy to participate in all areas of RNA-based drug discovery. As of June 30, 2007, Isis has earned approximately $5.0 million from Alnylam resulting from sublicenses of Isis' technology for the development of RNA interference therapeutics that Alnylam has granted to pharmaceutical partners. In the quarter in which Alnylam's transaction with Roche Holding AG receives Hart-Scott-Rodino clearance, Isis will earn additional licensing revenue of $26.5 million resulting from Alnylam's sublicense of Isis' technology for the development of RNA interference therapeutics to Roche. The transaction is expected to receive clearance in the third quarter of 2007.

As of June 30, 2007, Isis no longer owns any shares of Alnylam. At December 31, 2006, Isis' balance sheet included a short-term investment at carrying value of $5.6 million, which represented 290,000 shares of Alnylam's stock. During the first half of 2007 and 2006, Isis sold portions of its Alnylam stock for cash proceeds of $5.2 million and $4.4 million, respectively. Isis did not recognize any revenue from its relationship with Alnylam during the first half of 2007 and 2006.

Archemix

In August 2007, Isis and Archemix entered into a new strategic alliance focused on aptamer drug discovery and development. Archemix obtained a license to Isis' technology for aptamer drugs, which take advantage of the three-dimensional structure of oligonucleotides to bind to proteins rather than the mRNA-targeting aspect that antisense mechanisms, including RNAi, exploit. Through this licensing partnership, Isis is providing access to its oligonucleotide chemistry and other relevant patents to facilitate the discovery and development of aptamer drugs. Isis will receive a portion of any sublicensing fees Archemix generates as well as milestones and royalties on its drugs.

Ercole Biotech, Inc.

In May 2003, Isis and Ercole initiated a multi-year collaboration to discover antisense drugs that regulate alternative RNA splicing. Part of this collaboration includes a cross-license of Isis' respective splicing-related intellectual property with Ercole. Isis is combining its alternative splicing expertise with Ercole to discover antisense drugs that regulate alternative RNA splicing. As part of this collaboration, Isis granted Ercole a license to Isis' Bcl-x molecule and certain of its chemistry patents. In addition, Isis took an equity ownership position in Ercole with the initial funding, in the form of a convertible note, which the companies anticipate will convert into securities that Ercole issues in its next venture capital financing. Isis also has the option to make an additional equity investment in Ercole. Pursuant to the terms of a Note and Warrant Purchase Agreement, during 2003 and early 2004, Isis made cash payments to Ercole of $500,000 and $250,000, respectively in exchange for a convertible note. Isis expensed the payments when made. The note is secured by all of Ercole's assets, including intellectual property and licenses. The note will convert into securities that Ercole issues in a qualified financing, as defined by the agreement. During the first half of 2007 and 2006, Isis did not recognize any revenue from its relationship with Ercole.

Rosetta Genomics, Ltd.

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

Santaris Pharma A/S (formerly Pantheco A/S)

In November 1998 and September 2000, Isis entered into license agreements with Santaris, formerly Pantheco. Isis amended and restated the agreement in May 2003. Under the terms of the amended and restated license agreements, Isis licensed its novel antisense chemistry, Peptide Nucleic Acid, or PNA, to Santaris on a limited exclusive basis to develop products. The license restricts Santaris to a limited number of molecular targets that are subject to Isis' approval. Santaris has agreed to pay Isis royalties on any products developed under the license.

As part of its original license agreements with Pantheco, Isis received shares of Pantheco stock. In May 2003, Pantheco and Cureon A/S merged to form Santaris. Prior to the merger, Isis purchased additional shares of Pantheco for $55,000 as a result of anti-dilution provisions related to Pantheco's stock. As of June 30, 2007 and December 31, 2006, Isis' ownership interest in Santaris was less than 10%. Isis' balance sheets at June 30, 2007 and December 31, 2006 included a long-term investment of $625,000, respectively, related to this equity investment, reflecting the value of Isis' initial investment and additional purchase due to anti-dilution provisions. While there is no readily determinable market value for these securities, there has been no indication that Isis' investment in Santaris has been impaired; accordingly, Isis believes that the carrying value of this investment is equal to or below its current fair market value. During the first half of 2007 and 2006, Isis did not recognize any revenue from its relationship with Santaris.

Intellectual Property Licensing Agreements

In-Licensing Arrangements

Idera Pharmaceuticals, Inc., formerly Hybridon, Inc.

In May 2001, Isis entered into an agreement with Hybridon under which Isis acquired an exclusive license to all of Hybridon's antisense chemistry and delivery patents and technology. Hybridon retained the right to practice its licensed antisense patent technologies and to sublicense it to collaborators under certain circumstances. In addition, Hybridon received a non-exclusive license to Isis' suite of RNase H patents. In exchange for the license to

Hybridon's antisense patents, Isis paid $15.0 million in cash and agreed to pay Hybridon $19.5 million in Isis common stock before May 2003. In return for access to Isis' patents, Hybridon agreed to pay Isis $6.0 million in Hybridon common stock before May 2004. Isis' balance sheets at June 30, 2007 and December 31, 2006 reflected a licensing asset, net of amortization, of $16.7 million and $17.6 million, respectively. During 2004 and 2005, Isis sold all of its short term investment in Hybridon for net proceeds of approximately $665,000. In September 2005, Hybridon changed its name to Idera Pharmaceuticals, Inc. For the three and six months ended June 30, 2007, Isis earned revenue of $10,000 related to its relationship with Hybridon compared to $0 for the same periods in 2006.

Integrated DNA Technologies, Inc.

In March 1999, Isis further solidified its intellectual property leadership position in antisense technology by licensing certain antisense patents from Integrated DNA Technologies, Inc. ("IDT"), a leading supplier of antisense inhibitors for research. The patents Isis licensed from IDT are useful in functional genomics and in making certain antisense drugs. In December 2001, Isis expanded this license agreement to allow it to exclusively sublicense this intellectual property for functional genomics purposes. Under the license, Isis paid IDT $4.9 million in license fees and will pay royalties on drugs utilizing the technology IDT licensed to Isis.

Out-Licensing Arrangements; Royalty Sharing Agreements

Drug Royalty USA, Inc. (now Drug Royalty Trust 3)

In December 2004, Isis sold a portion of its royalty rights in Macugen to Drug Royalty USA, Inc. ("DRC"). In exchange for this sale, DRC has paid Isis $15.0 million to date and agreed to pay Isis an additional $9.0 million in the fourth quarter of 2007. Under the terms of the agreement, Isis and DRC share the royalty rights on Macugen through 2009. After 2009, Isis retains all royalties for Macugen under its Eyetech agreement. Under the agreement, through 2009, DRC will receive the royalties on the first $500 million of annual sales of Macugen. Isis and DRC will each receive 50 percent of royalties on annual sales between $500 million and $1.0 billion. Isis retains 90 percent of all royalties on annual sales in excess of $1.0 billion and 100 percent of all royalties after 2009. Isis has retained all milestones payable to Isis by Eyetech under the license agreement. During the first half of 2007 and 2006, Isis did not recognize any revenue from its relationship with DRC.

As part of the sale, Isis agreed to pay DRC liquidated damages if any one of a defined set of defaults occurs. The amount of liquidated damages will be calculated such that DRC will receive a ten percent per annum return, compounded quarterly on the total of all purchase price payments made by DRC to Isis through the default date minus the total of any royalties received by DRC through the default date. As of June 30, 2007, DRC has received $6.0 million in royalties. In addition, DRC may withhold any installment of the purchase price if immediately prior to such payment, Isis fails to meet a minimum liquidity requirement equal to the then outstanding balance on its loan with Silicon Valley Bank; plus the potential amount of liquidated damages, assuming that DRC has paid the impending purchase price installment; plus its cash burn over the most recent three months. As collateral for its obligations under the sale agreement, Isis granted DRC a first priority security interest in the patents licensed by Isis to Eyetech under the license agreement and in the license agreement itself. In June 2007, DRC alleged that Isis breached representations, warranties and covenants under its agreement with DRC. A more detailed discussion is included in Part II, Item 1 – Legal Proceedings.

Eyetech Pharmaceuticals, Inc.

In December 2001, Isis licensed to Eyetech Pharmaceuticals, Inc., a wholly owned subsidiary of OSI Pharmaceuticals, Inc., certain of its patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense drug for use in the treatment of ophthalmic diseases, that Eyetech is co-developing and commercializing with Pfizer. Eyetech paid Isis a $2.0 million upfront fee and agreed to pay Isis milestone and royalty payments in exchange for non-exclusive, worldwide rights to the intellectual property licensed from Isis.

During 2004, Isis earned $4.0 million in milestones associated with the filing of an NDA and FDA approval for Macugen for the treatment of wet age-related macular degeneration. Isis' license with Eyetech will also generate additional milestone payments aggregating up to $2.8 million for the achievement of specified regulatory milestones with respect to the use of Macugen for each additional therapeutic indication. During the first half of 2007 and 2006, Isis did not recognize any revenue from its relationship with Eyetech.

Ibis Collaborations

Isis developed, within Ibis, the Ibis T5000 Biosensor System with substantial funding from government agencies. Ibis continues to work with government collaborators to further develop the Ibis technology and applications for the Ibis T5000. Ibis is now commercializing the Ibis T5000 instrument, assay kits and its assay services to both government and non-government customers.

Commercial Agreements

Ibis plans to work with partners to manufacture, install and support Ibis T5000 instruments. For research markets Ibis is working with Bruker Daltonics to accomplish this. Ibis expects in the future to work with a partner to complete development, regulatory approval, and then market the Ibis instruments for the *in vitro* diagnostics market. Ibis plans to focus on the manufacture and sale of high-volume, high-margin consumables. Ibis also generates commercial revenue through its assay services laboratory, in which it analyzes customers' samples in its own facilities, providing prospective instrument customers the opportunity to assess the Ibis T5000 Biosensor System's capabilities before purchasing an instrument.

Bruker Daltonics, Inc.

In July 2006, Ibis 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 systems and Ibis assay kits for various government applications, and non-exclusive rights to sell to customers for all other applications except diagnostics. Ibis has maintained worldwide marketing rights to the diagnostics market.

Assay Services Collaboration

In July 2006, Ibis received a contract to perform forensic analyses of up to 10,000 samples in its assay services laboratory. Initial funding from this contract was $1.9 million. In June 2007, Ibis received additional funding of $1.6 million relating to this contract. For the three and six months ended June 30, 2007, Isis recognized $593,000 and $1.1 million, respectively, relating to this contract. This assay services capability represents a key part of the Ibis business strategy, as it not only has the potential to be an important revenue-generating opportunity for the business, but also represents an important resource for customers evaluating the capabilities of the Ibis T5000 and collaborating in applications development.

Research and Development Collaborations

To develop the Ibis T5000 Biosensor System and its applications, Ibis received contracts and grants from a number of government agencies, including Defense Advanced Research Projects Agency ("DARPA"), the Department of Homeland Security ("DHS"), the Centers for Disease Control ("CDC"), and the National Institute of Allergy and Infectious Diseases ("NIAID"), a part of the National Institutes of Health ("NIH"). Government collaborations continue to represent a significant source of funding for the Ibis T5000 program. As a result of these collaborations, Ibis is now developing various applications for the Ibis T5000 Biosensor System that it will sell to commercial customers, including government collaborators.

Biodefense

The earliest application of the Ibis T5000 Biosensor System to be funded by the government focused on bioagent detection. In March 2004, Ibis received a two-year contract from DARPA under a subcontract from Science Applications International Corporation ("SAIC") to further develop the Ibis biosensor system to identify infectious agents in biological warfare attacks. As part of this program, Ibis successfully demonstrated proof-of-principle of the Ibis biosensor system by identifying a variety of bacteria and viruses in both environmental and human clinical samples. In 2005, under a subcontract from SAIC and with support from DARPA, Ibis delivered its first Ibis biosensor system to the United States Army Medical Research Institute of Infectious Diseases ("USAMRIID") for use in biodefense.

Forensics

Microbial forensics is a type of forensics used to investigate crimes involving infectious organisms. Microbial forensics uses the "biological fingerprint" of an infectious organism to help pinpoint the source, allowing law enforcement and public health officials to effectively respond to a biological threat. Additionally, through a government grant, Ibis is continuing its ongoing development of an informational database on microbial agents. The program is a database of biological threat agents, their DNA sequences, and their effects, that law enforcement officials can use to confer deterrence and support forensic investigations. In 2005, under a subcontract from SAIC and with support from DARPA, Ibis installed its second biosensor system at the DHS's National Bioforensic Analysis Center ("NBFAC") for use in bioforensics.

Epidemiological Surveillance, Infectious Disease Research and Hospital-Associated Infection Control

Ibis and its government partners continue to develop applications for the T5000 Biosensor System to rapidly identify, monitor, and control infectious diseases. Specifically, in August 2005, Ibis received a three-year grant worth up to $4.9 million from the NIAID, a part of the NIH. The grant funds the continued development of applications to diagnose infectious diseases and to identify and control hospital-associated infections ("HAI") using the Ibis T5000 Biosensor System. In September 2006, Ibis successfully completed the first phase of this grant and has been granted funding for the second and third phases of the grant, which includes installing an Ibis T5000 Biosensor System at Johns Hopkins University Medical Center. The purpose of the grant is to develop infectious organism identification (ID) test kits to identify a broad range of respiratory and blood-borne infectious agents, including bacteria and viruses on the NIAID, a part of the NIH, priority list. In addition to deployment of an Ibis T5000 Biosensor System, the second and third phases of the grant—approximately $2.6 million—include funding for the purchase of assay kits to analyze human samples in validation studies.

In addition, in September 2003, Ibis received a three-year grant for up to $6.0 million from the CDC to develop and apply the Ibis biosensor system technology to the surveillance of human infectious disease in the United States. Ibis installed an Ibis biosensor system at the CDC in September 2006 under this contract. Earlier in 2006, Ibis installed a biosensor system at the Naval Health Research Center. The Navy is using the Ibis biosensor system in respiratory disease surveillance and has analyzed hundreds of samples on the Ibis biosensor system at its facility.

5. Symphony Warrant

In April 2006, Isis granted the members of Symphony GenIsis Holdings LLC warrants to purchase 4.25 million shares of common stock at an exercise price of $8.93 per share. These warrants expire on April 7, 2011 and can be settled with unregistered shares of Isis' common stock. At June 30, 2007, all of these warrants remained issued and outstanding. If Isis enters into a merger or acquisition in which the surviving or resulting "parent" entity is an entity other than Isis, then the holders of these warrants may exchange the warrants for a new warrant exercisable in return for shares of common stock of the surviving entity as follows:

- if the terms of such merger or acquisition provide for consideration that consists solely of stock of the surviving entity, and the surviving entity has a class of common stock traded on a major national exchange or foreign exchange ("Public Common Shares"), then any replacement warrants issued to the holders will be solely for such publicly traded common shares, at an exchange ratio reflecting the stock consideration paid at the time of such change in control; or

- if the terms of such merger or acquisition shall provide for consideration that consists of cash or a combination of cash and Public Common Shares of the surviving entity, then any replacement warrants issued to the holders will be solely for Public Common Shares of the surviving

entity, at an exchange ratio reflecting the total consideration paid by the surviving entity at the time of such change in control, as if the total consideration (including cash) for each share of Isis' common stock was instead paid only in Public Common Shares of the surviving entity at the time of such change of control; or

- if the surviving entity is a private corporation, closely held company or other entity that does not have a class of Public Common Shares, then the holders of the warrants may elect to surrender all outstanding warrants to Isis in consideration of a cash payment for each share of its common stock subject to purchase under the warrants in an amount equal to 40% of the per share cash consideration to be received by a holder of one share of its common stock to be tendered in the merger or acquisition, subject to an aggregate limit of $22,000,000.

In connection with the issuance of the warrants, Isis entered into a registration rights agreement with Symphony GenIsis Holdings LLC. Pursuant to the registration rights agreement, Isis filed a registration statement with the SEC covering the shares of common stock issuable upon exercise of the warrants. Isis is required to use commercially reasonable efforts to maintain the effectiveness of the registration statement over the term of the warrant.

Isis evaluated the provisions of the Registration Rights Agreement and the Warrant Purchase Agreement under EITF 00-19, *Accounting for Derivative Financial Instruments Indexed to, and Potentially Settled in, a Company's Own Stock,* and determined that the criteria for equity classification were met; therefore, the warrants were accounted for as part of stockholders' equity.

6. 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 June 30, 2007				
Revenue:				
Research and development	$ 1,591	$ 1,081	$ —	$ 2,672
Commercial revenue (1)	—	810	—	810
Licensing and royalty	331	—	—	331
Total segment revenue	$ 1,922	$ 1,891	$ —	$ 3,813
Loss from operations	$ (16,790)	$ (2,870)	$ —	$ (19,660)
Three Months Ended June 30, 2006				
Revenue:				
Research and development	$ 1,912	$ 2,410	$ —	$ 4,322
Licensing and royalty	53	—	—	53
Total segment revenue	$ 1,965	$ 2,410	$ —	$ 4,375
Income (Loss) from operations	$ (15,620)	$ (1,697)	$ 215	$ (17,102)

	Drug Discovery and Development	Ibis	Corporate	Total
Six Months Ended June 30, 2007				
Revenue:				
Research and development	$ 2,017	$ 2,026	$ —	$ 4,043
Commercial revenue (1)	—	1,441	—	1,441
Licensing and royalty	779	—	—	779
Total segment revenue	$ 2,796	$ 3,467	$ —	$ 6,263
Loss from operations	$ (34,557)	$ (6,004)	$ —	$ (40,561)
Six Months Ended June 30, 2006				
Revenue:				
Research and development	$ 3,183	$ 5,608	$ —	$ 8,791
Licensing and royalty	543	—	—	543
Total segment revenue	$ 3,726	$ 5,608	$ —	$ 9,334
Income (Loss) from operations	$ (31,296)	$ (2,000)	$ 178	$ (33,118)

(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. Additionally, 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 June 30,		Six Months Ended June 30,	
	2007	2006	2007	2006
Partner A	33%	0%	20%	0%
Partner B	28%	11%	32%	13%
Partner C	11%	2%	10%	1%
Partner D	10%	25%	14%	21%
Partner E	3%	9%	2%	12%
Partner F	2%	8%	2%	19%
Partner G	0%	25%	0%	12%
Partner H	0%	11%	0%	8%

For the three months ended June 30, 2007 and 2006, Isis derived approximately 50% and 55%, respectively, of its revenue from agencies of the United States Government compared to 55% and 60% for the six months ended June 30, 2007 and 2006, respectively. For the first half of 2007, four of the six significant partners listed above represent revenue from agencies of the United States Government.

Contract receivables from three significant partners comprised approximately 55%, 20% and 12% of contract receivables at June 30, 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 or projections. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, in developing and commercializing systems to identify infectious organisms that are effective and commercially attractive, and in the endeavor of building a business around such products. 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. SEC, and those identified within this Item entitled "Risk Factors" beginning on page 37 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. We have generated more than $81.9 million from our intellectual property licensing

program that helps support our internal drug discovery and development programs. Not included in this amount is the $26.5 million due to us from Alnylam resulting from Alnylam's sublicense of our technology to Roche. In the quarter in which Alnylam receives Hart-Scott-Rodino clearance, we will recognize the $26.5 million as revenue. The transaction is expected to receive clearance in the third quarter of 2007.

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 Biosensor System and related applications has been funded through government contracts and grants. As of June 30, 2007, we had earned $60.7 million in revenue under our government contracts and grants, and we had an additional $6.2 million committed under our existing contracts and grants.

Recent Events

Archemix

In August 2007, Archemix and us entered into a new strategic alliance focused on aptamer drug discovery and development. Archemix obtained a license to our technology for aptamer drugs, which take advantage of the three-dimensional structure of oligonucleotides to bind to proteins rather than the mRNA-targeting aspect that antisense mechanisms, including RNAi, exploit. Through this licensing partnership, we are providing access to our oligonucleotide chemistry and other relevant patents to facilitate the discovery and development of aptamer drugs. We will receive a portion of any sublicensing fees Archemix generates as well as milestones and royalties on its drugs.

Alnylam Collaboration

In the quarter in which Alnylam's transaction with Roche receives Hart-Scott-Rodino clearance, we will earn licensing revenue of $26.5 million resulting from Alnylam's sublicense of our technology for the development of RNA interference therapeutics to Roche. The transaction is expected to receive clearance in the third quarter of 2007. This payment is according to the terms of the 2004 strategic alliance agreement between Alnylam and us, through which Alnylam obtained an exclusive license to our intellectual property for double-stranded oligonucleotide therapeutics that mediate RNAi, such as small interfering RNAs (siRNAs), in return for an upfront payment, milestone payments, royalties and a portion of Alnylam's sublicensing revenue. Additionally, during the second quarter, Alnylam announced the achievement of an important milestone in its strategic alliance with us, in initiating IND-enabling studies with an RNAi therapeutic clinical candidate that utilizes technology and intellectual property licensed exclusively from us. Alnylam and we continue to collaborate on siRNA-related technology platform advancements.

Bristol-Myers Squibb Company

In May 2007, we entered into a collaboration agreement with BMS to discover, develop and commercialize novel antisense drugs targeting PCSK9. BMS paid us a $15 million upfront licensing fee, and under the terms of the agreement will provide us with at least $9 million in research funding over 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 pay us royalties on sales of products resulting from the collaboration.

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, we 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.

In May 2007, we reported results from three homozygous familial hypercholesterolemia (HoFH) patients who had completed twelve weeks of treatment with ISIS 301012 at a dose of 300mg/week. The three patients, all of whom were unable to meet target LDL-C levels with maximally-tolerated lipid-lowering therapies including high-dose statins, achieved additional LDL-C reductions of 45%, 50% and 51%, respectively, over levels achieved with maximally tolerated lipid-lowering therapy. ISIS 301012 continued to be well tolerated in the study.

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. We expect results from these studies later in the year. Additionally, we plan to start our 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.

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 cash interest payments by approximately $2.6 million, annually. In addition, the extended maturity date of the 2⅝% notes further strengthens our financial position.

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 the audit committee of our Board of Directors. There are specific risks associated with these critical accounting policies that we describe in the following paragraphs. For all of these policies, we caution that future events rarely develop exactly as expected, and that best estimates routinely require adjustment. Historically, our estimates have been accurate as we have not experienced any material differences between our estimates and our actual results. 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 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.

Descriptions of these critical accounting policies follow.

Revenue Recognition

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

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

We often enter into collaborations where we receive non-refundable upfront payments for prior or future expenditures. We recognize revenue related to upfront payments ratably over our period of performance relating to the term of the contractual arrangements. Occasionally, we are required to estimate

our period of performance when the agreements we enter into do not clearly define such information. Should different estimates prevail, revenue recognized could be materially different. To date our estimates have not required material adjustments. We have made estimates of our continuing obligations on several agreements, including our collaborations with Antisense Therapeutics Ltd., Lilly, OncoGenex and Pfizer. Our collaborative agreements typically include a research and/or development project plan that includes activities to be performed in the collaboration and the party responsible for performing them. We estimate the period of time over which we will complete the activities for which we are responsible and use that period of time as our period of performance for purposes of revenue recognition and amortize revenue over such period. When our collaborators have asked us to continue performing work in a collaboration beyond the initial period of performance, we have extended our amortization period to correspond to the new extended period of performance. In no case have adjustments to performance periods and related adjustments to revenue amortization periods had a material impact on our revenue.

Our collaborations often include contractual milestones. When we achieve these milestones, we are entitled to payment, as defined by the underlying agreements. We generally recognize revenue related to milestone payments upon completion of the milestone's performance requirement, as long as we are reasonably assured of collecting the resulting receivable and we are not obligated for future performance related to the achievement of the milestone. To date, we have earned milestone payments totaling $1.2 million under our Pfizer collaboration. Additionally, in January 2006, Lilly initiated clinical trials of LY2275796 for which we received a $750,000 milestone payment and Merck initiated clinical trials of a drug for HCV for which we earned a $1 million milestone payment.

We generally recognize revenue related to the sale of our drug inventory as we ship or deliver drugs to our partners. In several instances, we completed the manufacturing of drugs, but our partners asked us to deliver the drug on a later date. Under these circumstances, we ensured that the provisions in SAB 104 were met before we recognized the related revenue.

We often enter into agreements to license our proprietary patent rights on an exclusive or non-exclusive basis in exchange for license fees and/or royalties. We generally recognize as revenue immediately those licensing fees and royalties for which we have no future performance obligations and are reasonably assured of collecting the resulting receivable. We often enter into revenue arrangements that contain multiple deliverables. In these cases, we recognize revenue from each element of the arrangement as long as we are able to determine a separate value for each element, we have completed our obligation to deliver or perform on that element and we are reasonably assured of collecting the resulting receivable.

In the fourth quarter of 2006, we started to sell the Ibis T5000 Biosensor System commercially. The sale of each Ibis T5000 Biosensor System contains multiple elements. Since we had no previous experience commercially selling the Ibis T5000 Biosensor System, we had no basis to determine the fair values of the various elements included in each system; therefore, we account for the entire system as one deliverable and recognize revenue over the entire period of performance. The assay kits, which are sold separately from the instrument, are considered part of the entire system from an accounting perspective because the assay kits and the instrument are dependent on each other. For a one-year period following the sale, we have ongoing support obligations for the Ibis T5000 Biosensor System, therefore we are amortizing the revenue for the entire system including related assay kits, over a one-year period. Once we obtain a sufficient number of sales to enable us to identify each element's fair value, we will be able to recognize revenue separately for each element.

Valuation of Investments in Marketable Securities

We account for our investments in marketable securities in accordance with current accounting rules as set forth by SFAS 115, *Accounting for Certain Investments in Debt and Equity Securities*. We carry these investments at fair market value based upon market prices quoted on the last day of the fiscal quarter. We record unrealized gains and losses as a separate component of stockholders' equity, and include gross realized gains and losses in investment income.

In addition to our investments in marketable securities, we have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20% in each of the respective entities. In determining if and when a decrease in market value below our cost in our equity positions is other-than-temporary, we examine historical trends in the stock price, the financial condition of the issuer, near term prospects of the issuer, and our current need for cash. When we determine that a decline in value is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs. During the first half of 2007, we sold the remaining equity securities of Alnylam Pharmaceuticals, Inc. that we owned resulting in a realized gain of $3.5 million compared to a net gain on investments of $2.3 million during the same period in 2006. The net gain on investments during the first half of 2006 represented a gain of $2.7 million realized on the sale of a portion of the equity securities of Alnylam that we owned offset by a non-cash loss on investment of $465,000 related to the other-than-temporary impairment of our equity investment in Antisense Therapeutics Ltd. Since the impairment in the second quarter of 2006, we have recorded a net unrealized gain of $486,000 related to our equity investment in ATL as a separate component of stockholders' equity. This reflected the increase in the market value of the investment since the impairment.

Valuation of Long-Lived Assets

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

- Evidence of decreases in market value;
- Changes in the extent or manner in which we use an asset;
- Adverse changes in legal factors or in the business climate that would affect the value of an asset;
- An adverse action or assessment by a regulator;
- An accumulation of costs significantly in excess of amounts originally expected to acquire or construct an asset;

- Current period operating or cash flow loss combined with a history of operating or cash flow losses associated with an asset used for the purpose of producing revenue; and

- Challenges or potential challenges to our existing patents, the likelihood of applications being issued and the scope of our issued patents.

We recorded a charge of $337,000 and $463,000 for the first half of 2007 and 2006, respectively, primarily related to the write-down of intangible assets to their estimated net realizable values.

Valuation of Inventory

In accordance with SFAS 2, *Accounting for Research and Development Costs*, we capitalize the costs of raw materials that we purchase for use in producing our drugs because, until we use these raw materials, they have alternative future uses. We include in inventory raw material costs and related manufacturing costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. Each of our raw materials can be used in multiple products and, as a result, have future economic value independent of the development status of any single drug. For example, if one of our drugs failed, the raw materials allocated for that drug could be used to manufacture our other drugs. We expense these costs when we deliver our drugs to partners, or as we use these drugs in our own clinical trials. Also included in inventory are material costs and related manufacturing costs associated with our Ibis T5000 Biosensor System and related assay kits. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce our carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf lives of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs.

Estimated Liability for Clinical Development Costs

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

Valuation Allowance for Net Deferred Tax Assets

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

Segment Information

We provide segment financial information and results for our Drug Discovery and Development segment and our Ibis Biosciences, Inc. subsidiary based on the segregation of revenues and expenses used for management's assessment of operating performance and operating decisions. Expenses shared by the segments require the use of judgments and estimates in determining the allocation of expenses to the two segments. We have not made material changes to our allocation methodologies since we began reporting segment financial information and results. Different assumptions or allocation methods could result in materially different results by segment.

Stock-Based Compensation

On January 1, 2006, we adopted SFAS 123R, *Share-Based Payment*, which requires the measurement and recognition of compensation expense for all stock-based payment awards made to employees and directors including employee stock options and employee stock purchases related to our Employee Stock Purchase Plan based on estimated fair values. SFAS 123R supersedes our previous accounting under Accounting Principles Board Opinion ("APB") 25, *Accounting for Stock Issued to Employees and SFAS 123, Accounting for Stock-Based Compensation*, beginning January 1, 2006. In March 2005, the SEC issued SAB 107, *Share-Based Payment*, relating to SFAS 123R. We have applied the provisions of SAB 107 in our adoption of SFAS 123R.

We adopted SFAS 123R using the modified prospective transition method, which requires the application of the accounting standard as of January 1, 2006, the first day of our fiscal year 2006. Our Condensed Consolidated Statements of Operations for the three and six months ended June 30, 2007 and 2006 reflect the impact of SFAS 123R. In accordance with

the modified prospective transition method, our Condensed Consolidated Statements of Operations for prior periods have not been restated to reflect, and do not include, the impact of SFAS 123R. As of June 30, 2007, there was $13.1 million of total unrecognized compensation cost related to non-vested stock-based compensation plans. Total unrecognized compensation cost will be adjusted for future changes in estimated forfeitures. We expect to recognize that cost over a weighted average period of 1.4 years.

We utilize the Black-Scholes model and assumptions discussed in Note 1 for estimating the fair value of the stock-based awards we granted. Compensation expense for all stock-based payment awards is recognized using the accelerated multiple-option approach. Under the accelerated multiple-

option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period. Our risk-free interest rate assumption is based upon observed interest rates appropriate for the term of our employee stock options and our ESPP. The dividend yield assumption is based on our history and expectation of dividend payouts. We have not paid dividends in the past and do not expect to in the future. We use a weighted average of the historical stock price volatility of our stock to calculate the expected volatility assumption required for the Black-Scholes model consistent with SFAS 123R. The expected term of stock options granted represents the period of time that they are expected to be outstanding. For our 2002 Non-Employee Directors' Stock Option Plan, we estimate the expected term of options granted based on historical exercise patterns. For our employee stock option plans, the estimated expected term is a derived output of the simplified method, as allowed under SAB 107. We estimated forfeitures based on historical experience. There were no material changes to our estimated forfeitures for the first half of 2007 and 2006. For the periods prior to fiscal 2006, we accounted for forfeitures as they occurred in our pro forma information as required under SFAS 123.

Results of Operations

Revenue

Total revenue for the three and six months ended June 30, 2007 was $3.8 million and $6.3 million, respectively, compared to $4.4 million and $9.3 million for the same periods in 2006. Our 2007 year-to-date revenue reflects two months of revenue associated with our recent collaboration with BMS, which began in May 2007. Revenue was lower for the three and six months ended June 30, 2007 compared to the same period in 2006 because of lower revenue from our collaborations and differences in the timing of Ibis' 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 quarter in which Alnylam's transaction with Roche receives Hart-Scott-Rodino clearance, we will earn licensing revenue of $26.5 million resulting from Alnylam's sublicense of our technology for the development of RNA interference therapeutics to Roche. The transaction is expected to receive clearance in the third quarter of 2007.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2007	2006	2007	2006
Drug Discovery and Development:				
Research and development revenue	$ 1,591	$ 1,912	$ 2,017	$ 3,183
Licensing and royalty revenue	331	53	779	543
	$ 1,922	$ 1,965	$ 2,796	$ 3,726
Ibis Biosciences:				
Research and development revenue	$ 1,081	$ 2,410	$ 2,026	$ 5,608
Commercial revenue (1)	810	—	1,441	—
	$ 1,891	$ 2,410	$ 3,467	$ 5,608
Total Revenue:				
Research and development revenue	$ 2,672	$ 4,322	$ 4,043	$ 8,791
Commercial revenue (1)	810	—	1,441	—
Licensing and royalty revenue	331	53	779	543
	$ 3,813	$ 4,375	$ 6,263	$ 9,334

(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 and six months ended June 30, 2007 was $1.6 million and $2.0 million, respectively, compared to $1.9 million and $3.2 million for the same periods in 2006. The decrease was primarily a result of lower revenue from our research collaborations, including a decrease in revenue associated with our collaborations with Lilly and OncoGenex offset by revenue earned from our collaboration with BMS. 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 and six months ended June 30, 2007 was $331,000 and $779,000, respectively, compared to $53,000 and $543,000 for the same periods in 2006. The increase for the three and six months ended June 30, 2007 compared to the same periods in 2006 relates to the increased licensing revenue we received from Roche Molecular related to the royalty-bearing license we granted Roche in October.

Ibis Biosciences, Inc.

Ibis' revenue for the three and six months ended June 30, 2007 was $1.9 million and $3.5 million, respectively, compared to $2.4 million and $5.6 million for the same periods in 2006. Ibis earned commercial revenue of $810,000 and $1.4 million, respectively, for the three and six months ended June 30, 2007, which consisted of revenue from sales of Ibis' T5000 Biosensor Systems and assay kits, as well as revenue from Ibis' assay services business. Commercial revenue in the second quarter of 2007 increased by 28% over the first quarter of 2007 primarily due to additional revenue from the second commercial T5000 Biosensor System that was delivered late in the first quarter of 2007. 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 $1.1 million and $2.0 million, respectively, for the three and six months ended June 30, 2007 compared to $2.4 million and $5.6 million for the same periods 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. We expect that revenue from government contracts will continue to provide a solid revenue base going forward.

From inception through June 30, 2007, Ibis has earned $60.7 million in revenue from various government agencies to further the development of our Ibis T5000 Biosensor System and related assay kits. An additional $6.2 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 three and six months ended June 30, 2007 of $23.5 million and $46.8 million, respectively, compared to $21.5 million and $42.5 million for the same periods in 2006. Also contributing to the increase in operating expenses was an increase in non-cash compensation expense. Non-cash compensation expense related to stock options was $2.4 million and $4.8 million for the three and six months ended June 30, 2007, respectively, compared to $1.4 million and $2.8 million for the same periods in 2006, primarily reflecting an 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 June 30,		Six Months Ended June 30,	
	2007	2006	2007	2006
Research and development expenses	$ 18,432	$ 17,879	$ 36,455	$ 35,098
Non-cash compensation expense related to stock options	1,952	1,103	3,878	2,256
Total research and development expenses	$ 20,384	$ 18,982	$ 40,333	$ 37,354

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2007	2006	2007	2006
Drug Discovery and Development	$ 16,658	$ 15,708	$ 32,885	$ 30,800
Ibis Biosciences	3,726	3,274	7,448	6,554
Total research and development expenses	$ 20,384	$ 18,982	$ 40,333	$ 37,354

For the three and six months ended June 30, 2007, we incurred total research and development expenses, excluding stock compensation, of $18.4 million and $36.5 million, respectively, compared to $17.9 million and $35.1 million for the same periods in 2006. The increase is attributed to the continued development of our key programs.

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 excluding non-cash compensation expense were $3.2 million and $6.6 million, respectively, for the three and six months ended June 30, 2007 compared to $3.0 million and $6.2 million for the same periods 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 half 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 June 30,		Six Months Ended June 30,	
	2007	2006	2007	2006
Alicaforsen for Crohn's disease	$ —	$ —	$ —	$ 2
Other antisense development products	5,537	4,974	9,878	9,428
Development overhead costs	988	1,358	2,327	2,128
Non-cash compensation expense related to stock options	689	357	1,340	715
Total antisense drug development	$ 7,214	$ 6,689	$ 13,545	$ 12,273

Antisense drug development expenditures were $6.5 million and $12.2 million, excluding non-cash compensation expense for the three and six months ended June 30, 2007 compared to $6.3 million and $11.6 million for the same periods in 2006. The increase was primarily attributed to the continued development of our key programs. 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 $988,000 and $2.3 million, respectively, for the three and six months ended June 30, 2007 compared to $1.4 million and $2.1 million for the same periods in 2006.

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. Manufacturing and operations expenses excluding non-cash compensation expense for the three and six months ended June 30, 2007 were $1.5 million and $3.0 million, respectively, compared to $1.3 million and $3.0 million for the same periods 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. Also included in Ibis research and development expenses are cost of goods sold for its commercial activity. Further, we allocate a portion of R&D support costs to Ibis Biosciences and include this allocation in Ibis' research and development expenses.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2007	2006	2007	2006

Research and development costs	$ 2,748	$ 2,501	$ 5,444	$ 4,883
R&D support costs	674	605	1,399	1,286
Non-cash compensation expense related to stock options	304	168	605	385
Total Ibis' research and development expenses	$ 3,726	$ 3,274	$ 7,448	$ 6,554

Ibis' research and development expenses, excluding non-cash compensation expense related to stock options, for the three and six months ended June 30, 2007 were $3.4 million and $6.8 million, respectively, compared to $3.1 million and $6.1 million for the same periods in 2006. The increase in expenses primarily reflects an increase in costs necessary to support commercialization of the Ibis T5000 Biosensor System. 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 June 30,		Six Months Ended June 30,	
	2007	2006	2007	2006
Personnel costs	$ 1,468	$ 1,553	$ 3,004	$ 2,997
Occupancy	1,463	1,400	2,977	2,927
Depreciation and amortization	1,186	1,331	2,392	2,575
Insurance	250	265	487	520
Other	327	264	914	640
Non-cash compensation expense related to stock options	189	122	370	245
Total R&D support costs	$ 4,883	$ 4,935	$ 10,144	$ 9,904

R&D support costs excluding non-cash compensation expense for the three and six months ended June 30, 2007 were essentially flat at $4.7 million and $9.8 million, respectively, compared to $4.8 million and $9.7 million for the same periods in 2006.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2007	2006	2007	2006
Drug Discovery and Development	$ 4,209	$ 4,330	$ 8,745	$ 8,618
Ibis Biosciences	674	605	1,399	1,286
Total R&D support costs	$ 4,883	$ 4,935	$ 10,144	$ 9,904

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 June 30,		Six Months Ended June 30,	
	2007	2006	2007	2006
Selling, general and administrative expenses	$ 2,652	$ 2,415	$ 5,616	$ 4,760
Non-cash compensation expense related to stock options	437	295	875	516
Total selling, general and administrative expenses	$ 3,089	$ 2,710	$ 6,491	$ 5,276

Selling, general and administrative expenses, excluding non-cash compensation expense related to stock options, for the three and six months ended June 30, 2007 were $2.7 million and $5.6 million, respectively, compared to $2.4 million and $4.8 million for the same periods in 2006. The increase was a result of increased selling, general and administrative expenses associated with the commercialization of the Ibis T5000 Biosensor System. 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 June 30,		Six Months Ended June 30,	
	2007	2006	2007	2006
Drug Discovery and Development	$ 2,054	$ 1,877	$ 4,468	$ 4,222
Ibis Biosciences	1,035	833	2,023	1,054
Total selling, general and administrative expenses	$ 3,089	$ 2,710	$ 6,491	$ 5,276

Restructuring Activities

During the three and six months ended June 30, 2006, we recorded a benefit of $215,000 and $178,000, respectively, resulting from our decision to focus our resources on key programs. In the second quarter of 2006, we successfully negotiated a contract modification with one of our vendors. The amount of the contract modification was $265,000 less than the amount that had been previously accrued; therefore, we recognized a benefit for this amount in restructuring activities for the three and six months ended June 30, 2006. There were no restructuring activities in the first half of 2007.

Investment Income

Investment income for the three and six months ended June 30, 2007 totaled $3.1 million and $6.5 million, respectively, compared to $1.3 million and $2.2 million for the same periods in 2006. The increase in investment income was primarily due to a higher average cash balance during the first half of 2007 compared to the same period in 2006 as a result of the proceeds we received from the issuance of our 2¾% convertible subordinated notes in January 2007 and the $15 million upfront licensing fee that we received from our strategic partnership with BMS, offset by the repayment of our 5 ½% notes.

Interest Expense

Interest expense for the three and six months ended June 30, 2007 totaled $2.0 million and $4.6 million, respectively, compared to $2.3 million and $4.6 million for the same periods in 2006. We anticipate that interest expense will decrease in the second half of 2007 compared to the first half of 2007 because the 5¼% notes were fully repaid in the first half of 2007 and the 2¾% notes issued in early 2007 have a lower interest rate.

Gain on Investment

Gain on investments for the three and six months ended June 30, 2007 was $2.0 million and $3.5 million, respectively, compared to $2.3 million for the same periods in 2006. The 2007 gain on investments reflected a gain realized on the sale of the remaining equity securities of Alnylam that we owned. The 2006 gain on investments represented a gain of $2.7 million realized on the sale of a portion of the equity securities of Alnylam that we owned offset by a non-cash loss on investment of $465,000 related to the impairment of our equity investment in Antisense Therapeutics Ltd.

Loss on Early Retirement of Debt

Loss on early retirement of debt for the three and six months ended June 30, 2007 was $2.0 million and $3.2 million, respectively. The loss on early retirement of debt reflected the early extinguishment of our 5½% convertible subordinated notes in the first half of 2007. As a result of the repayment of the 5½% notes, we recognized a $3.2 million loss on the early retirement of debt in the first half of 2007, which included $1.2 million of non-cash unamortized debt issuance costs. There was no loss on early retirement of debt in the first half of 2006.

Net Loss Applicable to Common Stock

Net loss applicable to common stock for the three and six months ended June 30, 2007 was $11.0 million and $24.0 million, respectively, compared to $2.2 million and $19.7 million for the same periods in 2006. We recognized a benefit of $7.6 million and $14.4 million, respectively, for the three and six months ended June 30, 2007 in the loss attributed to noncontrolling interest in Symphony GenIsis, Inc. compared to $13.6 million for the same periods in 2006. Net loss applicable to common stock for the first half of 2007 was higher compared to the same period in 2006 because of an increase in the Company's loss from operations and the loss on early retirement of debt offset by higher interest income, net gain on investments and the benefit related to the loss attributed to noncontrolling interest in Symphony GenIsis, Inc.

Net Loss Per Share

Net loss per share for the three and six months ended June 30, 2007 was $0.13 per share and $0.29 per share, respectively, compared to $0.03 per share and $0.27 per share for the same periods in 2006. In the second half of 2006, we issued approximately 8.0 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. The increase in the net loss per share for the three months ended June 30, 2007 compared to the same period in 2006 was primarily a result of the decrease in the benefit related to the loss attributed to noncontrolling interest in Symphony GenIsis, Inc. which is discussed in the Net Loss Applicable to Common Stock section above. The minor increase in the net loss per share for the first half of 2007 compared to the same period in 2006 was a result of the increase in net loss applicable to common stock for the first half of 2007 compared to the same period in 2006 offset by the impact from the additional shares issued in the second half of 2006.

Liquidity and Capital Resources

We have financed our operations with revenue primarily from research and development under collaborative agreements. Additionally, we have earned licensing and royalty revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through June 30, 2007, we have earned approximately $514.0 million in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through June 30, 2007, we have raised net proceeds of approximately $730.7 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, including $125 million of 5 ½% convertible subordinated notes which we repaid in full in the first half of 2007.

At June 30, 2007, we had cash, cash equivalents and short-term investments of $202.7 million, which included $43.0 million of cash and cash equivalents held by Symphony GenIsis, consolidated working capital of $185.6 million and stockholders' equity of $47.3 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 primarily reflects the proceeds we received from the issuance of our 2⅝% convertible subordinated notes in January 2007 and the $15 million upfront licensing fee that we received from our strategic partnership with BMS, offset by the repayment of our 5 ½% notes. Further, our cash balance at June 30, 2007 does not include the $26.5 million we will receive from Alnylam, following regulatory clearance of Alnylam's recent transaction with Roche. The transaction is expected to receive clearance in the third quarter of 2007.

As of June 30, 2007, our debt and other obligations totaled $174.0 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 2 ⅝% convertible subordinated notes offset by the declining balance on our Silicon Valley Bank term loan. The significantly lower interest rate of the 2 ⅝% convertible subordinated notes from that of our recently repaid 5 ½% convertible subordinated notes reduces our cash interest payments by approximately $2.6 million annually. 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 funding requirements through at least the end of 2010.

The following table summarizes our contractual obligations as of June 30, 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**
2⅝% Convertible Subordinated Notes	162.5	—	—	—	162.5
Silicon Valley Bank Term Loan	10.7	7.0	3.7	—	—
Capital Lease and Other Obligations	0.8	0.5	—	—	0.3
Operating Leases	21.6	2.8	5.7	3.7	9.4

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 are amortizing 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 7.5% at June 30, 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 June 30, 2007 was $10.7 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. 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. Using the net proceeds from the issuance of our 2⅝% notes, we repaid the entire $125 million of our 5½% convertible subordinated notes due 2009.

In addition to contractual obligations, we had outstanding purchase orders as of June 30, 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 June 30, 2007, we had accumulated losses of approximately $840.8 million and stockholders' equity of approximately $47.3 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 end 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 June 30, 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 2[5]¤8% 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 six months ended June 30, 2007 and 2006, we derived approximately 55% and 60%, 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 June 30, 2007. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to June 30, 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

In June 2007, Drug Royalty Trust 3, successor-in-interest to Drug Royalty USA, Inc., alleged that Isis breached various representations, warranties and covenants contained in the Agreement for Sale and Assignment of Rights dated December 21, 2004 and has asserted its right to terminate the sale and assignment agreement. Isis has responded that in fact no breach has occurred and that DRC has no right to terminate the sale and assignment agreement. Direct discussions have been scheduled in an attempt to resolve this matter before formal dispute resolution proceedings commence. Isis believes that Drug Royalty Trust 3's claims are without merit, and Isis intends to vigorously defend its position. Isis believes it is reasonably possible, not probable, that it will ultimately pay any amounts to Drug Royalty Trust 3 related to this claim. As such, Isis has not recorded a loss related to this claim as of June 30, 2007.

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
April 1, 2007 to April 30, 2007			—	—
May 1, 2007 to May 31, 2007	$ 80,825,000	$ 1,015.71	—	—
June 1, 2007 to June 30, 2007	—	—	—	—
Total	$ 80,825,000			

(1) In January 2007, through privately negotiated transactions, we repurchased $44,175,000 aggregate principal amount of our 5 ½% convertible subordinated notes due 2009. The redemption price was $1,017 per $1,000 principal amount outstanding, plus $12.68 in accrued but unpaid interest per $1,000 principal amount outstanding. Additionally, in May 2007, we voluntarily redeemed all of the remaining outstanding balance, pursuant to Isis' optional redemption under paragraph 6 of the 5 ¹¤₂% convertible subordinated notes. 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. The accrued but unpaid interest was $1.375 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

On May 17, 2007, we held our Annual Meeting of Stockholders in Carlsbad, California for the following purposes:

(1) To elect three directors to serve as Class I directors of the Company until the 2010 Annual Meeting of Stockholders. For Director number one, Stanley T. Crooke, the number of votes for and withheld was 72,175,014 and 4,420,339, respectively. For Director number two, Joseph Klein III, the number of votes for and withheld was 75,565,147 and 1,030,206, respectively. For Director number three, John C. Reed, the number of votes for and withheld was 59,046,098 and 17,549,255, respectively.

(2) To ratify the appointment of Ernst & Young LLP as the Company's independent registered public accounting firm for the fiscal year ending December 31, 2007. The number of votes for, against and abstaining was 69,565,545; 411,971 and 159,956, respectively.

ITEM 5. OTHER INFORMATION

In May 2007, Isis and Bruker Daltonics Inc. amended their manufacturing, commercialization and development agreement to update the pricing and revenue sharing to reflect enhancements that the parties have made to the Ibis T5000 Biosensor System since the execution of the original manufacturing, commercialization and development agreement.

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Collaboration and License Agreement between the Registrant and Bristol-Myers Squibb Company dated May 8, 2007 (with certain confidential information deleted).
10.2	Amendment No. 1 to Manufacturing, Commercialization and Development Agreement Between the Registrant and Bruker Daltonics Inc. (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)	August 8, 2007
/s/ B. Lynne Parshall B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	August 8, 2007

Exhibit 10.1

EXECUTION COPY

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

COLLABORATION AND LICENSE AGREEMENT

between

ISIS PHARMACEUTICALS, INC.

and

BRISTOL-MYERS SQUIBB COMPANY

COLLABORATION AND LICENSE AGREEMENT

THIS COLLABORATION AND LICENSE AGREEMENT (the ***"Agreement"***) is made and entered into effective as of May 8, 2007 (the ***"Effective Date"***), by and between **Bristol-Myers Squibb Company**, a Delaware Corporation (***"BMS"***) and **Isis Pharmaceuticals, Inc.**, a Delaware Corporation (***"Isis"***). BMS and Isis each may be referred to herein individually as a ***"Party,"*** or collectively as the ***"Parties."***

WHEREAS, Isis possesses certain patent rights, know-how and technology with respect to certain oligonucleotide based therapeutic compounds;

WHEREAS, Isis and BMS each desire to collaborate in the performance of a Research Program for the purpose of discovery and preclinical development of Compounds suitable for development for human therapeutic uses, with the objective of identifying one or more Compounds for BMS to advance into human clinical trials; and

WHEREAS, BMS will have exclusive rights and will be solely responsible for the clinical development and commercialization of Products worldwide, in each case on the terms set forth in this Agreement.

NOW, THEREFORE, in consideration of the foregoing and the mutual covenants herein contained, the Parties do hereby agree as follows.

ARTICLE 1 - DEFINITIONS

The terms used in this Agreement with initial letters capitalized, whether used in the singular or the plural, shall have the meaning set forth in Appendix 1, or if not listed in Appendix 1, the meaning designated in places throughout the Agreement.

ARTICLE 2 -
GRANT OF RIGHTS; EXCLUSIVITY

Section 2.1 **License Grant to BMS.**

(a) **Exclusive License.** Subject to the terms and conditions of this Agreement and the limitations set forth in Section 2.4 below, Isis hereby grants to BMS an exclusive license, with the limited right to grant sublicenses as set forth in Section 2.1(b) below, under the Isis Know-How and Isis Patent Rights to research, develop, make, have made, use, sell, offer for sale, have sold, export and import Compounds and Products in the Field in the Territory. Without limiting the representations and warranties of Isis under Article 12, to the extent that Isis is only permitted to grant BMS a nonexclusive license with respect to any Isis Know-How and Isis Patent Right that is in-licensed by Isis under the applicable Third Party in-license agreement, the foregoing license to BMS shall be nonexclusive.

(b) **Sublicenses.** The licenses granted to BMS under this Section 2.1 are sublicensable only in connection with a license of a Compound or Product to any Affiliate of BMS or to any Third Party, in each case for the continued Development and Commercialization of such Compound or Product in accordance with the terms of this Agreement, *provided* that (i) such Affiliate or Third Party shall agree in writing to be bound by and subject to all applicable terms and conditions of this Agreement in the same manner and to the same extent as BMS, (ii)

BMS shall remain responsible for the performance of this Agreement and shall cause such Affiliate or Third Party to comply with the applicable terms and conditions of this Agreement, (iii) BMS names Isis as a third party beneficiary with the right to directly enforce Article 7 (Confidentiality) of this Agreement against such Affiliate or Third Party and (iv) BMS promptly notifies Isis in writing specifically identifying the Isis Know-How to be disclosed to such Third Party and identifying by name such Third Party. In addition to the requirements and limitations set forth above, with respect to the Isis Manufacturing Technology, BMS (or its Affiliate or Licensee) may only sublicense the Isis Permitted Manufacturing Technology, and in each case, BMS (or its Affiliate or Licensee) will use appropriate precautions and include provisions in such sublicense to protect the Isis Know-How such that the sublicensee will not use any Isis Know How to manufacture any other ASOs for Third Parties. In addition, the rights granted to BMS under Section 2.1 may be sublicensed or extended by BMS to Third Party contractors solely for purposes of having activities performed by such Third Party contractor on BMS' (or its Affiliate's or Licensee's) behalf for the Development and Commercialization of Compounds and Products.

Section 2.2 **Exclusivity.** During the Research Term and continuing thereafter so long as the exclusive license granted to BMS under Section 2.1 is in effect and subject to the limitations set forth in Section 2.4 below, Isis agrees that it will not work independently of this Agreement for itself or any Third Party (including the grant of any license to any Third Party) with respect to discovery, research, Development and/or Commercialization activities with respect to ASOs (or conjugates or prodrugs thereof) that [***] mRNA or pre-mRNA or that are designed to [***] mRNA or pre-mRNA or products containing such ASOs (or conjugates or prodrugs thereof).

Section 2.3 **Covenant Not to Sue.** Isis understands that Isis will be sharing and exposing BMS to the Isis Technology as part of this Agreement and that, from time to time, [***] (but not [***]) using certain Isis Technology. As such and in recognition of the significant collaborative relationship between Isis and BMS under this Agreement, Isis covenants, for itself and its Affiliates and their successors, not to either directly or indirectly make, file, bring or maintain any claim, demand or lawsuit (a **"Claim"**) against BMS or its Affiliates, which Claim asserts [***] any of (i) the [***] through the Research Term, (ii) the [***] or (iii) the [***]. This Section 2.3 shall survive any termination of this Agreement other than when terminated by Isis under Section 9.3.

Section 2.4 **License Conditions; Limitations.**

(a) During the Research Term, in order to maintain the license granted to BMS under Section 2.1, BMS must meet its obligations to fund the Research Program in accordance with Section 3.5 and Section 5.2. If BMS fails to meet such obligations to fund the Research Program, Isis shall have the right, as set forth in Section 9.3, to terminate the Agreement, including the licenses granted to BMS under Section 2.1.

(b) After the expiration of the Research Term, in order to maintain the license granted to BMS under Section 2.1, BMS must meet its obligations to use Commercially Reasonable Efforts under Section 4.1. If BMS fails to meet its obligations to use Commercially Reasonable Efforts under Section 4.1, Isis shall have the right, as set forth in Section 9.3, to terminate the Agreement, including the licenses granted to BMS under Section 2.1.

(c) The licenses and exclusivity granted under this Article 2 are subject to and limited by the (i) Isis In-License Agreements and (ii) Prior Third Party Agreements, each as listed in Appendix 6 attached hereto and incorporated herein by reference.

(d) In addition, notwithstanding any other provision of this Agreement, Isis retains the right to grant Permitted Licenses.

ARTICLE 3 - RESEARCH PROGRAM

Section 3.1 **Research Program.** During the Research Term, the Parties will collaborate in carrying out a research program to discover and preclinically Develop Compounds suitable for further clinical Development for human therapeutic uses (the ***"Research Program"***). The Research Program will be carried out in accordance with the Research Plan. The Research Program will initially focus on [***]The Research Program will also include activities directed toward[***] The objective of the Research Program will be to identify one or more Compounds for BMS to advance into human clinical trials and ultimately Commercialize as Products (the ***"Objective"***). As further set forth in the Research Plan and in accordance with the other terms and conditions of this Agreement, Isis will be responsible for (i) [***] Compounds suitable for clinical Development, (ii) the supply of all ASO compounds in support of the Research Program, (iii) the [***] testing of lead Compounds (with BMS), (iv) carrying out IND-Enabling Studies for ECNs (with BMS) and (v) the preparation of the CMC section relating to the API manufactured by Isis for any IND. In addition, as described further below, Isis shall be responsible for the supply of all API for IND-Enabling Studies and for use for clinical Development through completion of Phase IIb Trials.

The Research Program will be conducted by each Party in good scientific manner, and in compliance with all applicable good laboratory practices, and applicable legal requirements, to attempt to achieve efficiently and expeditiously the objectives of the Research Program. Each Party will comply with all Applicable Laws, in the performance of work under this Agreement.

Each Party will maintain laboratories, offices and all other facilities at its own expense and risk necessary to carry out its responsibilities under the Research Program pursuant to the Research Plan. Each Party agrees to make its employees reasonably available at their respective places of employment to consult with the other Party on issues arising during the performance of the Research Program. BMS and Isis will cooperate with each other in carrying out the Research Program, and each Party will contribute its relevant know-how and experience necessary to carry out the Research Program.

Section 3.2 **Research Term.**

3.2.1 The Research Program will be carried out during the [***] year period following the Effective Date (the ***"Research Term"***). BMS shall have the option to extend the Research Term for [***] additional 1 year periods on a year-by-year basis after the initial 3 year period. In order to exercise its option to extend the Research Term, BMS must provide Isis a written notice exercising BMS' right to extend the Research Term at least [***] days prior to the scheduled expiration of the Research Term (i.e., the applicable anniversary of the Effective Date). If BMS does not provide such written notice, the Research Term will end when scheduled (i.e., on the applicable anniversary of the Effective Date). In addition, at least [***] days prior to the scheduled expiration of the Research Term (i.e., the applicable anniversary of the Effective Date) BMS will provide Isis with a nonbinding, good faith indication of whether or not BMS intends to extend the Research Term.

3.2.2 For each extension of the Research Term under Section 3.2.1, the Parties will negotiate in good faith a mutually agreed amendment and restatement of the Research Plan

which will include an appropriate number of FTEs committed to perform the work required under such Research Plan.

Section 3.3 **Joint Research Committee; Working Group.** The Parties will establish and maintain a joint research committee (the ***"Joint Research Committee"*** or ***"JRC"***) comprised of an equal number of representatives from each Party to oversee the conduct of the Research Program. The JRC will be established, operated and governed in accordance with the policies and procedures set forth in Appendix 5 attached hereto (the ***"JRC Charter"***). The JRC Charter may be amended only with the unanimous approval of the JRC members.

The JRC will be responsible for the overall management of the Research Program, and for approving changes and updates to the Research Plan. The JRC will be responsible for reviewing and approving recommendations, plans, allocation of resources and other activities in support of the Research Program, and preparing and implementing the Research Plan, with the objective of expeditiously identifying Compounds and other objectives in accordance with the Research Plan. The JRC shall be responsible for the monitoring, reviewing and recording the progress of the Research Program. In addition, the JRC shall be responsible for setting, and monitoring the spending against, the budget for Research Program Costs, as set forth in the Research Plan.

Any changes to the Research Plan and assignment and allocation of work to be performed by the BMS-funded Isis FTEs shall require the approval of the JRC. The JRC will be responsible for review of progress of the Research Program and facilitate the prosecution of the Program Patent Rights in accordance with Article 8 below.

Unless the Parties agree otherwise, the JRC will be comprised of 6 members with 3 representatives appointed by Isis and 3 representatives appointed by BMS. The JRC shall be co-chaired jointly by a representative of each Party. Either Party may appoint substitute or replacement members of the JRC to serve as their representatives upon notice to the other Party. The initial members of the JRC shall be appointed by the Parties within 10 days following the Effective Date.

As needed, the JRC shall establish subcommittees and working groups that will report to the JRC to further the objectives of the Research Program.

The JRC and any subcommittees and working groups established by the JRC will dissolve at the end of the Research Term.

Section 3.4 **Research Plan.**

3.4.1 The Research Program will be carried out in accordance with a written research plan (the ***"Research Plan"***). The initial Research Plan, that has been agreed to by the Parties as of the Effective Date is hereby incorporated into this Agreement by reference and is made a part of this Agreement. The purpose of the Research Plan is to detail the responsibilities and activities of Isis and BMS with respect to carrying out the Research Program. The Research Plan will include a description of the specific activities to be performed by the Parties in support of the Research Program, the allocation of Isis FTEs to perform such activities, and projected timelines for completion of such activities and the desired specifications for the Compounds. In April of each Research Year (starting in 2008), the JRC will review and update the Research Plan. The Research Plan may only be amended with the approval of the JRC (as permitted by the JRC Charter) and is subject to Section 3.5.1 below. The Research Plan will be updated and amended from time to time, but at least annually.

3.4.2 In addition, at least [***] months prior to the beginning of the 3rd Research Year of the Research Term and at least [***] months prior to the beginning of any 1 year extension of the Research Term, the JRC will begin the process of updating the Research Plan for such 3rd Research Year or extension (as applicable). At least [***] months prior to the beginning of the 3rd Research Year of the Research Term, and at least [***] months prior to the beginning of any 1 year extension of the Research Term, the JRC will have agreed on an updated Research Plan for such 3rd Research Year or extension (as applicable).

Section 3.5 **Research Staffing; Funding.**

3.5.1 **Staffing.** BMS will fund at the FTE Rate, and Isis will supply, [***] Isis FTEs per Research Year during the initial [***] year period of the Research Term to perform activities in support of the Research Program, in accordance with the then-current Research Plan. The number of Isis FTEs dedicated to the Research Program [***] reduced in the [***] of the Research Program. The JRC may reduce the number of funded Isis FTEs during the [***] of the Research Term and any extension of the Research Term, *provided* that (i) the Research Plan has been updated and agreed to in accordance with Section 3.4.2 above and (ii) the number of funded Isis FTEs will be consistent with the amount of work required under the Research Plan and not be less than [***] qualified FTEs during the 3rd Research Year of the Research Term or less than [***] qualified FTEs per year during any such extension of the Research Term. Additionally, the JRC may increase the number of BMS-funded Isis FTEs to perform activities in support of the Research Program with a minimum of [***] months prior notice. At least [***] months prior to the beginning of the 3rd Research Year of the Research Term, the JRC will make a nonbinding, good faith estimate of the number of Isis FTEs to be provided and funded by BMS to perform the Research Program during the 3rd Research Year of the Research Term, and at least [***] months prior to the beginning of any 1 year extension of the Research Term, the JRC will make a nonbinding, good faith estimate of the number of Isis FTEs to be provided and funded by BMS to perform the Research Program during such Research Year of the Research Term. At least [***] months prior to the beginning of the 3rd Research Year of the Research Term, the JRC shall determine the number of Isis FTEs to be provided and funded by BMS to perform the Research Program during the 3rd Research Year of the Research Term, and at least [***] months prior to the beginning of any 1 year extension of the Research Term, the JRC shall determine the number of Isis FTEs to be provided and funded by BMS to perform the Research Program during such Research Year of the Research Term.

3.5.2 Funding; Expenses.

(a) Within 10 Business Days following the Effective Date and thereafter within 10 Business Days following the [***] of each Calendar Quarter, BMS will pay Isis [***] for the BMS-funded Isis FTEs assigned to the Research Program in accordance with Section 3.5.1 for such Calendar Quarter (a prorated amount shall be payable for any portion of a Calendar Quarter). Such FTE payment obligation of BMS will be subject to Isis providing such qualified FTE scientists. No later than 60 days following the end of each Calendar Quarter, Isis will provide BMS with a report of the number of FTEs assigned to the Research Program with a summary of their activities. Any overpayment by BMS may be applied by BMS to the funding of Isis FTEs in a subsequent Calendar Quarter. If the activities contemplated by the Research Plan at any time do not justify the number of Isis FTEs allocated to the Research Program, the Parties will work in good faith to mutually agree to modify the scope of the Research Plan or adjust the number of BMS-funded FTEs, *provided* that the minimum number of BMS-funded FTEs shall not be less than the minimum numbers set forth in Section 3.5.1 without the written agreement of both Parties.

(b) Isis will bear its own costs, including costs related to research supplies, consumables and applicable overhead costs, in performing its obligations under the Research Program, *provided* that BMS will make a payment to Isis for (i) [***] (ii) the costs of manufacturing ASOs in excess of an initial [***] quantity as set forth in Section 3.5.2(c) below and (iii) the costs of manufacturing approximately [***] of API for a lead Compound in accordance with Section 4.2 and as set forth in the Research Plan. [***] For each project under the Research Plan, the JRC will set a budget for the above costs and will update the Research Plan such that it includes such budget. At the end of each Calendar Quarter during the Research Term, Isis shall invoice BMS for the above costs incurred during such Calendar Quarter, *provided, however*, that (x) for any particular item of such cost in excess of the greater of $[***] or [***]% of the amount allocated for such item in the budget shall require the written approval of BMS prior to being incurred and (y) BMS shall not be responsible for payment for those items of such cost in excess of the greater of $[***] or [***]% of the amount allocated for such item in the budget that are incurred by Isis without BMS' prior written consent. BMS shall pay any such correct invoices within 30 days after receipt thereof. At BMS' option, Isis agrees to deliver to BMS, at BMS' expense, or to dispose of such Research Program-specific animals in Isis' possession following completion of the Research Term or earlier termination of this Agreement. The Parties agree that if Isis wishes to retain any such Research Program-specific animals, BMS will consider reasonable offers from Isis to purchase such Research Program-specific animals from BMS. Isis shall afford BMS a reasonable opportunity, from time to time, to verify [***] incurred by Isis.

(c) **Responsibility for Supply of ASO and Costs for ASO Supply**. Isis shall be responsible for the manufacture and supply of all ASOs for use in support of the Research Program, and all such manufacture will be performed at Isis' facilities. Isis shall not use a Third Party (sub)contractor for the manufacture of ASOs without the prior written approval of BMS. Isis shall bear its own costs for the manufacture of up to [***] of each ASO. For quantities in excess of such [***] for any ASO, BMS shall order such additional quantities in [***] increments. Isis will be responsible for the first $[***] cost to manufacture such additional quantities of ASOs in the aggregate, and thereafter, BMS will reimburse Isis for its costs of manufacturing such ASOs (subject to Section 3.5.2(b) above). The cost to manufacture such additional quantities of ASOs will be negotiated and agreed to in good faith by the Parties, but shall not exceed $[***] per gram for MOE Gapmers. As set forth in Section 4.2 and 4.3, Isis shall manufacture and supply API for use in IND-Enabling Studies and for use for clinical Development through completion of Phase IIb Trials, which cost shall not exceed $[***] per gram. All such API manufacture will be performed at Isis' facilities. Isis shall not use a Third Party (sub)contractor for the manufacture of such API without the prior written approval of BMS.

Section 3.6 **Research Program Records.** Isis will maintain complete and accurate records of all work conducted in the performance of the Research Program and all results, data, inventions and developments made in the performance of the Research Program. Such records will be in sufficient detail and in good scientific manner appropriate for patent and regulatory purposes. Isis shall maintain appropriate records sufficient to document the work performed by each of the individuals comprising the FTEs working in support of the Research Program and the time such individuals spent working in support of the Research Program. Isis shall provide BMS the right to inspect such records, and shall provide copies of all requested records, to the extent reasonably required for the performance of BMS' rights and obligations under this Agreement; *provided however*, that BMS shall maintain such records and the information of Isis in confidence in accordance with Article 7 hereof and shall not use such records or information except to the extent otherwise permitted by this Agreement.

In order to protect the Parties' Patent rights under U.S. law in any inventions conceived or reduced to practice during or as a result of the Research Program, each Party agrees to maintain a policy that requires its employees to record and maintain all data and information developed during the Research Program in such a manner as to enable the Parties to use such records to establish the earliest date of invention and/or diligence to reduction to practice. At a minimum, the policy shall require such individuals to record all inventions generated by them in standard laboratory notebooks or other suitable means that are dated and corroborated by non-inventors on a regular, contemporaneous basis.

Section 3.7 **Disclosure of Results of Research Program.** The results of all work performed by the Parties as part of the Research Program shall be promptly disclosed to the other Party in a reasonable manner as such results are obtained. Isis shall periodically provide BMS with written reports of the work performed under the Research Program and the results achieved by Isis. Isis and BMS will provide reports and analyses at each JRC meeting, and more frequently on reasonable request by the JRC, detailing the current status of the Research Program, including but not limited to the utilization of the Isis FTE resources. Within 30 days following the end of each Calendar Quarter, Isis and BMS shall each exchange and provide to the JRC a written report summarizing in reasonable detail the work performed by it under the Research Program and results achieved during the preceding Calendar Quarter. In addition, on reasonable request by a Party, the other Party will make presentations of its activities in the performance of the Research Program to inform such Party of the details of the work done in the performance of the Research Program. The results, reports, analyses and other information regarding the Research Program disclosed by one Party to the other Party pursuant hereto may be used only in accordance with the rights granted and other terms and conditions under this Agreement. Upon reasonable request by BMS, Isis shall provide BMS with additional data, results and other information with respect to the work performed by Isis in the performance of the Research Program. Any reports required under this Section 3.7 may take the form of and be recorded in minutes of the JRC that will contain copies of any slides relating to the results and presented to the JRC.

In addition, at BMS' request Isis will transfer to BMS all data, results, and information related to testing and studies of the Compounds (including analytical test results and non-clinical pharmacology and safety data) in the possession of Isis to the extent such data, results and/or information is necessary or useful for the continued Development and Commercialization of Products, including but not limited to any and all information directly relating to manufacturing methods (including related analytical methods) of the Compounds or Products.

Section 3.8 **Research Efforts.** Each Party shall use good faith Commercially Reasonable Efforts to perform the Research Program, including its responsibilities under the Research Plan.

Throughout the Research Term, Isis shall assign no less than the number of FTE qualified scientists specified in Section 3.5 to perform the work set forth in the then-applicable Research Plan. The mixture of skills and levels of such FTEs shall be appropriate to the scientific objectives of the Research Program. No later than 60 days following the end of each Calendar Quarter, during the Research Term Isis shall report to the JRC a listing of the Isis scientists comprising such FTEs and their percentage of time devoted to working on the Research Program. If BMS has concern regarding any specific scientist assigned to the Research Program, such concerns shall be communicated to the JRC for its consideration.

Section 3.9 **Responsibility for Expenses for Conduct of Research Program.** Except as set forth in Section 3.5.2 or specified in the budget of the Research Plan and as may be

otherwise specifically agreed to in writing by Isis and BMS, BMS shall not be responsible for reimbursing Isis for other costs and expenses.

Section 3.10 **Materials Transfer.** In order to facilitate the Research Program, either Party may provide to the other Party certain materials for use by the other Party in furtherance of the Research Program. All such materials shall be used by the receiving Party in accordance with the terms and conditions of this Agreement solely for purposes of performing its rights and obligations under this Agreement, and the receiving Party shall not transfer such materials to any Third Party unless expressly contemplated by this Agreement or upon the written consent of the supplying Party. Upon request by BMS during the Research Term Isis shall provide BMS with samples of Compounds for use by BMS in accordance with the terms and conditions of this Agreement. Any materials provided by BMS to Isis in support of the Research Program, including but not limited to any biological materials with respect to screening assays, including any progeny, expression products, mutants, replicates, derivatives and modifications thereof, (such materials being individually and collectively referred to as the ***"BMS Materials"***) shall be used by Isis solely for purposes of performing the Research Program and for no other purpose, and any remaining BMS Materials (including, as applicable, any progeny, expression products, mutants, replicates, derivatives and modifications thereof) will be returned to BMS (or destroyed as may be requested by BMS in writing) promptly following the end of the Research Term or earlier upon request by BMS. All information related to such BMS Materials shall be BMS Confidential Information. All such materials must be used with prudence and appropriate caution in any experimental work, since all of their characteristics may not be known. If Isis develops any assays used in the Research Program, upon request by BMS during the Research Term, Isis shall transfer to BMS the materials and information to enable BMS to use such assays in support of BMS's internal research and development activities consistent with BMS' rights under Section 2.3.

Section 3.11 **Subcontracting.** Except as provided in the Research Plan or as may be specifically permitted by the JRC, Isis shall not (sub)contract any of the work for which it is responsible in the performance of the Research Program. In the case of any (sub)contracting of Research Program activities by a Party to a Third Party, such Third Party must have entered into a written agreement with such Party that includes terms and conditions protecting and limiting use and disclosure of Confidential Information and Know-How at least to the same extent as under this Agreement. Each Party is responsible for compliance by such Third Party with the applicable terms and conditions of this Agreement in the same way and to the same extent as such Party. As set forth in Section 3.5.2(c), all ASOs provided by Isis under this Agreement shall be manufactured at Isis' facilities and Isis shall not use a Third Party (sub)contractor for the manufacture of such ASOs without the prior written approval of BMS.

Section 3.12 **Alliance Managers.** Each Party shall appoint one senior representative who possesses a general understanding of the scientific and business issues relevant to this Agreement to act as its respective alliance manager (each, an ***"Alliance Manager"***) for the relationship of the Parties under this Agreement. Each Party may change its designated Alliance Manager, who may not be a member of the JRC, from time to time upon notice to the other Party. Any Alliance Manager may designate a substitute to temporarily perform the functions of that Alliance Manager. Each Alliance Manager will take responsibility for ensuring that governance activities occur as set forth in this Agreement, in particular ensuring that the JRC meetings occur, and that any conflict is given prompt attention as set forth in Section 13.4.

The Alliance Managers shall be entitled to attend meetings of the JRC, but shall not have, or be deemed to have, any rights or responsibilities of a member of the JRC. Similarly, the Alliance Managers may attend meetings of the Working Group or any subcommittees of the JRC.

Each Alliance Manager may bring any matter to the attention the JRC where such Alliance Manager reasonably believes that such matter requires such attention. For purposes of clarification, in no event will the Alliance Managers have the power or authority to amend any provision of this Agreement.

Section 3.13 **Animal Testing.** In order to assure the appropriate care and use of animals used in the performance of the Research Program by Isis, Isis agrees to the following:

(a) If Isis is AAALAC accredited, it will follow procedures established as the basis of that accreditation. Isis represents and covenants that it will use all reasonable efforts to maintain such AAALAC accreditation during the Research Term. Further, upon request by BMS, Isis will provide BMS with a copy of the most recent accreditation letter and annual report. If during the course of the Research Program Isis loses its accreditation or receives any notice, warning or reprimand from AAALAC or any governmental or regulatory agency related to animal care and use, Isis will promptly notify BMS in writing.

(b) If Isis is not AAALAC accredited or loses its AAALAC accreditation at any time during the Research Term, it will, prior to the commencement (or continuation) of Research Program studies using animals provide BMS with sufficient documentation in such manner, format and frequency as BMS may require in its sole reasonable discretion, to assure appropriate care and use of animals. Such documentation may include, without limitation, government inspection reports, animal test methods, animal use protocols and any other written descriptions of animal care and use. Isis will also comply with all Applicable Laws governing animal research.

(c) Whenever possible, live animals used as part of the Research Program should remain the property of the applicable contract facility. Upon reasonable advance notice during the Research Term, representatives of BMS shall have the right to inspect the research facilities and to audit the care, treatment and use of the animals used in the Research Program. This includes the right to review any correspondence with or reports from governmental agencies or accrediting organizations responsible for animal welfare or quality assurance.

ARTICLE 4 -
DEVELOPMENT, COMMERCIALIZATION & MANUFACTURING

Section 4.1 **Development, Commercialization and Regulatory Responsibilities.** Other than Isis' responsibilities under the Research Program, BMS shall have sole responsibility, including without limitation sole responsibility for all funding, resourcing and decision-making, for all further Development and Commercialization with respect to the Compounds and Products. BMS hereby assumes all regulatory responsibilities in connection with Compounds and Products, including sole responsibility for all Regulatory Documentation and for obtaining all Approvals. BMS will comply with all Applicable Laws in connection with the Development and Commercialization of Compounds and Products. BMS (by itself or through its Affiliates, Licensees, (sub)contractors or agents, as applicable) shall use Commercially Reasonable Efforts to Develop and Commercialize at least one Compound or Product. For clarity, it is understood and acknowledged that Commercially Reasonable Efforts in the Development of a Product in a particular country may include sequential implementation of clinical trials and/or intervals between clinical trials for data interpretation and clinical program planning and approval, to the extent such implementation is consistent with the scientific, technical and commercial factors relevant to Development of such Product in such country. All INDs, NDAs, MAAs and other regulatory filings and Approvals for Products shall be owned by BMS. In addition to Isis' responsibilities with respect to the CMC section of the IND in accordance with the Research Plan,

upon request by BMS, Isis shall provide BMS with a reasonable level of assistance in the preparation of regulatory filings for Products and in interactions with any Regulatory Authority in connection with the Development of Products; *provided* that if BMS requests such assistance in excess of [***] aggregate hours of assistance, BMS shall reimburse Isis for its time incurred in providing such assistance in excess of such [***] hour limit at the at the then-applicable Isis FTE Rate per hour, plus any reasonable out-of-pocket expenses incurred by Isis in providing such assistance. Such reimbursement shall be made to Isis within 30 days after submission of an invoice by Isis reasonably detailing Isis' time expended, together with reasonable substantiation of any out-of-pocket expenses incurred.

Section 4.2 **IND-Enabling and Initial Phase I Supply of API**. Isis will be responsible for the manufacture and supply of an approximately [***] batch of API for the lead Compounds identified under the Research Plan and designated by the JRC to enter IND-Enabling Studies as specified in the Research Plan. Such API shall be manufactured with systems, processes and procedures consistent with cGMP practices. Such API shall be delivered and provided as a service for BMS with a supply services fee being $[***] per gram of API (which is Isis' good faith estimate of its fully burdened cost of manufacture of such API). BMS shall be entitled to conduct quality inspections of manufacturing areas, warehouses, laboratories and any related facilities upon reasonable notice to Isis and at mutually convenient times in connection with the manufacture of API by Isis under this Agreement. BMS shall be permitted to observe operations related to API manufacturing and testing. BMS shall be entitled to review Isis procedural documents and any related supporting documentation for compliance with cGMP regulations. BMS shall be entitled to conduct batch record audits on site at the manufacturing facility, or any other site where the batch records are stored, of each batch of API manufactured by Isis under this Agreement. If, following a GMP audit of a facility by BMS, BMS reasonably believes that a default or deficiency on the part of Isis exists, BMS shall be entitled to conduct additional quality audits (at mutually convenient times and consistent with what is reasonable and customary in the pharmaceutical industry) in order to satisfy itself that appropriate remedial measures have been, or are being, taken by Isis regarding the matters in question. In addition, if Isis has performed a comparable audit with respect to contract service providers involved in the manufacture of API, upon request by BMS, Isis will share the results of those audits with BMS, unless pre-existing agreements between Isis and the service provider preclude doing so. BMS will respect the confidentiality of Isis and any service providers during any audit or visit (including entering into an appropriate confidential disclosure agreement as necessary). Isis' obligation to supply BMS API under this Section 4.2 will expire upon the [***] year anniversary of the expiration of the Research Term (i.e., at [***] years following the expiration of the Research Term). Any API requested by BMS after the end of the Research Term will be manufactured pursuant a separate Clinical Supply Agreement as described in Section 4.3 below.

Section 4.3 **Clinical Supply of API Through Completion of Phase II and Phase IIb Trials.** BMS will obtain API for all clinical Development activities under this Agreement through the completion of Phase IIb Trials (the ***"Phase II Clinical Supply"***) from Isis. Isis shall be responsible for the manufacture and supply of BMS' requirements of the Phase II Clinical Supply. Such API shall be delivered and provided as a service for BMS with a supply services fee being $[***] per gram of API (which is Isis' good faith estimate of its fully burdened cost of manufacture of such API). The Parties may negotiate in good faith and mutually agree upon a reduction to this fee to the extent Isis' manufacturing costs decrease after the Effective Date. In addition, if Isis supplies active pharmaceutical ingredient for a similar ASO to a Third Party at similar volumes on terms when taken as a whole are more favorable than the terms provided BMS under this Agreement, BMS will have the right to receive the clinical supply of API on the same terms offered by Isis to such Third Party. Isis and BMS will enter into a manufacture and supply agreement for the Phase II Clinical Supply, including the related CMC activities and/or

any API requested by BMS after the end of the Research Term under Section 4.2 (the ***"Clinical Supply Agreement"***). Such Clinical Supply Agreement shall include the quality audit provisions set forth in Section 4.2 and other customary terms and conditions to be negotiated in good faith. Isis will not have any obligation under this Section 4.3 to negotiate or enter into any manufacturing or supply agreement or similar agreement beyond the scope set forth in this

Section 4.3, including without limitation any agreement covering clinical supply for Phase III Trials or commercial scale-up or supply. As part of the Phase II Clinical Supply, Isis will enable BMS' regulatory function to test and release all supplies of such API.

Section 4.4 **Failure to Supply.** In the case where Isis is unable or for any reason otherwise fails to supply API to BMS in accordance with the Clinical Supply Agreement, upon written request by BMS, Isis shall transfer to BMS all documentation and information, and permit BMS to reference and use any regulatory filings, and otherwise fully cooperate with BMS to enable BMS to make or have made API for use by BMS in accordance with this Agreement.

Section 4.5 **[***] and Commercial Manufacturing and Supply of Compound and Product.**

4.5.1 Product Manufacturing Responsibility. Except as otherwise provided in this Agreement, the Parties acknowledge and agree that BMS shall be solely responsible for the manufacturing of Compound and Product, including management of the overall manufacturing strategy and tactics, formulation, contract manufacturer selection for API and finished Product, associated audits, and stability testing.

4.5.2 Isis Right of First Negotiation.

(a) Isis will have a first right of negotiation with respect to the manufacture and supply to BMS of API for use in [***] as follows. In the event that BMS desires to outsource the manufacturing of the [***] supply of the API for [***] to a Third Party manufacturer, then BMS shall provide written notice of such desire to Isis and the Parties will negotiate in good faith with respect to an agreement for Isis to manufacture and supply the API for BMS for the [***] of the Product. If the Parties do not reach agreement within 120 days of such notice by BMS to Isis, BMS shall be free at its discretion (and subject to Section 4.5.3(b)) to enter into an agreement with any Third Party with respect to such [***] supply based on terms and other considerations (such other considerations including non-financial considerations including but not limited to quality, capacity, lead time, contingency planning, reliability and regulatory compliance) that when taken as a whole as reasonably determined by BMS are no less favorable to BMS than the terms and other considerations last presented to BMS by Isis. It is expected that such negotiations and decision by BMS regarding the manufacture and supply of API for [***] would need to occur at least [***] prior to the expected start of [***], in order, for example, to allow for any required manufacturing technology transfer and qualification of a Third Party manufacturer.

(b) In the case where Isis and BMS enter into an agreement for Isis to manufacture and supply BMS' requirements of API for [***], Isis shall have a first right of negotiation with respect to the manufacture and supply to BMS of API for the commercial requirements of the Product as follows. In the event that BMS desires to outsource the manufacturing of the commercial supply of the API to a Third Party manufacturer, then BMS shall provide written notice of such desire to Isis and the Parties will negotiate in good faith with respect to an agreement for Isis to manufacture and supply the API for BMS' commercial requirements of the Product. If the Parties do not reach agreement within [***] days of such notice by BMS to Isis, BMS shall be free at its discretion (and subject to Section 4.5.3(b)) to enter into an agreement with any Third Party with respect to such commercial supply on terms and other considerations

(such other considerations including non-financial considerations including but not limited to quality, capacity, lead time, contingency planning, reliability and regulatory compliance) that when taken as a whole as reasonably determined by BMS are no less favorable to BMS than the terms and other considerations last presented to BMS by Isis.

(c) In advance of any negotiations between the Parties under Section 4.5.2(a) or (b), upon request by BMS, Isis shall provide to BMS a summary of the manufacturing technology proposed to be used by or for Isis for the manufacturing of API, and other related information as reasonably requested by BMS.

4.5.3 Transfer of Manufacturing Technology.

(a) Upon request by BMS, solely for purposes of the manufacture and supply of BMS' requirements of API for [***] and/or commercial supply of Compound and/or Product pursuant to the exercise of BMS' rights under this Agreement, Isis shall transfer any Isis Manufacturing Technology to BMS, and/or any Isis Permitted Manufacturing Technology to a Third Party manufacturer selected by BMS. As soon as is practicable after its receipt of such request, Isis shall transfer to BMS the Isis Manufacturing Technology, or the Isis Permitted Manufacturing Technology to such Third Party manufacturer. For such purpose Isis shall transfer to BMS all documentation and information, and permit BMS to reference and use any regulatory filings, and otherwise fully cooperate with BMS to enable BMS to make or have made API for use by BMS in accordance with this Agreement. All documented out-of-pocket costs and expenses incurred by Isis in carrying out such transfer shall be reimbursed by BMS upon successful completion and confirmation of such transfer. In addition, upon request by BMS, Isis shall provide BMS with a reasonable level of technical assistance and consultation in connection with the transfer of such manufacturing technology to help enable BMS or such Third Party manufacturer (as applicable) to manufacture such API. For such purpose Isis shall provide BMS with reasonable access by teleconference or in-person at Isis' facilities to Isis personnel involved in the manufacturing of API, *provided* that if BMS requests such technical assistance in excess of [***] aggregate hours of technical assistance, BMS shall reimburse Isis for its time incurred in providing such assistance in excess of such [***] hour limit at the then-applicable Isis FTE Rate per hour, plus any reasonable out-of-pocket expenses incurred by Isis in providing such technical assistance requested by BMS. Such payment shall be made to Isis within 30 days after submission of an invoice by Isis reasonably detailing Isis' time expended, together with reasonable substantiation of any out-of-pocket expenses incurred.

(b) BMS and/or its Third Party manufacturer shall use any Isis Know-How and other documentation and information transferred pursuant to Section 4.5.3(a) solely for the purpose of manufacturing API and Product for BMS' (or its Affiliate's or Licensee's) benefit pursuant to the exercise of BMS' rights under this Agreement, and for no other purpose. BMS acknowledges and agrees that any such transfer of such manufacturing technology to a Third Party manufacturer shall satisfy the conditions set forth in Section 2.1(b) and will be subject to a written agreement between such Third Party manufacturer and BMS that contains obligations of confidentiality substantially equivalent to those of this Agreement.

(c) In the event that BMS desires to transfer to a Third Party manufacturer any Isis Manufacturing Technology which is not Isis Permitted Manufacturing Technology solely for purposes of the manufacture and supply of BMS' requirements of API for [***] and/or commercial supply of Compound and/or Product pursuant to the exercise of BMS' rights under this Agreement, upon written request by BMS, Isis shall use commercially reasonable efforts to enter into an agreement with such Third Party manufacturer to transfer such Isis Manufacturing Technology which is not Isis Permitted Manufacturing Technology for such purpose under terms

and conditions to be negotiated in good faith by Isis with such Third Party. Isis shall reasonably consult with BMS in connection with such negotiation to assure that any such agreement achieves the purpose and objectives sought by BMS in making such request.

Section 4.6 **Reports by BMS.** BMS shall, on or before each anniversary of the Effective Date following the Research Term, and continuing until such time as Approval of all Products under Development has been obtained in Europe, the United States and Japan, provide Isis with a summary written report of the status of BMS's efforts to Develop Compounds and Products hereunder. Such written report shall contain sufficient information to allow Isis to reasonably determine whether BMS is in compliance with its obligations to use Commercially Reasonable Efforts under Section 4.1.

Section 4.7 **Safety Database**

(a) 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, BMS will cooperate in connection with populating the Isis Database. In accordance with and subject to the Pharmacovigilance Agreement, Applicable Law and any applicable informed consents or other Third Party obligations, BMS will provide Isis with copies of toxicology, pharmacokinetic and serious adverse event final reports related to each PCSK9 Compound and Product. In addition, in connection with any reported serious adverse event (including any follow-up or amended reports), in accordance with and subject to the Pharmacovigilance Agreement, Applicable Law and any applicable informed consents or other Third Party obligations, BMS will provide Isis in a mutually acceptable format, the following patient data: (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 Product, severity and criteria making event serious, outcome); (e) dosing history (dates, quantity of Product administered, method of administration); (f) chemistry, urinalysis and hematology lab tests; and (g) any countermeasures taken for the event. All such information disclosed by BMS to Isis in connection with this Section shall be BMS Confidential Information; *provided, however*, that Isis may disclose any BMS Confidential Information contained in the Isis Database to any Third Party so long as Isis does not disclose to any Third Party the identity of the applicable Compound, the PCSK9 target or BMS (or any information that would foreseeably reveal the identity of the applicable Compound, the PCSK9 target or BMS) in connection with any such disclosure.

(b) From time to time, Isis utilizes the information in the Isis Database to conduct analyses to keep Isis and its partners informed regarding class generic properties of ASOs, including with respect to safety. As such, if and when Isis identifies safety or other related issues that may be relevant to a Product (including potential class-related toxicity liabilities), in accordance with and subject to the Pharmacovigilance Agreement, Isis will promptly inform BMS of such issues, and if requested, provide the data supporting Isis' conclusions regarding such issues.

Section 4.8 **Pharmacovigilance Agreement**. Subject to the terms of this Agreement, and within 3 months prior to the expected date of IND filing for a Compound, BMS and Isis (under the guidance of their respective pharmacovigilance departments, or equivalent thereof) shall define and finalize the responsibilities the Parties shall employ to protect patients and promote their well-being in a written pharmacovigilance agreement (hereafter referred to as the ***"Pharmacovigilance Agreement"***). These responsibilities shall include mutually acceptable

guidelines and procedures for the receipt, investigation, recordation, communication and exchange (as between the Parties) of adverse event reports and any other information concerning the safety of any Compound or Product. Such guidelines and procedures shall be in accordance with, and enable the Parties and their Affiliates to fulfill, local and national regulatory reporting obligations to government authorities. Furthermore, such agreed procedures shall be consistent with relevant International Council for Harmonization (ICH) guidelines, except where said guidelines may conflict with existing local regulatory safety reporting requirements, in which case local reporting requirements shall prevail. Each Party hereby agrees to comply with its respective obligations under such Pharmacovigilance Agreement (as it may be modified from time to time by mutual written agreement of the Parties) and to cause its Affiliates to comply with such obligations. In accordance with and subject to the Pharmacovigilance Agreement, each Party shall provide the other Party with information available to such Party that such other Party may reasonably require to comply with its pharmacovigilance responsibilities under Applicable Law, including notice of any adverse drug experiences from pre-clinical or clinical laboratory, animal toxicology and pharmacology studies, clinical trials and commercial experiences.

ARTICLE 5 -
FINANCIAL PROVISIONS

Section 5.1 **Up-Front Payment by BMS.** In partial consideration for the licenses and other rights granted under this Agreement, within 10 Business Days following the Effective Date, BMS will pay Isis an irrevocable, non-creditable and nonrefundable signing payment equal to $15,000,000.

Section 5.2 **Research Program Payments.** Research funding shall be provided by BMS to Isis as set forth in Section 3.5

Section 5.3 **Milestone Payments by BMS.**

(a) The milestone payments under Column 1 of Table 1 below shall be payable by BMS to Isis within 30 days after the first achievement of the specified milestone events by BMS, its Licensees or their Affiliates for the first Compound to reach the specified milestone event. The milestone payments under Column 2 of Table 1 below shall be payable as set forth below after the first achievement of the specified milestone events by BMS, its Licensees or their Affiliates for each subsequent Compound (i.e., each Compound after the first Compound) to reach the specified milestone event.

Table 1

Milestone Event	Column 1 Payment for First Compound	Column 2 Payment for Each Subsequent Compound
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]

(b) If development is discontinued for a Compound, any previously paid milestone payments for that Compound will be applied and credited toward the milestone payments for the next subsequent Compound in development upon achievement of such milestones. Only one set of milestone payments will be due (but payable as set forth in this paragraph) for a given Compound (i.e., for a given chemical entity). In addition, in order to trigger and be eligible for a milestone payment under this Section 5.3, the making, using or selling of the applicable Compound must be Covered by a Valid Claim of an Isis Patent Right in the U.S. or the European Patent Office.

(c) By way of example, in accordance with the foregoing, if the development of a first Compound is discontinued after the [***] milestone event is completed (with such milestone payment and earlier milestone payments having been paid for such first Compound), and a second follow-on Compound is subsequently advanced through development, no milestone payments would be payable for the second Compound through the [***] milestone, but milestone payments under Column 1 of Table 1 would be payable for any subsequent milestone events achieved by such second Compound (since such Compound would be the first Compound to achieve these subsequent milestone events).

Section 5.4 **Royalty Payments by BMS.** Subject to the other provisions of this Agreement, BMS shall pay to Isis royalties based on the Net Sales of each Product during the applicable Royalty Term. The royalty payable with respect to each particular Product shall be based on the level of aggregate annual worldwide Net Sales of such Product in a given Calendar Year period by BMS, its Affiliates and Licensees, with the royalty rate tiered based upon the level of such aggregate worldwide Net Sales in such Calendar Year period as set forth in the table below.

Royalty Rate	Annual Worldwide Net Sales
[***]	of annual worldwide Net Sales less than or equal to $[***]
[***]	of annual worldwide Net Sales greater than $[***] and less than $[***]
[***]	of annual worldwide Net Sales equal to or greater than $[***] billion

Royalties shall be calculated on a Product-by-Product and country-by-country basis using the applicable royalty rate or rates set out above and shall be determined based on the annual Net Sales of the relevant Product for the Calendar Year in question, and shall be paid at the rate applicable to the portion of Net Sales within each of the above Net Sales tiers during such Calendar Year. By way of example, for a particular Product in a given Calendar Year period, if the total worldwide Net Sales of such Product in such Calendar Year period is $[***], the royalty payable by BMS to Isis will be ([***]% x $[***] million) + ([***]% x $[***] million) = $[***] million (plus any applicable financial Pass Through Obligations and subject to any applicable reductions under Section 5.5 or 5.7).

Notwithstanding the foregoing or any other provision of this Agreement, a Product shall only be eligible for a royalty payment under this Section 5.4 in a given country, if, as of the date of the First Commercial Sale of such Product in such country, the making, using or selling of such Product (or the Compound contained in such Product) in the U.S. or a Major European Country is Covered by a Valid Claim of an Isis Patent Right in the U.S. or the European Patent Office. Accordingly, no royalty will be payable under this Section 5.4 on Net Sales of a Product in a country where, as of the date of the First Commercial Sale of such Product in such country, the making, using or selling of such Product (or the Compound contained in such Product) in the U.S. or a Major European Country was not then Covered by a Valid Claim of an Isis Patent Right in the U.S. or the European Patent Office. Once a Product is determined to be eligible for a royalty payment in accordance with the foregoing, it shall continue to be eligible for the applicable Royalty Term, subject to the other terms and conditions of this Agreement.

Section 5.5 **Third Party Payment Obligations.**

5.5.1 Isis In-License Agreements.

(a) Certain of the Isis Patent Rights Controlled by Isis as of the Effective Date that are licensed to BMS under Section 2.1 are in-licensed or were acquired by Isis under agreements with Third Party licensors or sellers, and certain milestone and/or royalty payments may become payable by Isis to such Third Party under such license or purchase agreements based on the Development and Commercialization of a Compound and Product by BMS under this Agreement (such license or purchase agreements in effect as of the Effective Date being the ***"Isis In-License Agreements"***). The Parties acknowledge that whether a milestone and/or royalty becomes payable by Isis to such Third Party licensor depends on the terms and conditions of the Isis In-License Agreement and on the properties of the Compound and Product being Developed or Commercialized by BMS under this Agreement. Isis represents and warrants that the Isis In-License Agreements that Isis considers in good faith to be most relevant to the manufacture, use or sale of Compounds and Products as contemplated under the initial Research Plan (together with any associated potential Pass Through Obligations) are included in the list of agreements identified in Appendix 6.

(b) BMS will be responsible for and hereby agrees to assume [***]% of the [***] Royalties, if any, with respect to any Product, *provided however*, that the amount of such [***] Royalties shall in no event exceed [***]% of net sales of a Product. Section 5.5.1(c) shall

not apply to the [***] Royalties and BMS shall not be entitled to reduce the royalty payable under Section 5.4 based on the payment of any [***] Royalties.

(c) During the Research Term, as changes are made to the Research Plan and as Compounds and Products are being considered by the JRC, and for each lead Compound and for each ECN (at such time that a Compound is being considered for designation as an ECN), Isis shall promptly inform BMS in writing through the JRC regarding any Isis Patent Rights licensed to BMS under Section 2.1 that are subject to Isis In-License Agreements and potential Pass Through Obligations that are potentially relevant to the manufacture, use or sale of such Compounds, Products, lead Compounds and ECN. BMS will be responsible for the payment of all financial Pass Through Obligations with respect to Compounds and Products, *provided* that BMS' obligation to pay royalties under Section 5.4 (including any reduction under Section 5.7) shall be reduced by [***]% of the amount of any such Pass Through Obligations paid by BMS, subject to Section 5.5.4 (with the amount of any non-royalty Pass Through Obligations not so applied by BMS to such reduction in a given Calendar Quarter, because of Section 5.5.4, to be [***]). If BMS does not agree to be responsible for the payment of any such Pass Through Obligation, then the applicable Isis In-License Patent will not be considered an Isis Patent Right licensed to BMS under this Agreement.

(d) Any royalties or milestones BMS is responsible for paying under subsection (b) or (c) of this Section 5.5.1 will be in addition to the royalties and milestones payable by BMS under Section 5.3 and 5.4 (including any reduction under Section 5.7 and any reduction as set forth in Section 5.5) and BMS shall satisfy such obligation by paying Isis directly.

5.5.2 Additional Third Party Agreements.

(a) After the Effective Date, Isis may in-license or acquire rights to Third Party Patents (such a Third Party in-license or acquisition agreement being an ***"Additional Third Party Agreement"***) which would be included in the Isis Patent Rights licensed to BMS under Section 2.1. In such event, Isis shall notify BMS regarding such Additional Third Party Agreement through the JRC (including the payments paid or potentially payable by Isis thereunder) and the Parties shall confer and discuss in good faith regarding the sharing of any upfront or similar acquisition payments that Isis paid or that would be payable to such Third Party. At such time, if BMS wishes to include such Third Party Patents under the licenses granted under Section 2.1, BMS will notify Isis of its desire to do so and the Parties will fairly allocate between Compounds (and Products) and compounds that are not Compounds (and products that are not Products) any upfront payments or similar acquisition payments made by Isis to such Third Party under the Additional Third Party Agreement. If BMS does not agree to reimburse Isis for [***]% of such amount of any upfront or similar acquisition payments fairly allocated to Compound and Products, and to be responsible for the payment of its share of any milestone and royalty payments as set forth below, then the Third Party Patents acquired or in-licensed by Isis under the Additional Third Party Agreement will not be considered an Isis Patent Right licensed to BMS under this Agreement.

(b) In the event that a milestone payment or a royalty on net sales of Product becomes payable by Isis to a Third Party under such Additional Third Party Agreement with respect to a Product Developed and Commercialized by BMS under this Agreement, and such milestone or royalty payment obligation is based on the Product being Covered by an Isis Patent Right which is licensed to BMS under Section 2.1 and which is licensed to or acquired by Isis under such Additional Third Party Agreement (such milestone and/or royalty payments being the ***"Isis Third Party Payment"***), then BMS shall be responsible for the payment of such Isis Third

Party Payment obligation, *provided* that BMS' obligation to pay royalties under Section 5.4 (including any reduction under Section 5.7) shall be reduced by [***]% of the Isis Third Party Payment paid by BMS, subject to Section 5.5.4 (with the amount of any non-royalty Isis Third Party Payment not so applied by BMS to such reduction in a given Calendar Quarter, because of Section 5.5.4, [***]). If BMS does not agree to be responsible for the payment of any such Isis Third Party Payment, then the applicable Isis In-License Patent will not be considered an Isis Patent Right licensed to BMS under this Agreement.

(c) Any royalties or milestones BMS is responsible for paying under subsection (a) or (b) of this Section 5.5.2 will be in addition to the royalties and milestones payable by BMS under Section 5.3 and 5.4 (including any reduction under Section 5.7 and any reduction as set forth in Section 5.5) and BMS shall satisfy such obligation by paying Isis directly.

5.5.3 BMS Third Party Licenses. BMS will be responsible for negotiating and entering into any Third Party licenses that BMS determines may be necessary or useful or may relate to the Development or Commercialization of Products. If BMS, in its reasonable judgment, is required to obtain a license from any Third Party (such Third Party shall include Isis and its Affiliates with respect to any patent that is not licensed to BMS under this Agreement) under any patent covering technology necessary or useful for the Development or Commercialization of a Product (including but not limited to technology for the delivery or formulation of a Product), and the infringement of such patent cannot reasonably be avoided by BMS, and (i) such infringement has been proved in a court of competent jurisdiction or (ii) BMS has settled the infringement with the relevant Third Party by way of out-of-court agreement; and if BMS is required to pay to such Third Party in consideration for such license for a Product any milestone payments with respect to a Product or a royalty calculated on sales of a Product, or if BMS is required by a court of competent jurisdiction to pay such milestone or royalty payments to such a Third Party (such milestone and royalty payments collectively being a ***"BMS Third Party Payment"***; such BMS Third Party Payment shall also include any upfront payments paid to such Third Party in consideration for such license where the license is limited to Compounds and Products), then BMS may reduce the royalty payable to Isis under Section 5.4 by up to [***]% of the amount of the BMS Third Party Payment (subject to Section 5.5.4) (with the amount of any such non-royalty BMS Third Party Payment not so applied by BMS to such reduction in a given Calendar Quarter, because of Section 5.5.4, [***]). Notwithstanding the foregoing, no reduction of the royalties payable to Isis under Section 5.4 shall be permitted with respect to BMS Third Party Payments with respect to any Third Party patent covering (x) methods or materials used in the [***] or (y) any active ingredient which is not a Compound (i.e., a non-Compound active ingredient in a Combination Product).

5.5.4 Except for the [***] Royalty, for any additional payments payable by BMS under Section 5.5.1, 5.5.2 or 5.5.3, BMS may reduce its obligation to pay Isis royalties under Section 5.4 by [***] of the amount of such additional payments payable by BMS as set forth in Sections 5.5.1, 5.5.2

and 5.5.3; *provided, however* that (i) with respect to royalties paid to Third Parties by BMS under Sections 5.5.1, 5.5.2 and 5.5.3 no such reduction(s) in the aggregate shall reduce the royalty payments payable to Isis under Section 5.4 in any given Calendar Quarter period below a royalty payable to Isis of [***]% of Net Sales and (ii) with respect to non-royalty payments paid to Third Parties by BMS under Sections 5.5.1, 5.5.2 and 5.5.3 no such reduction(s) in the aggregate shall reduce the royalty payments payable to Isis under Section 5.4 in any given Calendar Quarter period below a royalty payable to Isis of [***]%, [***]% and [***]% of Net Sales, as applicable (i.e. [***] of the applicable Royalty Rates set forth in the table in Section 5.4).

Section 5.6 **Pay-Down of [***].** If after the Effective Date Isis enters an agreement to pay a fee or other payment to reduce (in whole or in part) the [***] Royalties, Isis will present the agreement to BMS through the JRC and the Parties shall confer and discuss in good faith regarding the sharing of any such fee or other payment that Isis paid or is payable under such agreement. If BMS agrees to share the portion of such fees and payments determined appropriate by the mutual agreement of the Parties, BMS will be relieved of its obligation to pay the [***] Royalty to the extent of Isis' benefit under such new agreement reducing the [***] Royalty.

Section 5.7 **Generic Competition.** If there are one or more unauthorized Third Parties selling a Generic Product, BMS may reduce the royalties due to Isis under Section 5.4 above on a country-by-country and Product-by-Product basis by [***] the unit volume sales of such Generic Product(s) account for the [***] of the Product plus the Generic Product in such country as reported by IMS; *provided, however*, that, in no event will the royalties payable to Isis under Section 5.4 above be reduced below the amount of any [***]. By way of example, if the sales of a Generic Product in a country account for [***]% of the unit volume of the Product plus all Generic Products, BMS may reduce the royalties due to Isis under Section 5.4 by [***]% in such country.

Section 5.8 **Royalty Conditions.** The royalties under Section 5.4 shall be subject to the following conditions:

(i) that only one royalty shall be due to Isis hereunder with respect to the same unit of Product;

(ii) that no royalties shall be due upon the sale or other transfer of a Product among BMS, its Affiliates or Licensees, but in such cases the royalty shall be due and calculated upon BMS's or its Affiliate's or Licensee's sale of Product to the first unaffiliated Third Party customer, where Net Sales is as defined in Appendix 1;

(iii) no royalties shall accrue on the disposition of Product in reasonable quantities by BMS, its Affiliates or Licensees as part of an expanded access program or as part of Phase IV Trials or as bona fide samples or as donations to non-profit institutions or government agencies for non-commercial purposes, *provided*, in each case, that neither BMS, its Affiliate or Licensees receives any payment or other in-kind consideration for such Product.

Section 5.9 **Royalty Term.** Royalties payable under Section 5.4 (subject to and including any reduction set forth in Sections 5.5, 5.6 and 5.7) will be payable for each Product on a Product-by-Product and country-by-country basis from the First Commercial Sale of the applicable Product in such country until the date that is the later of (i) [***] years after the First Commercial Sale of the Product in such country or (ii) the expiration of the last to expire Valid Claim within the Product Specific Patents or Isis Core Technology Patents which would be infringed by the sale of the applicable Product in the applicable country by an unauthorized party or (iii) the expiration of any applicable period of exclusivity as contemplated under Section 8.6 for the Product in the applicable country; *provided* that royalties shall only accrue so long as the exclusive license granted by Isis to BMS under Section 2.1 with respect to such Product has not been terminated. Such period during which royalties are payable with respect to a Product in a country is referred to herein as the ***"Royalty Term"*** in such country with respect to such Product.

Section 5.10 **Royalty Report and Payment.** During the term of this Agreement following the First Commercial Sale of any Product, within 60 days after the end of each

Calendar Quarter, BMS shall pay to Isis royalty payments payable for such Calendar Quarter and provide a royalty report showing, on a Product-by-Product and country-by-country basis:

(a) the Net Sales of Products sold by BMS, its Licensees and their respective Affiliates during such Calendar Quarter reporting period;

(b) the royalties payable in United States Dollars which shall have accrued hereunder with respect to such Net Sales;

(c) withholding taxes, if any, required by Applicable Law to be deducted with respect to such royalties; and

(d) the rate of exchange used by BMS in determining the amount of United States dollars payable hereunder.

In addition, during the term of this Agreement following the First Commercial Sale of any Product, within 30 days after the end of each Calendar Quarter, BMS shall provide Isis a preliminary quarterly royalty report showing the total Net Sales of Product and royalty payable for such Calendar Quarter.

If no royalty or payment is due for any royalty period hereunder, BMS shall so report. BMS shall keep, and shall require its Licensees and their respective Affiliates to keep (all in accordance with generally accepted accounting principles, consistently applied), complete and accurate records in sufficient detail to properly reflect the Net Sales and to enable the royalties payable hereunder to be determined. Upon reasonable request by Isis, BMS shall report to Isis the quantity of Product (not subject to royalties) distributed by BMS, its Affiliates or Licensees as part of an expanded access program or as part of Phase IV trials or as bona fide samples or as donations to not-for-profit institutions or government agencies for non-commercial purposes. All information disclosed by BMS to Isis under this Section 5.10 shall be BMS Confidential Information.

Section 5.11 **Manner of Payment And Exchange Rate.** All payments to be made by BMS to Isis under this Agreement shall be made in Dollars and shall be paid by electronic transfer in immediately available funds to such bank account in the United States designated in writing by Isis. In the case of Net Sales outside the United States, the rate of exchange to be used in computing the amount of currency equivalent in United States Dollars payable shall be the rate of exchange used by BMS for its own financial reporting purposes in connection with its other products, which shall be consistent with GAAP. Upon request by Isis, BMS shall inform Isis regarding BMS's then-current currency exchange policy.

Section 5.12 **Audits of Royalty Reports.**

Upon the written request of Isis and not more than once in each Calendar Year, BMS shall permit an independent certified public accounting firm of nationally recognized standing selected by Isis and reasonably acceptable to BMS, at Isis' expense and upon execution of a confidentiality agreement with BMS, to have access during normal business hours to such records of BMS and/or its Affiliates as may be reasonably necessary to verify the accuracy of the royalty reports hereunder for any Calendar Year ending not more than 36 months prior to the date of such request. These audit rights (but not any obligation to pay unpaid royalties for such periods) with respect to any Calendar Year shall terminate 3 years after the end of any such Calendar Year. Isis shall provide BMS with a copy of the accounting firm's written report within 30 days of completion of such report.

If such accounting firm correctly concludes that an overpayment or underpayment was made, then the owing Party shall pay the amount due within 30 days of the date Isis delivers to

BMS such accounting firm's written report so correctly concluding. Isis shall bear the full cost of such audit unless such audit correctly discloses that the additional payment payable by BMS for the audited period is more than [***] of the amount of the royalties paid for that audited period, in which case BMS shall pay the reasonable fees and expenses charged by the accounting firm.

BMS shall include in each sublicense granted by it to any Licensee a provision requiring the Licensee to maintain records of sales made pursuant to such license and to grant access to such records by BMS's independent accountant to the same extent and under the same obligations as required of BMS under this Agreement. BMS shall advise Isis in advance of each audit of any Licensee with respect to Product sales. BMS will provide Isis with a summary of the results received from the audit and, if Isis so requests, a copy of the audit report with respect to Product sales. BMS shall pay the reasonable fees and expenses charged by the accounting firm, except that Isis shall pay for all additional services requested exclusively by Isis from BMS's independent accountant unless the audit discloses that the additional payments payable to Isis for the audited period differ by more than [***] from the amount of the royalties otherwise paid.

All financial information subject to review under this Section or under any license agreement with a Licensee shall be BMS Confidential Information and shall be treated in accordance with the confidentiality provisions of this Agreement. As a condition precedent to Isis' audit rights under this Section, Isis' accounting firm will enter into a confidentiality agreement with BMS obligating it to treat all such financial information in confidence pursuant to such confidentiality agreement. Isis may provide Third Parties to which Isis owes Pass Through Royalties on Products information in such audit report that are relevant and required to comply with such Third Party's audit rights under the applicable license agreement between Isis and such Third Party, *provided* that such Third Party agrees in writing to keep such information confidential under terms no less restrictive than Isis' obligations of confidentiality under this Agreement.

Section 5.13 **Taxes.** Isis will pay any and all taxes levied on account of all payments it receives under this Agreement. If laws or regulations require that taxes be withheld with respect to such payments, BMS will: (i) deduct those taxes from the remittable payment; (ii) pay the taxes to the proper taxing authority; and (iii) send evidence of the obligation together with proof of tax payment to Isis on a timely basis following that tax payment. Each Party agrees to cooperate with the other Party in claiming refunds or exemptions from such deductions or withholdings under any relevant agreement or treaty which is in effect. Such cooperation may include BMS making payments from a single source in the U.S., where not impracticable. The Parties shall discuss applicable mechanisms for minimizing such taxes to extent possible in compliance with Applicable Law. In addition, the Parties shall cooperate in accordance with Applicable Law to minimize indirect taxes (such as value added tax, sales tax, consumption tax and other similar taxes) in connection with this Agreement.

Section 5.14 **Blocked Currency.** In each country where the local currency is blocked and cannot be removed from the country, royalties accrued in that country will be paid to Isis in the country in local currency by deposit in a local bank designated by Isis, unless the Parties otherwise agree.

Section 5.15 **Sublicenses.** In the event BMS grants licenses or sublicenses to a Licensee to sell Products which are subject to royalties under Section 5.4, such licenses or sublicenses will include an obligation for the Licensee to account for and report its sales of Products on the same basis as if such sales were Net Sales by BMS, and BMS will pay, or will ensure that Licensee will pay, to Isis, with respect to such sales, royalties as if such sales of the Licensee were Net Sales of BMS.

Section 5.16 **Interest.** If BMS fails to make any payment due to Isis under this Agreement, then interest will accrue on a daily basis at the greater of an annual rate equal to 1.0% above the then-applicable prime commercial lending rate of CitiBank, N.A. San Francisco, California, or at the maximum rate permitted by Applicable Law, whichever is the lower.

ARTICLE 6 - PRESS RELEASES & PUBLICATIONS

Section 6.1 **Press Releases; Public Disclosure.**

6.1.1 Upon execution of this Agreement, the Parties shall issue a joint press release announcing the existence of this Agreement in a form and substance agreed to in writing by the Parties. Each Party agrees not to issue any other press release or other public statement disclosing other information relating to this Agreement or the transactions contemplated hereby without the prior written consent of the other Party, which consent shall not be unreasonably withheld or delayed, *provided however*, that each Party may make disclosures permitted by, and in accordance with, Article 7. Each Party agrees to provide to the other Party a copy of any public announcement regarding this Agreement or the subject matter thereof as soon as reasonably practicable under the circumstances prior to its scheduled release. Except under extraordinary circumstances, each Party shall provide the other with an advance copy of any such announcement at least 5 Business Days prior to its scheduled release. Each Party shall have the right to expeditiously review and recommend changes to any such announcement and, except as otherwise permitted by Article 7, the Party whose announcement has been reviewed shall remove any information the reviewing Party reasonably deems to be inappropriate for disclosure. The contents of any announcement or similar publicity which has been reviewed and approved by the reviewing Party can be re-released by either Party without a requirement for re-approval.

6.1.2 Each Party will immediately notify (and 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 6.1.1 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 5 Business Days in advance of such proposed public disclosure, which approval will not be unreasonably withheld or delayed.

Section 6.2 **Publication of Research Results.**

6.2.1 **Publication by Isis.** Isis shall not publish, present or otherwise disclose to the public the Research Results exclusively licensed to BMS hereunder, except subject to the prior review and comment by BMS as follows. Isis shall provide BMS with the opportunity to review any such proposed disclosure which if made would or may be considered a public disclosure, whether written or oral, (such as an abstract, manuscript or presentation) that contains such Research Results by delivering a copy thereof to BMS no less than thirty (30) days before its intended submission for publication, presentation or other public disclosure. BMS shall have thirty (30) days from its receipt of any such proposed disclosure in which to notify Isis in writing of approval of the disclosure, such approval not to be unreasonably withheld or delayed. In the event BMS objects to the proposed disclosure in writing within such thirty (30) days period, or requests a delay in the disclosure beyond such thirty (30) day period for the filing of a patent application, Isis agrees not to make the proposed disclosure or submit the publication or abstract or make the presentation containing the objected-to information until the Parties have agreed to the content of the proposed disclosure, or, where applicable, such patent application has been filed, and Isis shall delete from the proposed disclosure any Confidential Information of BMS

(including any Confidential Information of both Parties) upon request by BMS. Once any such abstract or manuscript is accepted for publication, at BMS' request, Isis will provide BMS with a copy of the final version of the presentation, manuscript or abstract.

6.2.2 **Publication by BMS.** BMS shall not publish, present or otherwise disclose to the public the Research Results exclusively licensed to BMS hereunder, except subject to the prior review and comment by Isis as follows. BMS shall provide Isis with the opportunity to review any such proposed disclosure which if made would or may be considered a public disclosure, whether written or oral, (such as an abstract, manuscript or presentation) that contains such Research Results by delivering a copy thereof to Isis no less than thirty (30) days before its intended submission for publication, presentation or other public disclosure. Isis shall have thirty (30) days from its receipt of any such proposed disclosure in which to notify BMS in writing of approval of the disclosure, such approval not to be unreasonably withheld or delayed. In the event Isis objects to the proposed disclosure in writing within such thirty (30) days period, or requests a delay in the disclosure beyond such thirty (30) day period for the filing of a patent application, BMS agrees not to make the proposed disclosure or submit the publication or abstract or make the presentation containing the objected-to information until the Parties have agreed to the content of the proposed disclosure, or, where applicable, such patent application has been filed, and BMS shall delete from the proposed disclosure any Confidential Information of Isis (including any Confidential Information of both Parties) upon request by Isis. Once any such abstract or manuscript is accepted for publication, at Isis' request, BMS will provide Isis with a copy of the final version of the presentation, manuscript or abstract.

6.2.3 For clarification, this Section 6.2 shall not apply with respect to the use and disclosure of Confidential Information as specifically provided for in Section 6.1 or Article 7 (i.e., a disclosure expressly permitted and made in accordance with Section 6.1 or Article 7).

ARTICLE 7 - CONFIDENTIALITY

Section 7.1 **Disclosure and Use Restriction.** Each Party agrees that, for so long as this Agreement is in effect and for a period of 5 years thereafter, a Party (the ***"Receiving Party"***) receiving Confidential Information of the other Party (the ***"Disclosing Party"***) shall (i) maintain in confidence such Confidential Information using not less than the efforts such Receiving Party uses to maintain in confidence other proprietary industrial information of similar kind and value, (ii) not disclose such Confidential Information except to the Receiving Party's employees having a need-to-know such Confidential Information solely for purposes of performing Receiving Party's obligations under this Agreement, (iii) not disclose such Confidential Information to any Third Party without the prior written consent of the Disclosing Party, except for disclosures expressly permitted by this Agreement, and (iv) not use such Confidential Information for any purpose except those expressly permitted by this Agreement. For avoidance of doubt, Isis shall be permitted to use the BMS Confidential Information solely for purposes of performing the Research Program in accordance with the Research Plan and for no other purpose. Upon completion of the Research Program or earlier upon written request by BMS, Isis shall return to BMS or destroy any BMS Confidential Information.

Section 7.2 **Authorized Disclosure.** To the extent (and only to the extent) that it is reasonably necessary or appropriate to fulfill its obligations or exercise its rights under this Agreement, a Party may disclose Confidential Information belonging to the other Party in the following instances:

(a) filing or prosecuting patent applications in accordance with this Agreement;

(b) made to the Regulatory Authorities as necessary for the Development or Commercialization of a Product in a country, as required in connection with any filing, application or request for Approval; *provided, however,* that reasonable measures will be taken to assure confidential treatment of such information;

(c) prosecuting or defending litigation;

(d) complying with applicable governmental laws and regulations (including, without limitation, the rules and regulations of the Securities and Exchange Commission or any national securities exchange, and compliance with tax laws and regulations) and with judicial process, if (i) in the reasonable opinion of the Receiving Party's counsel, such disclosure is necessary for such compliance and (ii) such disclosure is made in accordance with Section 7.3 or 7.4 as applicable; and

(e) disclosure, in connection with the performance of this Agreement and solely on a need-to-know basis, to Affiliates, potential or actual collaborators (including potential Licensees), potential or actual investment bankers, investors, lenders, or acquirers, or employees, independent contractors (including without limitation consultants and clinical investigators) or agents, each of whom prior to disclosure must be bound by written obligations of confidentiality and non-use no less restrictive than the obligations set forth in this Article 7; *provided, however*, that the Receiving Party shall remain responsible for any failure by any Person who receives Confidential Information pursuant to this Article 7 to treat such Confidential Information as required under this Article 7.

If and whenever any Confidential Information is disclosed in accordance with this Section 7.2, such disclosure shall not cause any such information to cease to be Confidential Information except to the extent that such permitted disclosure results in a public disclosure of such information (other than by breach of this Agreement). Where reasonably possible and subject to Sections 7.3 and 7.4, the Receiving Party shall notify the Disclosing Party of the Receiving Party's intent to make such disclosure pursuant to clauses (a) through (d) of this Section 7.2 sufficiently prior to making such disclosure so as to allow the Disclosing Party adequate time to take whatever action it may deem appropriate to protect the confidentiality of the information.

For purposes of this Article 7, for as long as and to the extent the exclusive license granted to BMS under Section 2.1 remains in effect, the Research Results shall be treated as Confidential Information of both Parties. Accordingly, each Party shall be considered the Receiving Party with respect to the Research Results and shall be subject to all of the restrictions and obligations of this Article 7 with respect to the disclosure and use of such Research Results to the same extent as applicable to Confidential Information disclosed to such Party by the other Party.

Section 7.3 **Required Disclosure.** A Receiving Party may disclose Confidential Information pursuant to interrogatories, requests for information or documents, subpoena, civil investigative demand issued by a court or governmental agency or as otherwise required by Law; *provided however*, that the Receiving Party shall notify the Disclosing Party promptly upon receipt thereof, giving (where practicable) the Disclosing Party sufficient advance notice to permit it to oppose, limit or seek confidential treatment for such disclosure, and to file for patent protection if relevant; and *provided, further*, that the Receiving Party shall furnish only that portion of the Confidential Information which it is advised by counsel is legally required whether or not a protective order or other similar order is obtained by the Disclosing Party.

Section 7.4 **Securities Filings.** In the event either Party proposes to file with the Securities and Exchange Commission or the securities regulators of any state or other jurisdiction a registration statement, periodic report, or any other disclosure document which describes or refers to this Agreement under the Securities Act of 1933, as amended, the Securities Exchange Act, of 1934, as amended, or any other applicable securities Law, the Party shall notify the other Party of such intention and shall provide such other Party with a copy of relevant portions of the proposed filing not less than three (3) business days prior to such filing (*provided* that, whenever practicable, such portions shall be provided not less than 5 business days prior to such filing) (and any revisions to such portions of the proposed filing a reasonable time prior to the filing thereof), including any exhibits thereto relating to the Agreement, and shall obtain confidential treatment of any information concerning the Agreement that such other Party requests be kept confidential (*except* to the extent advised by counsel that confidential treatment is not available for such information), and shall only disclose Confidential Information which it is advised by counsel is legally required to be disclosed. No such notice shall be required under this Section 7.4 if the substance of the description of or reference to this Agreement contained in the proposed filing has been included in any previous filing made by the either Party hereunder or otherwise approved by the other Party.

Section 7.5 **Terms of Agreement.** The existence and the terms and conditions of the Agreement that the Parties have not specifically agreed to disclose pursuant to Article 6 or Section 7.4 shall be considered Confidential Information of both Parties. Either Party may disclose such terms to a *bona fide* potential Licensee, investor, investment banker, acquirer, merger partner or other potential financial partner, and their attorneys and agents, *provided* that each such Person to whom such information is to be disclosed is informed of the confidential nature of such information and has entered into a written agreement with the Party requiring such Person to keep such information confidential.

Section 7.6 **Injunctive Relief.** The Parties hereto understand and agree that remedies at Law may be inadequate to protect against any breach of any of the provisions of this Article 7 by either Party or their employees, agents, officers or directors or any other person acting in concert with it or on its behalf. Accordingly, each Party shall be entitled to seek injunctive relief by a court of competent jurisdiction against any action that constitutes any such breach of this Article 7.

ARTICLE 8 - PATENTS

Section 8.1 **Ownership of Inventions and Patents.**

(a) Title to inventions, discoveries, improvements and other technology, whether or not patentable, conceived, made or reduced to practice in the performance of the Research Program under this Agreement (collectively, the ***"Program Inventions"***) and any Patents claiming such Program Inventions (***"Program Patent Rights"***), are retained by the Party that is the employer of the inventor (or, in the case of consultants and (sub)contractors, the Party for which the consultant or (sub)contractor is providing its services). The Parties agree that the United States federal patent law on inventorship shall determine

the inventorship of any invention and the names of the inventors on any patent filings, whether sole or joint inventions, which arise in connection with activities conducted pursuant to this Agreement. BMS shall own Program Inventions invented solely by employees, consultants and/or (sub)contractors of BMS (the ***"BMS Inventions"***) and any Patents claiming such Program Inventions (the ***"BMS Program Patent Rights"***). Isis shall own Program Inventions invented solely by employees, consultants and/or (sub)contractors of Isis (the ***"Isis Inventions"***) and any Patents claiming such Program

Inventions (the ***"Isis Program Patent Rights"***). Isis and BMS shall own jointly such Program Inventions invented jointly by employees, consultants and/or (sub)contractors of Isis and BMS (the ***"Joint Inventions"***) and any Patents claiming such Program Inventions (the ***"Joint Patents"***). Isis shall promptly disclose to BMS any such Isis Invention or Joint Invention, and BMS shall promptly disclose to Isis any BMS Invention or Joint Invention, arising from or made in the performance of the Research Program and any patent or patent application claiming such Program Invention.

(b) This Agreement shall be understood to be a joint research agreement to discover Compounds and associated uses and to Develop Products in accordance with 35 U.S.C. § 103(c)(3).

(c) Each Party has entered or will enter into binding agreements obligating all employees, consultants and/or (sub)contractors performing activities in the performance of the Research Program or in the manufacture of API by Isis for BMS, to assign (or, in the case of (sub)contractors, assign or license) the employee's, consultant's and/or (sub)contractor's interest in any invention and related intellectual property conceived or reduced to practice in the course of such activities to the Party for which such employee, consultant and/or (sub)contractor is providing its services.

Section 8.2 **Filing, Prosecution and Maintenance of Patent Rights.**

8.2.1 Solely Owned Patents. Subject to the other sections of this Article 8, including the other subsections of this Section 8.2 below, each Party will have the sole right, at its cost and expense and at its sole discretion, to prepare, file, prosecute (including, without limitation, to control any interferences, reissue proceedings, oppositions and reexaminations), maintain, enforce and defend throughout the world any Patents solely owned or Controlled by such Party, including with respect to Isis, the Isis Core Technology Patents and the Isis Manufacturing Patents.

8.2.2 Filing, Prosecution and Maintenance of Isis Core Technology Patents and Isis Manufacturing Patents.

(a) As between Isis and BMS, Isis shall be responsible for the preparation, filing, prosecution (including, without limitation, any interferences, reissue proceedings, oppositions and reexaminations) and maintenance of Isis Core Technology Patents and Isis Manufacturing Patents, and Isis shall be responsible for all costs incurred by Isis with respect to such preparation, filing, prosecution and maintenance of Isis Core Technology Patents and Isis Manufacturing Patents. At BMS' reasonable request, Isis, or its outside counsel, shall promptly provide BMS with an update of the filing, prosecution and maintenance status for each of the Isis Core Technology Patents and Isis Manufacturing Patents, including without limitation an update of Appendix 3 and 4. In addition, Isis will cooperate with BMS in the preparation, filing and prosecution of any Isis Core Technology Patents and Isis Manufacturing Patents that disclose ASOs targeting PCSK9 or Compounds or Products. Accordingly, Isis will not file any Isis Core Technology Patents and Isis Manufacturing Patents that disclose ASOs targeting PCSK9 or Compounds or Products without first consulting with BMS' patent counsel regarding the filing of such Patent. Upon request by BMS' patent counsel, a separate application shall be filed concurrently with such Isis Core Technology Patent or Isis Manufacturing Patent with claims specifically directed to a Compound or Product (including claims specifically directed to a method of use or making such Compound or Product) and such separate application will be considered and treated as a Product Specific Patent under this Agreement, and shall be subject to without limitation the provisions of Sections 8.2.3 and 8.4.1.

(b) In addition, Isis will cooperate with BMS to prepare, file and prosecute continuing applications (including divisionals, continuations or continuations-in-part) for any Patent within the Isis Core Technology Patents or Isis Manufacturing Patents for the purposes of securing claims that more directly or specifically cover a Compound or Product. Accordingly, Isis will not file or add during the prosecution of any Isis Core Technology Patents or Isis Manufacturing Patents claims specifically directed to a Compound or Product (including claims specifically directed to a method of use or making such Compound or Product) without first consulting with BMS' patent counsel regarding such claims. Upon request by BMS' patent counsel, any such claims specifically directed to a Compound or Product (including claims specifically directed to a method of use or making such Compound or Product) shall be filed as a continuing application (such as a divisional, continuation or continuations-in-part) of any Patent within the Isis Core Technology Patents or Isis Manufacturing Patents. Once filed, these continuing applications (including divisionals, continuations or continuations-in-part) will be considered and treated as Product Specific Patents under this Agreement, and shall be subject to without limitation the provisions of Sections 8.2.3 and 8.4.1.

8.2.3 Filing, Prosecution and Maintenance of Product Specific Patents. In accordance with this Section 8.2.3 and subject to Section 8.2.4, unless the Parties otherwise agree in writing, BMS shall have lead responsibility (using internal or outside counsel selected by BMS), and Isis shall cooperate fully, with respect to the preparation, filing, prosecution (including, without limitation, any interferences, reissue proceedings, oppositions and reexaminations) and maintenance of the Product Specific Patents. BMS shall be responsible for all out-of-pocket costs (including reasonable out-of-pocket costs incurred by Isis in performing activities at the prior written request of BMS) with respect to such preparation, filing, prosecution and maintenance of Product Specific Patents for which BMS assumes such lead responsibility. Isis shall cooperate with BMS in the filing and prosecution of such patent applications, including consulting with and assisting BMS and its patent counsel in drafting patent applications and responses. In addition, upon request by BMS, Isis will provide such assistance and execute such documents as are reasonably necessary to permit the filing, prosecution and/or maintenance of such patent or patent application or the issuance, maintenance and/or extension of any resulting patent or permit enforcement of such patent application or any such patent. BMS, or its outside counsel, shall provide Isis with an update of the filing, prosecution and maintenance status for each of the Product Specific Patents on a periodic basis for which BMS assumes lead responsibility and shall reasonably consult with and cooperate with Isis with respect to the preparation, filing, prosecution and maintenance of such Product Specific Patents, including providing Isis with drafts of proposed filings in sufficient time to allow Isis's review and comment before such filings are due. BMS, or its outside counsel, shall provide to Isis copies of any papers relating to the filing, prosecution and maintenance of such Product Specific Patents promptly upon their being filed or received. In the event that BMS elects not to pursue or

continue the filing, prosecution (including any material reduction in claim scope) or maintenance of any Patents included in such Product Specific Patents in any country, BMS shall provide Isis with an opportunity to assume responsibility for such filing, prosecution or maintenance of such Product Specific Patents as set forth in Section 8.2.4. In the case where Isis wishes to pursue subject matter BMS has deleted from a claim (where BMS has elected to not otherwise pursue the subject matter of such claim in the same or another application), Isis may pursue such subject matter in a corresponding continuation or divisional application (where permissible under law) in accordance with and subject to Section 8.2.4. For so long as BMS retains responsibility under this Section 8.2.3 with respect to a particular Product Specific Patent, BMS shall not knowingly take any action or knowingly fail to take any action during the filing, prosecution and/or maintenance of such Product Specific Patents that would materially adversely affect such Product Specific Patents (including any material reduction in claim scope), without providing Isis written notice and information as set forth above. In the case where BMS assumes responsibility for the

preparation, filing, prosecution or maintenance of any patent or patent application as set forth above, and has used all good faith, reasonable efforts to comply with its obligations to provide notice and information as set forth in this Section 8.2.3 and 8.2.4, BMS will not be liable to Isis in any way with respect to its handling of, or the results obtained from, the filing, prosecution, issuance, extension or maintenance of such application or any resulting patent or any failure by it to so file, prosecute, extend or maintain.

8.2.4 Filing, Prosecution and Maintenance of Product Specific Patents by Isis. In no event will BMS, for so long as BMS retains responsibility for the filing, prosecution and maintenance of the Product Specific Patents as set forth in Section 8.2.3, knowingly permit any such Product Specific Patent to be abandoned in any country, or elect not to file a new patent application claiming priority to a patent application within such Product Specific Patents either before such patent application's issuance or within the time period required for the filing of an international (i.e., Patent Cooperation Treaty), regional (including European Patent Office) or national application, without Isis's written consent or Isis otherwise first being given an opportunity to assume full responsibility (at Isis's expense) for the continued prosecution and maintenance of such Product Specific Patents, or the filing of such new patent application. Accordingly, BMS, or its outside counsel, shall provide Isis with notice of the allowance and expected issuance date of any patent within the Product Specific Patents, or any of the aforementioned filing deadlines, and Isis shall provide BMS with prompt notice as to whether Isis desires BMS to file any such new patent application. In the event that BMS decides either (i) not to continue the prosecution or maintenance of a patent application or patent within Product Specific Patents in any country or (ii) not to file such new patent application requested to be filed by Isis as provided above, BMS shall provide Isis with notice of this decision at least thirty (30) days prior to any pending lapse or abandonment thereof, and Isis may thereafter assume responsibility for such filing, prosecution and maintenance in accordance with this Section 8.2.4. In the event that Isis assumes such responsibility for such filing, prosecution and maintenance, Isis shall have the right to transfer the responsibility for such filing, prosecution and maintenance of such patent applications and patents to patent counsel (outside or internal) selected by Isis, and Isis, or its outside counsel, shall provide BMS with an update of the filing, prosecution and maintenance status for each of the Product Specific Patents on a periodic basis for which Isis assumes lead responsibility and shall reasonably consult with and cooperate with BMS with respect to the preparation, filing, prosecution and maintenance of such Product Specific Patents, including providing BMS with drafts of proposed filings in sufficient time to allow BMS's review and comment (or the filing of Product Specific Patents by BMS in accordance with Section 8.2.3) before such filings are due. Isis, or its outside counsel, shall provide to BMS copies of any papers relating to the filing, prosecution and maintenance of such Product Specific Patents promptly upon their being filed or received. In the case where Isis takes over the preparation, filing, prosecution or maintenance of any patent or patent application as set forth above, and has used all good faith, reasonable efforts to comply with its obligations to provide notice and information as set forth is this Section 8.2.4, Isis will not be liable to BMS in any way with respect to its handling of, or the results obtained from, the filing, prosecution, issuance, extension or maintenance of such application or any resulting patent or any failure by it to so file, prosecute, extend or maintain.

8.2.5 Filing, Prosecution and Maintenance of Certain Program Patent Rights. This Section 8.2.5 shall apply to Program Patent Rights that are not Product Specific Patents (the preparation, filing, prosecution and maintenance of the Program Patent Rights that are Product Specific Patents are governed by Sections 8.2.3 and 8.2.4). In accordance with this Section 8.2.5, unless the Parties otherwise agree in writing, BMS shall have lead responsibility, and Isis shall cooperate fully, with respect to the preparation, filing, prosecution (including,

without limitation, any interferences, reissue proceedings, oppositions and reexaminations) and maintenance of the Program Patent Rights, for so long as BMS retains relevant rights hereunder. BMS shall be responsible for all out-of-pocket costs (including reasonable out-of-pocket costs incurred by Isis in performing activities at the prior written request of BMS) with respect to such preparation, filing, prosecution and maintenance of Program Patent Rights for which BMS assumes such lead responsibility. Isis shall promptly disclose to BMS any Program Inventions, and BMS shall have the right in accordance with this Section 8.2.5 to file and prosecute any new patent application claiming such inventions to the extent BMS has rights hereunder to the relevant invention. Isis shall cooperate with BMS in the filing and prosecution of such patent applications, including consulting with and assisting BMS and its patent counsel in drafting patent applications and responses. In addition, upon request by BMS, Isis will provide such assistance and execute such documents as are reasonably necessary to permit the filing, prosecution or maintenance of such patent or patent application or the issuance, maintenance or extension of any resulting patent or permit enforcement of such patent application or any such patent. BMS, or its outside counsel, shall provide Isis with an update of the filing, prosecution and maintenance status for each of the Program Patent Rights on a periodic basis for which BMS assumes lead responsibility and shall reasonably consult with and cooperate with Isis with respect to the preparation, filing, prosecution and maintenance of such Program Patent Rights, including providing Isis with drafts of proposed filings in sufficient time to allow Isis' review and comment before such filings are due. BMS, or its outside counsel, shall provide to Isis copies of any papers relating to the filing, prosecution and maintenance of such Program Patent Rights promptly upon their being filed or received. In the event that BMS elects not to pursue or continue the filing, prosecution or maintenance of any Program Patent Rights in any country, BMS shall provide Isis with an opportunity to assume responsibility for such filing, prosecution or maintenance of such Patents to the same manner as applicable to the Product Specific Patents as provided in Section 8.2.4, such that such Program Patent Rights will be treated in the same manner as Product Specific Patents under Section 8.2.4. In the case where BMS assumes responsibility for the preparation, filing, prosecution or maintenance of any patent or patent application as set forth above, and has used all good faith, reasonable efforts to comply with its obligations to provide notice and information as set forth is this Section 8.2.5, BMS will not be liable to Isis in any way with respect to its handling of, or the results obtained from, the filing, prosecution, issuance, extension or maintenance of such application or any resulting patent or any failure by it to so file, prosecute, extend or maintain.

8.2.6 Cooperation. In accordance with the foregoing, each Party will cooperate reasonably in the preparation, filing, prosecution, and maintenance of the Product Specific Patents and Program Patent Rights. Such cooperation includes (a) promptly executing all papers and instruments and requiring employees (and other persons under obligation to assign Patents to such Party) to execute such papers and instruments as reasonable and appropriate so as to enable such other Party, to prepare, file, prosecute, and maintain such 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.

Section 8.3 **Patent Term Extension.** Isis and BMS shall each cooperate with one another and shall use commercially reasonable efforts in obtaining patent term extensions (including without limitation, any pediatric exclusivity extensions as may be available) or supplemental protection certificates or their equivalents in any country with respect to patent rights covering those Products licensed by BMS hereunder. If elections with respect to obtaining such patent term extensions or supplemental protection are to be made, BMS shall have the right to make such election, *provided* that such election will be made in accordance with applicable Law so as to maximize the period of marketing exclusivity for the Product.

Section 8.4 **Enforcement of Patents**

8.4.1 Enforcement by BMS of Product Specific Patents. In the event that Isis or BMS becomes aware of a suspected infringement in the Field of any Product Specific Patent, or any such Product Specific Patent is challenged in any action or proceeding (other than any interferences, reissue proceedings, oppositions or reexaminations, which are addressed above), such Party shall notify the other Party promptly, and following such notification, the Parties shall confer. BMS shall have the right, but shall not be obligated, to defend any such action or proceeding or bring an infringement action with respect to such infringement to the extent in the Field and relevant to BMS's exclusive rights hereunder at its own expense, in its own name and entirely under its own direction and control, or settle any such action, proceeding or dispute by license (to the extent such sublicense is permitted under this Agreement), subject to the following. Isis shall reasonably assist BMS in any action or proceeding being defended or prosecuted if so requested, and shall lend its name to such actions or proceedings if reasonably requested by BMS or required by Applicable Law. BMS shall reimburse Isis for the documented out-of-pocket costs Isis reasonably incurs in providing such assistance as specifically requested in writing by BMS. In the event Isis is a required party to the proceeding or action, Isis shall have the right to be represented by its own counsel (such selection to be subject to BMS's approval, such approval not to be unreasonably withheld), and BMS shall reimburse Isis for the documented out-of-pocket costs Isis reasonably incurs that are reasonably related to the proceeding or action, including attorneys fees, *provided* that BMS shall retain overall responsibility for the prosecution of such action or proceeding in such event. In the event that Isis is not a necessary party to the proceeding or action, Isis shall have the right to participate and be represented in any such suit by its own counsel at its own expense, *provided* that BMS shall retain overall responsibility for the prosecution of such action or proceedings in such event. No settlement of any such action or proceeding which restricts the scope, or adversely affects the enforceability, of an Isis Patent Right, or which could be reasonably expected to have a material adverse financial impact on Isis, may be entered into by BMS without the prior written consent of Isis, which consent shall not be unreasonably withheld, delayed or conditioned.

8.4.2 Enforcement by Isis. If BMS elects not to settle, defend or bring any action for infringement described in Section 8.4.1 and so notifies Isis, including following any request by Isis to do so, then Isis may defend or bring such action at its own expense, in its own name, *provided however* that, Isis agrees not to so settle, defend or bring any action for infringement of a Product Specific Patent Right upon BMS's request based on BMS's good faith reasonable determination, the basis for which shall be provided to Isis, that it is not in the best interest of the Parties to so settle, defend or bring such action for infringement. In the case where Isis proceeds to settle, defend or bring an action for such infringement, the following shall apply. BMS shall reasonably assist Isis in any action or proceeding being defended or prosecuted if so requested, and shall lend its name to such actions or proceedings if requested by Isis or required by Applicable Law. Isis shall reimburse BMS for the documented external costs BMS reasonably incurs in providing such assistance as specifically requested in writing by Isis. BMS shall have the right to participate and be represented in any such suit by its own counsel at its own expense, *provided* that Isis shall retain overall responsibility for the prosecution of such suit or proceedings in such event. No settlement of any action or proceeding defended or brought by Isis with respect to a Product Specific Patent, which restricts the scope, or adversely affects the enforceability, of a Product Specific Patent Right, or which could be reasonably expected to have a material adverse financial impact on BMS, may be entered into by Isis without the prior written consent of BMS, which consent shall not be unreasonably withheld, delayed or conditioned. In addition, if BMS elects not to settle, defend or bring any action for infringement against an infringing Third Party described in Section 8.4.1, then any infringing products sold by such Third Party will not be included in the calculation of sales of Generic Products under Section 5.7.

8.4.3 Withdrawal. In addition to Section 8.4.2, if either Party brings an action or proceeding under this Section 8.4 and subsequently ceases to pursue or withdraws from such action or proceeding, it shall promptly notify the other Party and the other Party may substitute itself for the withdrawing Party and pursue such action or proceeding in accordance with the terms of this Section 8.4 (including but not limited to the proviso in the first sentence of Section 8.4.2).

8.4.4 Enforcement and Defense of Joint Patent Rights. With respect to infringement of a Joint Patent that is not a Product Specific Patent, the Party responsible for filing, prosecution and maintenance of such Joint Patent under Section 8.2.5 will have the first right to bring and control any enforcement action or proceeding with respect to such Joint Patent, and will bear all expenses thereof, and the other Party will have the right, at its own expense, to be represented in any such action.

8.4.5 Cooperation. The Party not enforcing the applicable Patent will provide reasonable assistance to the other Party (at such other 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.

8.4.6 Damages. In the event that either Party exercises the rights conferred in this Section 8.4 and recovers any damages or other sums in such action, suit or proceeding or in settlement thereof, such damages or other sums recovered shall first be applied to all out-of-pocket costs and expenses incurred by the Parties in connection therewith, including, without limitation, attorneys fees. Except as otherwise provided in this Section 8.4, each Party will bear its own expenses with respect to any suit or other proceeding against an infringer. If such recovery is insufficient to cover all such costs and expenses of

both Parties, it shall be shared pro rata in proportion to the total of such costs and expenses incurred by each Party. If after such reimbursement any funds shall remain from such damages or other sums recovered, such funds shall be divided as follows: (i) as to ordinary damages based on lost sales or profit, BMS shall retain such funds and such funds will be treated as Net Sales and royalties will be payable by BMS to Isis with respect to such Net Sales in accordance with this Agreement and (ii) as to special or punitive damages, the Party that brought the enforcement action at its expense shall receive [***]% of the amount of such special or punitive damages and the other Party shall receive [***]% of the amount of such special or punitive damages.

8.4.7 Enforcement of Isis Core Technology Patents and Isis Manufacturing Patents by BMS. In the event that Isis or BMS becomes aware of a suspected infringement of any Isis Core Technology Patents and Isis Manufacturing Patents by a Third Party where such infringement involves the manufacture, use or sale of an ASO targeting PCSK9 (including but not limited to infringement which is the subject of a notice under Section 8.5), the Parties shall confer and discuss in good faith an enforcement strategy with respect to such Isis Core Technology Patents and Isis Manufacturing Patents against such Third Party, and Isis shall consider in good faith and not unreasonably deny or delay BMS' request to enforce such Isis Core Technology Patents and Isis Manufacturing Patents in the same manner as a Product Specific Patent as set forth above in this Article 8. Isis shall not bring any enforcement action for such infringement with respect to such Isis Core Technology Patents and Isis Manufacturing Patents without BMS having the first opportunity to bring such action in the same manner as a Product Specific Patent as set forth above in this Article 8.

Section 8.5 **Notification of Patent Certification.** Isis shall notify and provide BMS with copies of any allegations of alleged patent invalidity, unenforceability or non-infringement

of an Isis Patent Right Covering a Compound or Product (including methods of use thereof) pursuant to a Paragraph IV Patent Certification by a Third Party filing an Abbreviated New Drug Application, an application under §505(b)(2) or other similar patent certification by a Third Party, and any foreign equivalent thereof for a Generic Product. Such notification and copies shall be provided to BMS by Isis as soon as practicable and at least within five (5) days after Isis receives such certification, and shall be sent by facsimile and overnight courier to the address set forth below:

Bristol-Myers Squibb Company
P.O. Box 4000
Route 206 & Province Line Road
Princeton, New Jersey 08543-4000
Attention: Vice President and Chief Intellectual Property Counsel
Telephone: 609-252-4825
Facsimile: 609-252-7884

Section 8.6 **Data Exclusivity and Orange Book Listings.** With respect to data exclusivity periods (such as those periods listed in the FDA's Orange Book (including without limitation any available pediatric extensions) or periods under national implementations of Article 11.1(a)(iii) of Directive 2001/EC/83, or similar periods as may be applicable to a biologic, and all international equivalents), BMS shall use commercially reasonable efforts consistent with its obligations under applicable law (including any applicable consent order) to seek, maintain and enforce all such data exclusivity periods available for the Products exclusively licensed by BMS hereunder. With respect to filings in the FDA Orange Book or other similar filings or listings as may be applicable (and foreign equivalents) for issued patents for a Product, upon reasonable request by BMS, Isis shall provide reasonable cooperation to BMS in filing and maintaining any such listing and filings. BMS shall not list Isis Core Technology Patents in the FDA Orange Book without Isis' prior written consent, such consent not to be unreasonably withheld or delayed. In no event shall Isis shall withhold or delay such consent where the listing of such Isis Core Technology Patent is required under applicable law.

Section 8.7 **Further Actions.** Each Party shall, upon the reasonable request of the other Party, provide such assistance and execute such documents as are reasonably necessary for such Party to exercise its rights and/or perform its obligations pursuant to this Article 8; *provided however*, that neither Party shall be required to take any action pursuant to Article 8 that such Party reasonably determines in its sole judgment and discretion conflicts with or violates any applicable court or government order or decree.

Section 8.8 **Infringement Claims; Oppositions.** BMS and Isis shall promptly inform the other in writing of any written notice to it of alleged infringement or misappropriation, based on the research, development, making, using, importing, exporting or selling of a Compound or Product, of a Third Party's intellectual property rights of which it shall become aware. The Parties shall confer on the handling of such matter. Isis shall not acknowledge to a Third Party the validity of any such allegation or admit liability without the prior written consent of BMS, and BMS shall not acknowledge to a Third Party the validity of any such allegation or admit liability without the prior written consent of Isis to the extent such action would reasonably be expected to create any liability for Isis. BMS and Isis shall each keep the other advised of all material developments in the conduct of any proceedings in defending any claim of such alleged infringement or misappropriation and shall cooperate with the other in the conduct of such defense. In no event may either Party settle any such infringement or misappropriation claim in a manner that would limit the rights of the other Party or impose any obligation on the other Party,

without such other Party's prior written consent, such consent not to be unreasonably withheld or delayed.

BMS and Isis shall promptly inform the other in writing of any written notice to it of actual or threatened opposition related to the Product Specific Patents. The Parties shall confer on the handling of such matter and such matters will be handled in accordance with Section 8.2.3 and 8.2.4 above.

Section 8.9 **Records Regarding Isis Patent Rights.** Each Party shall assign patent counsel representatives who shall be responsible for coordinating activities between the Parties in accordance with this Article 8. Such representatives will use good faith diligent efforts to maintain a report listing the Isis Patent Rights that are subject to the license granted to BMS under Section 2.1. Such report shall be used to facilitate the identification and tracking of the Isis Patent Rights licensed under this Agreement, but shall not, unless specifically agreed to in a separate written agreement signed by

authorized representatives of both Parties, be considered to be a then-current complete and binding list of the Isis Patent Rights licensed under this Agreement.

ARTICLE 9 -
TERM AND TERMINATION

Section 9.1 **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 9 or Article 10, will continue until the expiration of all obligations to pay royalties on all Products to Isis (including any Pass Through Royalties).

Section 9.2 **BMS Right to Terminate Without Cause.** BMS may terminate this Agreement (including its license rights under this Agreement) in full (but not in part), effective upon [***] calendar days prior written notice in the case where Approval has not been obtained for the applicable Product or upon [***] calendar days prior written notice in the case where Approval has been obtained for the applicable Product. For purposes of clarification, milestone payments will be due on milestones achieved during the period between notice of termination and the effective date of termination.

Section 9.3 **Material Breach.**

(a) If either Party believes that the other is in material breach of this Agreement (other than with respect to a breach of BMS's obligations under Section 4.1, which is governed by Section 9.4), then the non-breaching Party may deliver notice of such breach to the other Party. In such notice the non-breaching Party shall identify the actions or conduct that it wishes such Party to take for an acceptable and prompt cure of such breach; *provided* that such identified actions or conduct shall not be binding upon the other Party with respect to the actions that it may need to take to cure such breach. The allegedly breaching Party shall have [***] days to either cure such breach (except to the extent such breach involves the failure to make a payment when due, which breach must be cured within [***] days following such notice) or, if cure cannot be reasonably effected within such [***] day period, to deliver to the other Party a plan for curing such breach which is reasonably sufficient to effect a cure within a reasonable period. Following delivery of such plan, the breaching Party shall use commercially reasonable efforts to carry out the plan and cure the breach. If the Party receiving notice of breach fails to cure such breach within the [***] day period, or the Party providing the notice reasonably determines that the proposed corrective plan or the actions being taken to carry it out is not commercially practicable, the Party originally delivering the notice may declare a breach hereunder upon [***] days

advance written notice. Subject to Section 8.3(b), such notice shall effectively terminate this Agreement upon expiration of such [***] day period.

(b) Notwithstanding the foregoing, if the allegedly breaching Party disputes in good faith the existence or materiality of any such breach which is not a payment breach, and provides notice to the other Party (the ***"Other Party"***) of such dispute within such [***] day period, the Other Party shall not have the right to terminate this Agreement in accordance with this Section 8.3 unless and until it has been determined in accordance with Section 13.4 that this Agreement was materially breached by the allegedly breaching Party and that Party fails to cure such breach within [***] days following such determination. It is understood and acknowledged that during the pendency of such a dispute, all of the terms and conditions of this Agreement shall remain in effect and the Parties shall continue to perform all of their respective obligations hereunder.

(c) This Section 9.3 shall be subject to and shall not limit the provisions of Section 9.4 and Section 9.5.

Section 9.4 **Termination by Isis For Failure of BMS to Use Commercially Reasonable Efforts.**

(a) Subject to Section 9.4(b) and 9.4(c), at any time after the expiration of the Research Term, Isis shall have the right to terminate the License granted under Section 2.1(a) Agreement on a country-by-country basis if BMS is in breach of its obligations to use Commercially Reasonable Efforts as set forth in Section 4.1, *provided however*, that the Agreement shall not so terminate unless (i) BMS is given [***] months prior written notice by Isis of Isis's intent to terminate, stating the reasons and justification for such termination and recommending steps which BMS should take, and (ii) BMS, or its Licensee, has not used good faith Commercially Reasonable Efforts during the [***] month period following such notice to diligently pursue the Development and/or Commercialization of at least one Compound or Product. Any such termination shall be limited in force and effect to the country or countries to which such breach relates. For clarity, it is understood and acknowledged that Commercially Reasonable Efforts in the Development of a Product in a particular country may include sequential implementation of clinical trials and/or intervals between clinical trials for data interpretation and clinical program planning and approval, to the extent such implementation is consistent with the scientific, technical and commercial factors relevant to Development of such Product in such country.

(b) It is understood and acknowledged that if BMS (by itself or through its Affiliates or Licensees) uses Commercially Reasonable Efforts to Develop a Product through an MAA Filing, BMS shall be deemed to be in compliance with its obligation under Section 4.1 to use Commercially Reasonable Efforts to Develop a Product with respect to all countries in the EU. Termination under this Section 9.4 shall apply to all Compounds and Products, but only for the affected country or countries, *provided however*, that if the applicable termination event relates to a country in the EU, then Isis shall not have the right to terminate this Agreement with respect to such country if BMS is then in compliance with its obligations under Section 4.1 with respect to three Major European Countries in the EU.

(c) If BMS disputes in good faith the existence or materiality of an alleged breach specified in a notice provided by Isis pursuant to Section 9.4(a), and BMS provides notice to Isis of such dispute within the [***] days following such notice provided by Isis, Isis shall not have the right to terminate this Agreement unless and until the existence of such material breach or failure by BMS has been determined in accordance with Section 13.4 and BMS fails to cure such breach within [***] days following such determination. It is understood and acknowledged that

during the pendency of such a dispute, all of the terms and conditions of this Agreement shall remain in effect and the Parties shall continue to perform all of their respective obligations hereunder.

Section 9.5 **Consequences of Termination.**

9.5.1 Licenses. Upon early termination of this Agreement in its entirety by either Party pursuant to this Article 9, the licenses granted by Isis to BMS hereunder will terminate; *provided however*, that BMS' rights and Isis' obligations under Section 2.3 shall survive termination of this Agreement other than when terminated by Isis under Section 9.3.

9.5.2 Return of Information and Materials. Upon early termination of this Agreement in its entirety by either Party pursuant to this Article 9, BMS will return to Isis (or destroy, as directed by Isis) all data, files, records and other materials containing or comprising Isis' Confidential Information. Notwithstanding the foregoing, BMS will be permitted to retain one copy of such data, files, records, and other materials for archival purposes.

Section 9.6 **Accrued Rights; Surviving Obligations.**

9.6.1 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. For clarification, no milestone payments or royalty payments under Article 5 shall be payable by BMS following termination of this Agreement, except to the extent that the milestone event was achieved (in the case of milestone payments) or the Product was sold (in the case of royalty payments) prior to such termination.

9.6.2 Survival. Articles 6, 7, 8, 9, 10, 11 and 13, and Section 5.12 and Section 12.4 of this Agreement will survive expiration or termination of this Agreement for any reason.

Section 9.7 **Rights in Bankruptcy.** All rights and licenses granted under or pursuant to this Agreement by Isis or BMS are, and shall otherwise be deemed to be, for purposes of Section 365(n) of the U.S. Bankruptcy Code (i.e., Title 11 of the U.S. Code) or analogous provisions of Applicable Law outside the United States, licenses of rights to "intellectual property" as defined under Section 101 of the U.S. Bankruptcy Code or analogous provisions of Applicable Law outside the United States. The Parties agree that each Party, as licensee of such rights under this Agreement, shall retain and may fully exercise all of its rights and elections under the U.S. Bankruptcy Code or any other provisions of Applicable Law outside the United States that provide similar protection for 'intellectual property.' The Parties further agree that, in the event of the commencement of a bankruptcy proceeding by or against a Party under the U.S. Bankruptcy Code or analogous provisions of Applicable Law outside the United States, the Party that is not subject to such proceeding will be entitled to a complete duplicate of (or complete access to, as appropriate) such intellectual property and all embodiments of such intellectual property, which, if not already in the non subject Party's possession, shall be promptly delivered to it upon the non subject Party's written request therefor. Any agreements supplemental hereto shall be deemed to be "agreements supplementary to" this Agreement for purposes of Section 365(n) of the U.S. Bankruptcy Code.

ARTICLE 10 -
ISIS REVERSION RIGHT; TECHNOLOGY TRANSFER TO BMS

Section 10.1 **Isis Reversion Rights.**

(a) If BMS terminates the Agreement under Section 9.2 or Isis terminates the Agreement under Section 9.3 or 9.4, Isis may elect to continue to Develop and Commercialize any Compound or Product by notice in writing to BMS within [***] of such termination (an ***"Election Notice"***) that Isis is exercising its rights under this Section 10.1, in which case BMS will (i) grant to Isis a fully-paid (except for the royalty payments specified in Section 10.1(b) below), sublicensable, worldwide license or sublicense, as the case may be, to [***] as of the date of the Election Notice solely as they are necessary to make, have made, use, sell, offer for sale, have sold and import Compounds identified as of the date of the Election Notice and Products containing such Compounds identified as of the date of the Election Notice and (ii) transfer to Isis, for Isis' use with respect to the Development and Commercialization of the Compounds or Products, [***] as of the date of the Election Notice that relate to such Compounds and Products.

(b) In consideration for the rights granted by BMS to Isis under this Article 10, Isis shall pay a royalty on net sales of Products by Isis, its Affiliates and licensees as follows: (i) [***]% of net sales of a Product if the Election Notice occurs after [***] but prior to establishing [***] for the applicable Compound or Product, (ii) [***]% of net sales of a Product if the Election Notice occurs after establishing [***] for the applicable Compound or Product but prior to [***] and (iii) [***]% of net sales of a Product if the Election Notice occurs after the Compound or Product [***]. Such royalty payment obligation shall be governed by Sections 5.8 through 5.16 which shall apply to Isis in the same way as they applied to BMS prior to such termination of the Agreement.

(c) Notwithstanding the foregoing, the licenses granted by BMS to Isis under this Section 10.1 shall be of no force or effect with respect to any given Compound(s) or Product(s) where BMS terminated the pre-clinical development, clinical development and/or commercialization of such Compound(s) or Product(s) due to Safety Reasons. For purposes of this Section 10.1(c), ***"Safety Reasons"*** means it is BMS' or any of its Affiliates' or Licensee's reasonable belief that there is an unacceptable risk for harm in humans based upon: (i) pre-clinical safety data, including data from animal toxicology studies or (ii) the observation of serious adverse effects in humans after a Compound or Product has been administered to or taken by humans, such as during a clinical trial or after the launch of a Product. BMS shall provide Isis with all relevant data for such Compound or Product terminated for Safety Reasons but shall not be obligated to provide Isis with any rights of reference to any regulatory documents or filings relating to such terminated Compound or Product. In cases where this Section 10.1(c) applies, Isis will [***].

Section 10.2 **[***] to BMS in the Event of Material Breach.**

(a) In the event that, subsequent to a Change of Control of Isis, Isis (or its successor) materially breaches its obligations to BMS with respect to Isis' performance of activities under this Agreement, then BMS shall have the right to receive a [***] with respect to any Isis Know-How and materials (including samples of Compounds and materials used in the preparation of Compounds) Controlled by Isis that are [***] for BMS to perform the activities otherwise assigned to Isis with respect to this Agreement, *provided however*, that BMS may not exercise this right unless (i) Isis is given [***] months prior written notice by BMS of BMS' intent to exercise its rights hereunder, stating the reasons and justification for such breach and recommending steps which Isis should take, and (ii) Isis has not used good faith commercially reasonable efforts during the [***] month period following such notice to diligently remedy such breach and perform its obligations to BMS with respect to Isis' performance of activities under the Research Plan. BMS' rights under this Section 10.2 shall be limited to the performance of

such activities that are necessary or reasonably useful for, and solely for the purposes originally licensed hereunder to, BMS to enjoy the benefit of the licenses granted hereunder with respect to the Compounds and Products, and any materials and Isis Know-How [***] pursuant to this Section 10.2 shall be used solely for such purpose. BMS shall be entitled to seek specific performance with respect to the remedy described in this Section 10.2 as set forth in Section 13.4, and Isis hereby stipulates to the fairness and reasonableness of such a remedy and covenants not to allege or assert, nor to allow any of its Affiliates to assert, nor further to cause or support any other Third Parties to assert, that such remedy is inappropriate or unenforceable or illegal in any way. For purposes of clarification, if BMS exercises its rights under this Section 10.2(a), except as specifically set forth in this Section, or as otherwise determined by an arbitrator under Section 13.4, all other provisions of this Agreement (including but not limited to Article 5) will remain in full force and effect.

(b) For the purposes of this Agreement, (1) ***"Change of Control"*** of Isis means that during the Term (i) Isis shall have become an Affiliate controlled by an entity that is a Drug Company, (ii) any sale, lease, exchange or other transfer (in one transaction or a series of related transactions) of all or substantially all of the assets of Isis shall have occurred to a Drug Company, or (iii) any Drug Company (whether individually or as part of a group) shall have become the owner, directly or indirectly, of voting securities entitled to cast more than fifty percent (50%) of the votes in the election of directors of Isis, and (2) ***"Drug Company"*** means any entity that conducts any research and/or development activities, or that manufactures, promotes, markets, distributes and/or sells any products, in the biotechnology or pharmaceutical industry.

ARTICLE 11 -
INDEMNIFICATION, INSURANCE AND LIMITATION OF LIABILITY

Section 11.1 **Indemnification of Isis.** BMS agrees to defend Isis, its Affiliates and their respective directors, officers, employees and agents, and their respective successors, heirs and assigns (collectively, the ***"Isis Indemnitees"***), and shall indemnify and hold harmless the Isis Indemnitees, from and against any liabilities, losses, costs, damages, fees or expenses payable to a Third Party, and reasonable attorney's fees and other legal expenses with respect thereto (collectively, ***"Losses"***) arising out of any claim, action, lawsuit or other proceeding by a Third Party (collectively, ***"Third Party Claims"***) brought against any Isis Indemnitee and resulting from or occurring as a result of: (a) whether or not negligence is found, the Development, manufacture, use, handling, storage, sale or other Commercialization or disposition of any Product in the Territory by BMS or its Affiliates or Licensees, (b) any breach by BMS of any of its representations or warranties pursuant to this Agreement or (c) the gross negligence or willful misconduct of BMS or any BMS Affiliate or Licensee in connection with this Agreement; *except* in any such case to the extent such Losses result from: (i) the gross negligence or willful misconduct of any Isis Indemnitee or (sub)contractor of Isis, (ii) any breach by Isis of any of its representations, warranties, covenants or obligations pursuant to this Agreement or under any agreement with a Third Party, or (iii) any breach of Applicable Law by any Isis Indemnitee or (sub)contractor of Isis.

Section 11.2 **Indemnification of BMS.** Isis agrees to defend BMS, its Affiliates, Licensees and their respective directors, officers, employees and agents, and their respective successors, heirs and assigns (collectively, the ***"BMS Indemnitees"***), and shall indemnify and hold harmless the BMS Indemnitees, from and against any Losses and Third Party Claims brought against any BMS Indemnitee and resulting from or occurring as a result of: (a) any breach by Isis of its representations or warranties pursuant to this Agreement or (b) the gross negligence or willful misconduct of any Isis Indemnitee or any (sub)contractor of Isis in

connection with this Agreement; *except* in any such case to the extent such Losses result from: (i) the gross negligence or willful misconduct of any BMS Indemnitee or (sub)contractor of BMS, (ii) any breach by BMS of any of its representations, warranties, covenants or obligations pursuant to this Agreement or under any agreement with a Third Party, or (iii) any breach of Applicable Law by any BMS Indemnitee or (sub)contractor of BMS.

Section 11.3 **Notice of Claim.** All indemnification claims provided for in Sections 11.1 and 11.2 shall be made solely by such Party to this Agreement (the ***"Indemnified Party"***). The Indemnified Party shall give the indemnifying Party prompt written notice (an ***"Indemnification Claim Notice"***) of any Losses or the discovery of any fact upon which the Indemnified Party intends to base a request for indemnification under Section 11.1 or 11.2, but in no event shall the indemnifying Party be liable for any Losses to the extent such Losses result from any delay in providing such notice. Each Indemnification Claim Notice must contain a description of the claim and the nature and amount of such Loss (to the extent that the nature and amount of such Loss is known at such time). The Indemnified Party shall furnish promptly to the indemnifying Party copies of all papers and official documents received in respect of any Losses and Third Party Claims.

Section 11.4 **Defense, Settlement, Cooperation and Expenses.**

(a) **Control of Defense.** At its option, the indemnifying Party may assume the defense of any Third Party Claim by giving written notice to the Indemnified Party within thirty (30) calendar days after the indemnifying Party's receipt of an Indemnification Claim Notice. The assumption of the defense of a Third Party Claim by the indemnifying Party shall not be construed as an acknowledgment that the indemnifying Party is liable to indemnify the Indemnified Party in respect of the Third Party Claim, nor shall it constitute a waiver by the indemnifying Party of any defenses it may assert against the Indemnified Party's claim for indemnification. Upon assuming the defense of a Third Party Claim, the indemnifying Party may appoint as lead counsel in the defense of the Third Party Claim any legal counsel selected by the indemnifying Party. In the event the indemnifying Party assumes the defense of a Third Party Claim, the Indemnified Party shall as soon as is reasonably possible deliver to the indemnifying Party all original notices and documents (including

court papers) received by the Indemnified Party in connection with the Third Party Claim. Should the indemnifying Party assume the defense of a Third Party Claim, except as provided in Section 11.4(b), the Indemnified Party shall be responsible for the legal costs or expenses subsequently incurred by such Indemnified Party in connection with the analysis, defense or settlement of the Third Party Claim. In the event that it is ultimately determined that the indemnifying Party is not obligated to indemnify, defend or hold harmless the Indemnified Party from and against the Third Party Claim, the Indemnified Party shall reimburse the indemnifying Party for any and all costs and expenses (including attorneys' fees and costs of suit) and any Third Party Claims incurred by the Indemnifying Party solely attributed to the defense of the Third Party Claim on behalf of the Indemnified Party (but not those costs and expenses otherwise attributable to the defense of the Indemnifying Party).

(b) **Right to Participate in Defense.** Without limiting Section 11.4(a), any Indemnified Party shall be entitled to participate in, but not control, the defense of such Third Party Claim and to employ counsel of its choice for such purpose; *provided, however*, that such employment shall be at the Indemnified Party's own cost and expense unless (i) the employment thereof has been specifically authorized by the indemnifying Party in writing, (ii) the indemnifying Party has failed to assume the defense and employ counsel in accordance with Section 11.4(a) (in which case the Indemnified Party shall control the defense) or (iii) the interests of the Indemnified Party and the indemnifying Party with respect to such Third Party Claim are sufficiently adverse to prohibit the representation by the same counsel of both Parties

under Applicable Law, ethical rules or equitable principles in which case the indemnifying Party shall be responsible for any such costs and expenses of counsel for the Indemnified Party.

(c) **Settlement.** With respect to any Third Party Claims relating solely to the payment of money damages in connection with a Third Party Claim and that shall not admit liability or violation of Law on the part of the Indemnified Party or result in the Indemnified Party's becoming subject to injunctive or other relief or otherwise adversely affecting the business of the Indemnified Party in any manner (such as granting a license or admitting the invalidity of a Patent Controlled by an Indemnified Party), and as to which the indemnifying Party shall have acknowledged in writing the obligation to indemnify the Indemnified Party hereunder, the indemnifying Party shall have the sole right to consent to the entry of any judgment, enter into any settlement or otherwise dispose of such Loss, on such terms as the indemnifying Party, in its sole discretion, shall deem appropriate. With respect to all other Losses in connection with Third Party Claims, where the indemnifying Party has assumed the defense of the Third Party Claim in accordance with Section 11.4(a), the indemnifying Party shall have authority to consent to the entry of any judgment, enter into any settlement or otherwise dispose of such Loss provided it obtains the prior written consent of the Indemnified Party (which consent shall not be unreasonably withheld). The indemnifying Party shall not be liable for any settlement or other disposition of a Loss by an Indemnified Party that is reached without the written consent of the indemnifying Party. Regardless of whether the indemnifying Party chooses to defend or prosecute any Third Party Claim, no Indemnified Party shall admit any liability with respect to or settle, compromise or discharge, any Third Party Claim without the prior written consent of the indemnifying Party, such consent not to be unreasonably withheld.

(d) **Cooperation.** Regardless of whether the indemnifying Party chooses to defend or prosecute any Third Party Claim, the Indemnified Party shall, and shall cause each other Indemnified Party to, cooperate in the defense or prosecution thereof and shall furnish such records, information and testimony, provide such witnesses and attend such conferences, discovery proceedings, hearings, trials and appeals as may be reasonably requested in connection therewith. Such cooperation shall include access during normal business hours afforded to indemnifying Party to, and reasonable retention by the Indemnified Party of, records and information that are reasonably relevant to such Third Party Claim, and making Indemnified Parties and other employees and agents available on a mutually convenient basis to provide additional information and explanation of any material provided hereunder, and the indemnifying Party shall reimburse the Indemnified Party for all its reasonable out-of-pocket costs and expenses in connection therewith.

(e) **Costs and Expenses.** Except as provided above in this Section 11.4, the costs and expenses, including attorneys' fees and expenses, incurred by the Indemnified Party in connection with any claim shall be reimbursed on a Calendar Quarter basis by the indemnifying Party, without prejudice to the indemnifying Party's right to contest the Indemnified Party's right to indemnification and subject to refund in the event the indemnifying Party is ultimately held not to be obligated to indemnify the Indemnified Party.

Section 11.5 **Insurance.** Each Party shall maintain at its sole cost and expense, an adequate liability insurance or self-insurance program (including clinical trials and product liability insurance) to protect against potential liabilities and risk arising out of activities to be performed under this Agreement and any agreement related hereto and upon such terms (including coverages, deductible limits and self-insured retentions) as are customary in the U.S. pharmaceutical industry for the activities to be conducted by such Party under this Agreement. As applicable, BMS will name Isis as an additional insured and will upon request provide Isis

with a certificate of insurance. BMS will promptly notify Isis of any material change in insurance or self-insurance coverage or lapse in coverage in that regard.

Section 11.6 **Limitation of Liability.** Neither Party hereto will be liable for indirect, incidental, consequential, special, exemplary, punitive or multiple damages arising in connection with this Agreement or the exercise of its rights hereunder, or for lost profits arising from or relating to any breach of this Agreement, regardless of any notice of such damages, *provided however*, that this Section 11.6 shall not limit or restrict (i) damages available for breaches of confidentiality obligations Article 7 and (ii) damages available for willful breaches of Article 12. In addition, the rights of termination by Isis under Section 9.4 and the effect of such termination as set forth in Sections 9.5 and 10.1 shall be Isis's only remedy and BMS's only liability with respect to or resulting from BMS's breach of its obligations as set forth in Section 4.1.

ARTICLE 12 -
REPRESENTATIONS AND WARRANTIES

Section 12.1 **Representations, Warranties and Covenants.** Each Party hereby represents and warrants as of the Effective Date and covenants to the other Party that:

(a) it has the power and authority and the legal right to enter into this Agreement and perform its obligations hereunder, and that it 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;

(b) 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;

(c) 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;

(d) the execution and delivery of this Agreement and the performance of such Party's obligations hereunder (i) 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 (ii) 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; and

(e) it has and will have enforceable written agreements with all of its employees who receive Confidential Information under this Agreement assigning to such Party ownership of all intellectual property rights created in the course of their employment.

Section 12.2 **Isis Representations, Warranties, and Covenants**. Isis hereby represents and warrants as of the Effective Date and covenants to BMS that:

(a) subject to the limitations set forth in Appendix 6, Isis has the sufficient legal and/or beneficial title and ownership or right to license (or sublicense as the case may be) with respect to the Isis Patent Rights as is necessary to fulfill its obligations under this Agreement and to grant the licenses (or sublicenses as the case may be) to BMS pursuant to this Agreement;

(b) with respect to agreements between Isis and any Third Party existing on the Effective Date, the only financial Pass Through Obligations for Products utilizing MOE Gapmers are the [***] Royalties, which total [***]% of net sales for such Products;

(c) to the best of Isis' knowledge, no actions, suits, claims, disputes, or proceedings concerning the Isis Patent Rights licensed hereunder are currently pending or are threatened in writing, that if determined adversely to Isis would have a material adverse effect on the Research Program or Isis' ability to perform its obligations or to grant the licenses to BMS under this Agreement, or that would have a material adverse effect on or would impair BMS' right to practice under the licenses granted under this Agreement by Isis to BMS;

(d) subject to the limitations set forth in Appendix 6, it has the ability to grant to BMS the licenses granted by Isis under this Agreement on the terms set forth herein;

(e) subject to the limitations set forth in Appendix 6, it is not currently subject to any agreement with any Third Party or to any outstanding order, judgment or decree of any court or administrative agency that restricts it in any way from granting to BMS the licenses granted by Isis under this Agreement on the terms set forth herein or the right of BMS to exercise such license rights;

(f) to its knowledge as of the Effective Date, all fees required to maintain the issued Isis Patent Rights set forth in the Appendices to this Agreement have been paid to date;

(g) subject to the limitations set forth in Appendix 6, it has not granted, or permitted to be attached, and it will not grant or permit to be attached during the term of the Agreement, any lien, security interest or other encumbrance with respect to the Isis Technology, Research Results or Program Inventions which would adversely effect the rights granted to BMS hereunder;

(h) to Isis's knowledge, as of the Effective Date, the Isis Technology does not include any trade secrets that have been misappropriated from any Third Party or obtained in breach of any contractual obligation of Isis or its employees to a Third Party;

(i) subject to the limitations set forth in Appendix 6, Isis has not entered into any agreement pursuant to which it has agreed to transfer, whether by asset sale, operation of law or otherwise, title to any of the Isis Technology licensed to BMS hereunder;

(j) all inventors of any inventions of Patents which Isis has represented as being owned by Isis and included in the Isis Technology licensed to BMS hereunder have assigned or have a contractual obligation to assign their entire right, title and interest in and to such inventions and the corresponding Patents to Isis;

(k) it has no knowledge as of the Effective Date of claims to inventorship by persons not already listed as inventors with respect to the Product Specific Patent Rights;

(l) during the Term, Isis shall use commercially reasonable efforts to maintain and not to breach any agreements with Third Parties that provide a grant of rights from such Third Party to Isis that are Controlled by Isis and are licensed or become subject to a license from Isis to BMS under this Agreement; as of the Effective Date, Isis is in compliance in all material respects with any aforementioned agreements with Third Parties;

(m) it has not granted, and that during the Term that it will not grant, any license, option or other rights to Alnylam or any other Third Party with respect to any Product Specific Patents (with the exception of the material transfer agreements listed as number 35-37 in Appendix 6);

(n) subject to the limitations set forth in Appendix 6, it has not granted any right, license or interest in or to, or an option to acquire any of the foregoing with respect to, the intellectual property rights licensed to BMS hereunder that is in conflict with the rights or licenses granted or to be granted to BMS under this Agreement; and

(o) it has disclosed to BMS all Third Party patents and patent applications of which Isis has knowledge as of the Effective Date that are believed by Isis to be potentially required for freedom-to-operate with respect to the manufacture, use or sale of MOE Gapmers targeting PCSK9.

Section 12.3 **BMS Representation and Covenant.** BMS hereby represents and covenants to Isis that:

(a) BMS has the requisite personnel, facilities, equipment, expertise, experience and skill to perform its obligations under this Agreement;

(b) BMS' sales representatives will perform in a professional, timely, competent and efficient manner in the performance of its rights and obligations under this Agreement; and

(c) BMS, its Affiliates, and its Licensees will at all times comply with all Applicable Laws in the performance of its rights and obligations under this Agreement.

Section 12.4 **DISCLAIMER OF WARRANTY.** EXCEPT FOR THE EXPRESS WARRANTIES SET FORTH IN THIS ARTICLE 12 AND IN SECTIONS 2.2, 5.5.1 AND 5.5.2, BMS 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 BMS 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 13 - MISCELLANEOUS

Section 13.1 **Assignment.** Except as expressly set forth in this Agreement, 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 any Third Party with which it has merged or consolidated, or to which it has transferred all or substantially all of its assets or stock to which this Agreement relates 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 or (ii) Isis may assign or transfer its rights under Article 5 (but no liabilities) to a Third Party in connection with a royalty factoring transaction. Any purported assignment or transfer in violation of this Section 13.1 will be void *ab initio* and of no force or effect.

Section 13.2 **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 13.3 **Governing Law; Jurisdiction.** This Agreement will be governed by and construed and enforced in accordance with the laws of the State of New York, USA without reference to any rules of conflicts of laws. Each of the Parties hereby irrevocably and unconditionally submits, for itself and its property, to the nonexclusive jurisdiction of any federal court of the United States of America sitting in the City of Chicago, Illinois and any appellate court from any jurisdiction thereof, in any action or proceeding arising out of or relating to this Agreement, or for recognition or enforcement of any judgment, and each of the Parties hereby irrevocably and unconditionally agrees that all claims in respect of any such action or proceeding may be heard and determined in any such federal court in Chicago. For clarification, any dispute relating to the scope, validity, enforceability or infringement of any Patents shall be governed by and construed and enforced in accordance with the patent laws of the applicable jurisdiction.

Section 13.4 **Dispute Resolution**.

13.4.1 Resolution by Senior Representatives. The Parties shall seek to settle amicably any and all disputes, controversies or claims arising out of or in connection with this Agreement. Any dispute within the JRC's decision-making authority shall be finally decided as set forth in Appendix 5. Any dispute between the Parties which is outside the JRC's decision-making authority shall be promptly presented to the Alliance Managers and the JRC for resolution, and if the Alliance Managers and the JRC are unable to resolve such dispute, such dispute shall then be presented to the [***] of Isis (the ***"Senior Representatives"***), or their respective designees, for resolution. Such Senior Representatives, or their respective designees, will meet in-person or by teleconference 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 a dispute between the Parties arising out of or relating to the validity or interpretation of, compliance with, breach or alleged breach of or termination of this Agreement cannot be resolved within [***] days of presentation to the Senior Representatives, or their respective designees, for resolution, either Party may refer such dispute to binding arbitration to be conducted as set forth below in this Section 13.4. For clarification, any dispute relating to any Patent will not be subject to arbitration, and any dispute within the JRC's decision-making authority will not be subject to arbitration.

13.4.2 Arbitration. If a dispute between the Parties arising out of or relating to the validity or interpretation of, compliance with, breach or alleged breach of or termination of this Agreement cannot, in accordance with Section 13.4.1, be resolved within ninety (90) days of presentation to the Senior Representatives, or their respective designees, for resolution, either Party may refer such dispute to binding arbitration to be conducted as set forth below in this Section 13.4.2.

(a) A Party may submit such dispute to arbitration by notifying the other Party, in writing, of such dispute. Within thirty (30) days after receipt of such notice, the Parties shall designate in writing a single arbitrator to resolve the dispute; *provided, however*, that if the Parties cannot agree on an

arbitrator within such thirty (30) day period, the arbitrator shall be selected by the Chicago, Illinois office of the American Arbitration Association (the "AAA") or, if such office does not exist or is unable to make a selection, by the office of the AAA nearest to Chicago, Illinois. For any disputed breach under Section 4.1 related to an alleged failure to use Commercially Reasonable Efforts as described in Section 4.1, the arbitrator shall be an individual with experience and expertise in the worldwide Development and Commercialization of

pharmaceuticals and the business, legal and scientific considerations related thereto. Otherwise, the arbitrator shall be a lawyer knowledgeable and experienced in the Applicable Laws concerning the subject matter of the dispute. In any case the arbitrator shall not be an Affiliate, employee, consultant, officer, director or stockholder of either Party, or otherwise have any current or previous relationship with either Party or their respective Affiliates. The governing law in Section 13.3 shall govern any such proceedings. The language of the arbitration shall be English. 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 13.4.2. The place of arbitration will be Chicago, Illinois. Either Party may apply to the arbitrator for interim injunctive relief until the arbitration award is rendered or the controversy is otherwise resolved.

(b) Within sixty (60) days after the designation of the arbitrator, the arbitrator and the Parties shall meet, and each Party shall provide to the arbitrator a written summary of all disputed issues, such Party's position on such disputed issues and such Party's proposed ruling on the merits of each such issue.

(c) The arbitrator shall set a date for a hearing, which shall be no later than thirty (30) days after the submission of written proposals pursuant to Section 13.4.2(b), for the presentation of evidence and legal argument concerning each of the issues identified by the Parties. The Parties shall have the right to be represented by counsel. Except as provided herein, the arbitration shall be governed by the Commercial Arbitration Rules of the AAA applicable at the time of the notice of arbitration pursuant to Section 13.4.2(a); *provided, however*, that the Federal Rules of Evidence shall apply with regard to the admissibility of evidence in such hearing. In any such arbitration proceeding, the Parties shall be entitled to all remedies to which they would be entitled in a United States District Court and to full discovery to the same degree permitted under the Federal Rules of Civil Procedure, including monetary damages and injunctive relief, *provided* that the arbitrator may not order the granting or termination of licenses or assign rights to a Product to either of the Parties.

(d) The arbitrator shall use his or her best efforts to rule on each disputed issue within thirty (30) days after completion of the hearing described in Section 13.4.2(c). The determination of the arbitrator as to the resolution of any dispute shall be binding and conclusive upon all Parties. All rulings of the arbitrator shall be in writing and shall be delivered to the Parties as soon as is reasonably possible. Nothing contained herein shall be construed to permit the arbitrator to award punitive, exemplary or any similar damages. The arbitrator shall render a "reasoned decision" within the meaning of the Commercial Arbitration Rules which shall include findings of fact and conclusions of law. The Parties undertake to satisfy any award without delay.

(e) The (i) attorneys' fees of the Parties in any arbitration, (ii) fees of the arbitrator and (iii) costs and expenses of the arbitration shall be borne by the Parties in a proportion determined by the arbitrator.

(f) Any arbitration pursuant to this Section 13.4 shall be conducted in Chicago, Illinois, unless the Parties otherwise agree to a different location. Any arbitration award may be entered in and enforced by a court in accordance with Section 13.3.

(g) Notwithstanding anything in this Section 13.4, each Party shall have the right to seek injunctive or other equitable relief from a court of competent jurisdiction pursuant to Section 13.3 that may be necessary to avoid irreparable harm, maintain the status quo or preserve the subject matter of the arbitration.

(h) The Parties agree that any payments that are made by one Party to the other Party pursuant to this Agreement pending resolution of any dispute shall be promptly refunded if an arbitrator or court determines pursuant to this Section 13.4.2 that such payments are to be refunded by one Party to the other Party.

(i) 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 arbitration, and the arbitrator will conduct the arbitration so as to resolve the dispute as expeditiously as possible.

(j) Except to the extent necessary to confirm an award or as may be required by Applicable Law, neither a Party nor an arbitrator may disclose the existence, content, or results of an arbitration without the prior written consent of both Parties. In no event will an 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 Delaware statute of limitations.

(k) **Disputes Regarding Material Breach.** If the Parties are in dispute as to whether one Party is in material breach of this Agreement, then the arbitrator 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 9.3 (or 10.2, as applicable). If the material breach is not cured within the time period provided pursuant to Section 9.3 (or 10.2, as applicable), the arbitration will continue and the arbitrator will, as part of the same arbitration, award actual direct damages to the non-defaulting Party.

Section 13.5 **Notices.** Except as otherwise provided for in this Agreement, 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 BMS, to:

Bristol-Myers Squibb Company
P.O. Box 4000
Route 206 & Province Line Road
Princeton, NJ 08543-4000
Attention: Vice President, Business Development
Telephone: 609-252-4418
Facsimile: 609-252-7128

With copy to:
Bristol-Myers Squibb Company
P.O. Box 4000
Route 206 and Province Line Road
Princeton, NJ 08543-4000
Attention: Vice President and Senior Counsel, Corporate &
Business Development
Phone: 609-252-5328
Facsimile: 609-252-4232

If to Isis, to:

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

With a copy to:
Attention: General Counsel
Facsimile: (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 13.5 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 13.6 **Entire Agreement; Modifications**. This Agreement (including the attached Appendices and the Research Plan) 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 13.7 **Headings.** The headings of Articles and Sections of this Agreement are for ease of reference only and shall not affect the meaning or interpretation of this Agreement in any way.

Section 13.8 **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 13.9 **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 13.10 **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 13.11 **No Benefit to Third Parties.** The representations, warranties, covenants and agreements set forth in this Agreement are for the sole benefit of the Parties hereto and their successors and permitted assigns, and they will not be construed as conferring any rights on any other parties.

Section 13.12 **Further Assurances.** 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 13.13 **Force Majeure.** Neither Party will be charged with any liability for delay in performance of an obligation under this Agreement to the extent such delay is due to a cause beyond the reasonable control of the affected Party, such as war, riots, labor disturbances, fire, explosion, and compliance in good faith with any governmental Law, regulation or order. The Party affected will give prompt written notice to the other Party of any material delay due to such causes.

Section 13.14 **Interpretation.**

(a) Each of the Parties acknowledges and agrees that this Agreement has been diligently reviewed by and negotiated by and between them, that in such negotiations each of them has been represented by competent counsel and that the final agreement contained herein, including the language whereby it has been expressed, represents the joint efforts of the Parties hereto and their counsel. Accordingly, in the event an ambiguity or a question of intent or interpretation arises, this Agreement shall be construed as if drafted jointly by the Parties and no presumption or burden of proof shall arise favoring or disfavoring any Party by virtue of the authorship of any provisions of this Agreement.

(b) The definitions of the terms herein shall apply equally to the singular and plural forms of the terms defined. Whenever the context may require, any pronoun shall include the corresponding masculine, feminine and neuter forms. The words "include", "includes" and "including" shall be deemed to be followed by the phrase "without limitation". The word "will" shall be construed to have the same meaning and effect as the word "shall". The word "any" shall mean "any and all" unless otherwise clearly indicated by context.

(c) Unless the context requires otherwise, (i) any definition of or reference to any agreement, instrument or other document herein shall be construed as referring to such agreement, instrument or other document as from time to time amended, supplemented or otherwise modified (subject to any restrictions on such amendments, supplements or modifications set forth herein or therein), (ii) any reference to any Applicable Laws herein shall be construed as referring to such Applicable Laws as from time to time enacted, repealed or amended, (iii) any reference herein to any person shall be construed to include the person's successors and assigns, (iv) the words "herein", "hereof" and "hereunder", and words of similar import, shall be construed to refer to this Agreement in its entirety and not to any particular provision hereof, and (v) all references herein to Articles, Sections or Appendices, unless

otherwise specifically provided, shall be construed to refer to Articles, Sections and Appendices of this Agreement.

(d) References to sections of the Code of Federal Regulations and to the United States Code shall mean the cited sections, as these may be amended from time to time.

[SIGNATURE PAGE FOLLOWS]

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.

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall

Name: B. Lynne Parshall

Title: Executive Vice President & CFO

BRISTOL-MYERS SQUIBB COMPANY

By: /s/ Andrew Bonfield

Name: Andrew Bonfield

Title: EVP & CFO

APPENDIX 1

DEFINITIONS

"Additional Third Party Agreement" has the meaning set forth in Section 5.5.

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

"Agreement" means this Collaboration and License Agreement, together with all Appendices attached hereto and the Research Plan, as the same may be amended or supplemented from time to time in accordance with the terms of this Agreement.

"Alliance Manager" has the meaning set forth in Section 3.12.

"Applicable Law" or **"Law"** means all applicable laws, statutes, rules, regulations and other pronouncements having the effect of law of any federal, national, multinational, state, provincial, county, city or other political subdivision, agency or other body, domestic or foreign, including but not limited to any applicable rules, regulations, guidelines, or other requirements of the Regulatory Authorities that may be in effect from time to time, but excluding patent laws.

"Approval" means, with respect to any Product in any regulatory jurisdiction, approval from the applicable Regulatory Authority sufficient for the manufacture, distribution, use and sale of the Product in such jurisdiction in accordance with Applicable Laws. In jurisdictions where the applicable Regulatory Authority sets the pricing authorizations necessary for a Product, Approval will be deemed to have occurred even if the final approval to market and sell the Product is being withheld because BMS (or its Affiliates or Licensee) and the Regulatory Authority have not yet determined pricing so long as all other approvals, licenses, registrations or authorizations necessary for marketing, sale, and/or use of such Product in such jurisdiction have been obtained.

"**API**" means the bulk active pharmaceutical ingredient Compound manufactured in accordance with cGMP for a Product. References to the weight of a quantity of API refer to the gross mass of the API after lyophilization.

"**ASO**" means an [***] of such gene target.

"BMS" means Bristol-Myers Squibb Company.

"BMS Materials" has the meaning set forth in Section 3.10.

"BMS Third Party Payment" has the meaning set forth in 5.5.3.

"Business Day" means any day, other than Saturday, Sunday or any statutory holiday in the United States.

"Calendar Quarter" means the respective periods of three consecutive calendar months ending on March 31, June 30, September 30 and December 31.

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

"Clinical Supply Agreement" has the meaning set forth in Section 4.3.

"Combination Product" means a Product that includes at least one additional active ingredient (whether coformulated or copackaged) which is not a Compound.

"Commercialize", **"Commercializing"** and **"Commercialization"** means activities directed to manufacturing, obtaining pricing and reimbursement approvals, carrying out Phase IV Trials for, marketing, promoting, distributing, importing or selling a Product.

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

"Commercially Reasonable Efforts" means, with respect to a Compound and Product, the carrying out of Development or Commercialization activities using good faith commercially reasonable and diligent efforts, using the efforts that the applicable Party would reasonably devote to a compound or product of similar market potential or profit potential at a similar stage in development or product life resulting from its own research efforts, based on conditions then prevailing and taking into account, without limitation, issues of safety and efficacy, regulatory authority-approved labeling, product profile, the competitiveness of alternative products in the marketplace, the likely timing of the product's entry into the market, the patent and other proprietary position, the likelihood of regulatory approval and other relevant scientific, technical and commercial factors.

"Compound" means any ASO, or a conjugate or prodrug thereof, that modulates the expression of PCSK9 and [***] mRNA or pre-mRNA and that:

(a) is specifically identified by Isis in the performance of the Research Program; or

(b) is within the scope of a Valid Claim of a Patent Controlled by Isis or its Affiliates; or

(c) is identified by BMS during the period ending on the [***] year anniversary of the end of the Research Term through use of technology Covered by a Valid Claim of the Isis Patent Rights and/or use of the Isis Confidential Information.

"Confidential Information" means all information and Know-How and any tangible embodiments thereof provided by or on behalf of the Disclosing Party to the Receiving Party either in connection with the discussions and negotiations pertaining to this Agreement or in the course of performing this Agreement, including without limitation 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; regardless of whether any of the foregoing are marked "confidential" or "proprietary" or communicated to the other by the Disclosing Party in oral, written, graphic or electronic form. For all purposes of this Agreement, the Research Results (for so long as and to the extent BMS has rights hereunder) shall be treated as being Confidential Information of both Parties. Accordingly, each Party shall be considered the Receiving Party with respect to the Research Results and shall be subject to all of the

restrictions and obligations of this Agreement with respect to the disclosure and use of such Research Results to the same extent as applicable to Confidential Information disclosed to such Party by the other Party.

Notwithstanding the foregoing, information or Know-How of a Party will not be deemed Confidential Information for purposes of this Agreement to the extent that the Receiving Party can show by competent proof that such information or Know-How:

(a) was already known to the Receiving Party or any of its Affiliates, without any obligation to the Disclosing Party to keep it confidential or restricting its use, prior to 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 the 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 or any of its Affiliates by a Third Party lawfully in possession thereof, and was not obtained indirectly or directly from the Disclosing Party or in connection with the Research Program; or

(e) was independently discovered or developed outside of the Research Program by employees or (sub)contractors of the Receiving Party or any of its Affiliates, without the aid, application or use of Confidential Information of the Disclosing Party.

"Control" means, with respect to any Know-How, Patent or other intellectual property right, possession by a Party (including its Affiliates) of the right (whether by ownership, license or otherwise) to grant to the other Party access, ownership, a license, sublicense and/or other right to or under such Know-How, Patent or other intellectual property right as provided for herein without violating the terms of any agreement or other arrangement with any Third Party. Notwithstanding anything to the contrary under this Agreement, with respect to any Third Party that later becomes an Affiliate of Isis after the Effective Date (including a Third Party acquirer), no intellectual property of such Third Party will be included in the licenses granted hereunder by virtue of such Third Party becoming an Affiliate of Isis, in each case where such intellectual property (1) exists at the time such Third Party became an Affiliate of Isis or (2) (i) is created by such Third Party after it becomes an Affiliate and (ii) does not otherwise qualify as a Product Specific Patent or Isis Core Technology Patent.

"Cover", **"Covered"** or **"Covering"** means, with respect to a Patent, that, but for rights granted to a Person under such Patent, the practice by such Person of an invention claimed in such Patent would infringe a Valid Claim included in such Patent, or in the case of a Patent that is a patent application, would infringe a Valid Claim in such patent application if it were to issue as a patent.

"Development" means non-clinical and clinical drug discovery, research and/or development activities reasonably related to or leading to the development and submission of information to a Regulatory Authority, including, without limitation, compound screening, medicinal chemistry, chemical synthesis, toxicology, pharmacology and other discovery and pre-clinical efforts, test method development and stability testing, manufacturing process

development, formulation development, delivery system development, quality assurance and quality control development, manufacturing, statistical analysis, and clinical studies. When used as a verb, **"Develop"** means to engage in Development.

"Disclosing Party" has the meaning set forth in Section 7.1.

"Dollars" or **"$"** means the lawful currency of the United States.

"ECN" means a Compound that has been designated as an Early Candidate Nomination by BMS, such that such Compound has been shown to meet the internal standards and criteria established by BMS to qualify such Compound for full pre-clinical development, which standards and criteria are consistent with those customarily used by BMS for its other drug development projects. Such designation corresponds to what is referred to internally by BMS as BMS's [***].

"Effective Date" means the date specified in the initial paragraph of this Agreement.

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

"EU" means the European Union, as its membership may be altered from time to time, and any successor thereto, and which, as of the Effective Date, consists of Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom, and that certain portion of Cyprus included in such organization.

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

"Field" means all indications and uses, including but not limited to the prevention, treatment, diagnosis and/or control of any disease, disorder or condition in humans.

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

"FTE" means the equivalent of the work of one (1) employee working on a dedicated full time basis for one (1) year (consisting of at least a total of [***] hours per year of dedicated effort, excluding vacations and holidays) of work on or directly related to the Research Plan, carried out by an Isis employee, or Third Party mutually agreed upon by the JRC. Overtime will not be counted toward the number of hours that are used to calculate the FTE contribution. No one person will be permitted to account for more than [***] hours of FTE contribution per year. Any person who devotes less than [***] hours per year shall be treated as an FTE on a pro-rata basis, based upon the actual number of hours worked divided by [***]. Scientific work performed in the performance of the Research Program by an Isis FTE (or a Third Party FTE mutually agreed upon by the JRC) may include, but is not limited to, experimental laboratory work, recording and writing up results, reviewing literature and references, and holding scientific discussions.

"FTE Rate" means the rate that BMS will fund Isis FTEs which is $[***] per FTE per year for the initial Calendar Year of the Research Term, and such FTE rate will [***] by a factor [***] per annum starting as of the beginning of the 2nd Calendar Year of the Research Term (i.e.,

beginning in 2008) and each Calendar Year thereafter during the Research Term, *provided* that any such [***] shall not [***] [***]% per annum.

"GAAP" means generally accepted accounting principles of the United States consistently applied.

"Generic Product(s)" means a product or products containing an active ingredient having the same or substantially the same chemical structure as the Compound contained in a Product, whether approved under an NDA, ANDA, an application under 505(b)(2), or any equivalent thereof, or otherwise by a Regulatory Authority.

"[***] Royalties" means the royalty obligations of Isis, if any, applicable with respect to a Product under Isis' agreement with [***], Inc. dated [***] and Isis' agreement with [***].

"IMS" means IMS America Ltd. of Plymouth Meeting, Pennsylvania or any successor to thereof, or any other independent pharmaceutical sales auditing firm reasonably agreed upon by the Parties.

"IND" means an Investigational New Drug Application (as defined in the Food, Drug and Cosmetic Act, as amended) filed with the FDA or its foreign counterparts.

"IND Acceptance" means the acceptance (or deemed acceptance) of the filing of an IND by the applicable Regulatory Authority.

"IND-Enabling Studies" means the pharmacokinetic and toxicology studies required to meet the regulations for filing an IND.

"**Initiation of Phase II Trial"** means the first dosing of Product in a human patient in a Phase II Trial.

"Initiation of Phase III Trial" means the first dosing of Product in a human patient in a Phase III Trial. In the case where a Phase IIb/III Trial precedes any Phase III Trial for a given Product, the first dosing of such Product in a human patient following the review of interim data and decision to extend the period of such Phase IIb/III Trial in order to provide sufficient evidence of safety and efficacy to be included as a Phase III Trial in filings with Regulatory Authorities shall be deemed to be the "start of Phase III Trial" for such Product.

"**Isis Core Technology Patents**" means Patents Controlled by Isis or its Affiliates on the Effective Date and/or at any time through the period ending on the [***] year anniversary of the expiration of the Research Term, in each case that are [***] for the Development and Commercialization of Compound and Products; *provided however*, that for any such Patents that include Pass Through Obligations, the provisions of Section 5.5 will govern whether such Patent will be included as an Isis Core Technology Patent. In addition, Isis Core Technology Patents shall exclude the Product Specific Patents and the Isis Manufacturing Patents. A representative list of the Isis Core Technology Patents as of the Effective Date are listed in Appendix 3 hereto. For clarification, any Isis Program Patent Rights or any Joint Patent satisfying the definition above, will be considered an Isis Core Technology Patent. For clarification, any such Isis Core Technology Patent that qualifies as an Isis Core Technology Patent on the [***] year anniversary of the expiration of the Research Term will remain an Isis Core Technology Patent throughout the Term of the Agreement.

"Isis In-License Agreements" has the meaning set forth in Section 5.5.1.

"**Isis Inventions"** has the meaning set forth in Section 8.1.

"**Isis Know-How"** means all Know-How that encompass or relate to any Compounds or Products or that are otherwise useful for the research, discovery, Development, manufacturing and commercialization of Compounds and/or Products in the Field that are Controlled by Isis or its Affiliates as of the Effective Date and/or at any time through the period ending on the [***] year anniversary of the expiration of the Research Term (including but not limited to all chemical, biological and structure activity relationship information relating to Compounds). The Isis Know-How shall include the Research Results. For clarification, any such Isis Know-How shall remain Isis Know-How after the [***] year anniversary of the expiration of the Research Term throughout the Term of the Agreement

"**Isis Manufacturing Patents"** means Patents Controlled by Isis or its Affiliates on the Effective Date and/or [***], in each case that claim methods and materials used in the synthesis of ASOs; *provided however*, that for any such Patents that include Pass Through Obligations, the provisions of Section 5.5 will govern whether such Patent will be included as an Isis Manufacturing Patent. A representative list of Isis Manufacturing Patents is attached hereto as Appendix 4. Isis Manufacturing Patents shall exclude the Product Specific Patents and the Isis Core Technology Patents. For clarification, any Isis Program Patent Rights or any Joint Patent satisfying the definition above, will be considered an Isis Manufacturing Patent.

"**Isis Manufacturing Technology"** means the Isis Know-How and Isis Manufacturing Patents claiming inventions made on or after the Effective Date solely to the extent necessary or useful to manufacture a Compound and/or Product by or for BMS (or its Affiliate or Licensee)**.**

"**Isis Patent Rights"** means the Isis Core Technology Patents, the Product Specific Patents and the Isis Manufacturing Patents.

"**Isis Permitted Manufacturing Technology"** means (i) the Isis Know-How and Isis Manufacturing Patents claiming inventions made [***] the Effective Date solely to the extent necessary or useful to manufacture a Compound and/or Product for and on behalf of BMS (or its Affiliate or Licensee) and (ii) the Isis Know-How [***] the Effective Date and Isis Manufacturing Patents [***] the Effective Date solely to the extent necessary to manufacture a Compound and/or Product for and on behalf of BMS (or its Affiliate or Licensee)**.**

"**Isis Program Patent Rights"** has the meaning set forth in Section 8.1.

"**Isis Technology"** means collectively the Isis Know-How and the Isis Patent Rights.

"Joint Invention" has the meaning set forth in Section 8.1

"Joint Patent" means any Patent that claims, and only to the extent that it claims, a Joint Invention(s).

"Joint Research Committee" or **"JRC"** has the meaning set forth in Section 3.3.

"JRC Charter" has the meaning set forth in Section 3.3.

"JNDA" means a New Drug Application filed with the Koseisho required for marketing approval for the applicable Product in Japan.

"JNDA Approval" means the Approval of a JNDA by the Koseisho for the applicable Product in Japan.

"Know-How" means technical information and materials, including without limitation, technology, software, instrumentation, devices, data, biological materials, assays, constructs, compounds, inventions, practices, methods, knowledge, know-how, trade secrets, skill and experience.

"Koseisho" means the Japanese Ministry of Health and Welfare, or any successor agency thereto.

"Licensee" means any Third Party which is sublicensed by BMS or any of its Affiliates to market and sell Product, but shall not include any wholesaler or distributor.

"Losses" has the meaning set forth in Section 11.1.

"Major European Country" means France, Germany, Italy, Spain or the United Kingdom.

"MAA Approval" shall be achieved upon receiving the first Approval for the applicable Product in any of the Major European Countries.

"MAA Filing" means filing with the EMEA of a marketing authorization application (***"MAA"***) for the applicable Product under the centralized European procedure. If the centralized EMEA filing procedure is not used, MAA Filing will be achieved upon the first filing of an MAA for the applicable Product in any Major European Country.

"MOE Gapmer" means a single stranded ASO of less than [***] nucleotides (i) wherein [***] backbone linkages are modified by substituting a sulfur at the non-bridging oxygen (phosphorothioate) and (ii) comprising a region of at least [***] unsubstituted 2' deoxy nucleotides with the remaining nucleotides having a 2'-O-(methoxyethyl) substitution at the 2' position.

"NDA" means a New Drug Application filed with the FDA after completion of clinical trials to obtain marketing approval for the applicable Product in the United States.

"NDA Approval" means the Approval of an NDA by the FDA for the applicable Product in the U.S.

"NDA Filing" means the acceptance by the FDA of the filing of an NDA for the applicable Product.

"Net Sales" means, with respect to any Product, the amount billed by BMS, an Affiliate of BMS, or any permitted Licensee for sales of such Product in arm's length transactions to Third Parties, after deduction (if not already deducted in the amount invoiced) of the following items with respect to sales of such Product:

(a) trade, cash, and/or quantity discounts, retroactive price reductions, charge-back payments and rebates actually taken and allowed, including discounts or rebates to governmental or managed care organizations;

(b) credits or allowances given or recorded for rejection or return of previously sold Product (including, without limitation, returns of Product in connection with recalls or withdrawals);

(c) freight out, postage, shipping and insurance charges actually incurred for delivery of such Product;

(d) any tax, tariff, duty or government charge (including any tax such as a value added or similar tax or government charge other than an income tax) levied on the sale, transportation or delivery of a Product and borne by the seller thereof without reimbursement from any Third Party; and

(e) amounts written off by reason of uncollectible debt.

Net Sales and all of the foregoing deductions from the gross invoiced sales prices of Product shall be determined in accordance with BMS's standard accounting procedures and in accordance with GAAP. In the event that BMS, its Affiliates or Licensees make any adjustments to such deductions after the associated Net Sales have been reported pursuant to this Agreement, the adjustments shall be reported and reconciled with the next report and payment of any royalties due. In the case of any Combination Product sold in the Territory, Net Sales for such Combination Product shall be calculated by multiplying actual Net Sales of such Combination Product by the fraction A/(A+B) where A is the invoice price of the Product if sold separately without the other active ingredient(s), and B is the total invoice price of the other active ingredient(s) in the Combination Product, if sold separately. If, on a country-by-country basis, such other active ingredient(s) in the Combination Product are not sold separately in said country, Net Sales for the purpose of determining royalties of the Combination Product shall be calculated by multiplying actual Net Sales of such Combination Product by the fraction A/D, where A is the invoice price of the Product if sold separately, and D is the invoice price of the Combination Product. If neither the Product nor such other active ingredient(s) are sold separately in a given country, the Parties shall in good faith, determine Net Sales for such Combination Product by mutual agreement.

In the event, in a particular country, BMS or any of its Affiliates sells a Product to an unaffiliated distributor or wholesaler at a price that is less than an arm's length price and such distributor or wholesaler pays BMS or its Affiliates any additional amount related to such sale, then BMS will adjust such selling price for purposes of calculating Net Sales so as to bring it to an arm's length basis.

Net Sales shall not include (x) any payments among BMS, its Affiliates and Licensees, unless such paying party is the end user of the relevant Product or (y) any payments in consideration of supplies of the applicable Product for use in clinical trials.

"Objective" has the meaning set forth in Section 3.1.

"Pass Through Royalties" means any royalty on net sales of Product that becomes payable by Isis to a Third Party under an Isis In-License Agreement with respect to a Product Developed and Commercialized by BMS under this Agreement, where such royalty obligation is based on the manufacture, use or sale of the Product being Covered by an Isis Patent Right licensed to BMS under Section 2.1 which Isis Patent Right is licensed to Isis under such Isis In-License Agreement.

"Pass Through Obligations" means any development milestone payment or royalty on net sales of Product that becomes payable by Isis to a Third Party under an Isis In-License

Agreement with respect to a Product Developed and Commercialized by BMS under this Agreement or any or other non-financial obligation, where such milestone payment, royalty payment or other obligation is based on the manufacture, use or sale of the Product being Covered by an Isis Patent Right licensed to BMS under Section 2.1 which Isis Patent Right is licensed to or acquired by Isis under such Isis In-License Agreement. Pass Through Obligations includes any Pass Through Royalties.

"Patents" means (a) patents and patent applications in any country or jurisdiction, (b) all priority applications, divisionals, continuations, and continuations-in-part of any of the foregoing, and (c) all patents issuing on any of the foregoing patent applications, together with all registrations, reissues, renewals, re-examinations, confirmations, supplementary protection certificates, and extensions of any of (a), (b) or (c).

"PCSK9" means proprotein convertase subtilisin/kexin type 9 (GenBank accession # NM_174936.2), or any [***], mutants, polymorphisms and fragments thereof.

"Permitted License" means a license granted by Isis to a Third Party (i) under the Isis Core Technology Patents or the Isis Manufacturing Patents (but not under the Product Specific Patents) to use ASOs (or supply ASOs to end users) [***] solely to conduct Research, or (ii) under the Isis Manufacturing Patents (but not under [***] Product Specific Patents) to enable such Third Party to [***] ASOs, where such Third Party is primarily engaged in providing contract manufacturing or services and is not engaged in drug discovery, development or commercialization; *provided further*, that any such license under clause (i) and (ii) shall be limited to patent claims that are generally [***] in general, and do not relate to any [***] sequence. For avoidance of doubt, Permitted License shall not include any license specific to any Compound or Product or under any Patent claim directed to or specific to any Compound or Product (including the use or manufacture thereof).

"Person" means any individual, firm, corporation, partnership, limited liability company, trust, business trust, joint venture company, governmental authority, association or other entity.

"Phase II Trial" means a human clinical trial of a Product, the principal purpose of which is a determination of preliminary short-term safety and efficacy in the target patient population, as described in 21 C.F.R. 312.21(b) for the United States, or a similar clinical study prescribed by the Regulatory Authorities in a foreign country.

"Phase IIb Trial" means a Phase II Trial, designed to support and immediately precede the initiation of a Phase III Trial program without any further Phase II Trials, to evaluate the dose-dependent effectiveness of a pharmaceutical product for a particular indication or indications in patients with the disease or condition under study and to determine the common side effects and risks associated with the pharmaceutical product.

"Phase IIb/III Trial" means a human clinical trial of a Product, the principal purpose of which is a further determination of efficacy and safety, in the target population, at the intended clinical dose or doses or range of doses, on a sufficient number of subjects and for a sufficient period of time to confirm the optimal manner of use of the Product (dose and dose regimen) prior to initiation of the pivotal Phase III Trials, and which itself provides sufficient evidence of safety and efficacy to be included as a Phase III Trial in filings with Regulatory Authorities.

"Phase III Trial" means a human clinical trial of a Product on a sufficient number of subjects that is designed to establish that a pharmaceutical product is safe and efficacious for its intended use, and to determine warnings, precautions and adverse reactions that are associated

with such pharmaceutical product in the dosage range to be prescribed, which trial is intended to support Approval of a Product, as described in 21 C.F.R. 312.21(c) for the United States, or a similar clinical study prescribed by the Regulatory Authorities in a foreign country.

"Phase IV Trial" means a human clinical trial for a Product commenced after receipt of Approval in the country for which such trial is being conducted and that is conducted within the parameters of the Approval for the Product. Phase IV Trials may include, without limitation, epidemiological studies, modeling and pharmacoeconomic studies, investigator sponsored clinical trials of Product and post-marketing surveillance studies.

"Prior Third Party Agreements" means certain licenses granted prior to the Effective Date by Isis to Third Parties under a Patent Controlled by Isis under an agreement included in the agreements listed in Appendix 6.

"Product" means any pharmaceutical product containing a Compound (alone or with other active ingredients), in all forms, presentations, formulations and dosage forms.

"Product Specific Patents" means all Patents (including all claims and the entire scope of claims therein) Controlled by Isis or its Affiliates on the Effective Date and/or at any time through the period ending on the [***] year anniversary of the expiration of the Research Term, in each case claiming inventions specifically directed to any Compounds or Products, including but not limited to patents and patent applications specifically claiming such Compounds or Products, methods of using such Compounds or Products, methods and materials specific to the synthesis of such Compounds or Products, and methods and materials specific to formulating and administering such Compounds or Products (including by way of example and without limitation, such Patents claiming (a) the sequence or a portion thereof corresponding to the PCSK9 gene sequence or a portion thereof, (b) the specific composition of matter of a Product, (c) methods of using a Product as a therapeutic or (d) methods of using a Compound as a therapeutic); *provided however*, that (x) for any such Patents that include Pass Through Obligations, the provisions of Section 5.5 will govern whether such Patent will be included as an Product Specific Patent Right and (y) unless the Parties otherwise agree in writing, Patents that include claims that are directed to subject matter and have a scope that is applicable to ASOs in general, and not specifically directed to a Compound or Product, shall be considered to be Isis Core Technology Patents (or Isis Manufacturing Patents, as applicable). For clarification, any Isis Program Patent Rights or any Joint Patent satisfying the definition above, will be considered a Product Specific Patent. The Product Specific Patents as of the Effective Date are listed in Appendix 2 attached hereto. For clarification, any such Product Specific Patent qualifying as a Product Specific Patent on the [***] year anniversary of the expiration of the Research Term shall remain a Product Specific Patent throughout the Term of the Agreement.

"Program Inventions" has the meaning set forth in Section 8.1.

"Program Leader" has the meaning set forth in Section 3.3.

"Program Patent Rights" has the meaning set forth in Section 8.1.

"Proof of Concept" means that a Compound or Product has demonstrated sufficient short-term safety and efficacy in a Phase II Trial to warrant the initiation of Phase IIb Trials (or, as applicable, the extension of a Phase II Trial into the Phase IIb Trial portion of the trial). For purposes of clarification, the dosing of the first human in a Phase IIb Trial (or, as applicable, in the Phase IIb Trial portion of a Phase II Trial) for a Product or Compound will conclusively demonstrate the achievement of Proof of Concept for such Compound or Product.

"Ready for Pivotal Quality Trials" means that a Compound or Product has demonstrated sufficient safety profile and dose-dependent effectiveness for a particular indication(s) in Phase IIb Trials (or, as applicable, a Phase IIb/III Trial) to warrant the initiation of Phase III Trials (or, as applicable, the extension of the Phase IIb/III Trial into the the Phase III Trial portion of the Phase IIb/III Trial). For purposes of clarification, the dosing of the first human in a Phase III Trial (or, as applicable, in the Phase III Trial portion of a Phase IIb/III Trial) for a Product or Compound will conclusively demonstrate that such Compound or Product is Ready for Pivotal Quality Trials.

"Receiving Party" has the meaning set forth in Section 7.1.

"Regulatory Authority" means any governmental authority, including without limitation FDA, EMEA or Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto), that has responsibility for granting any licenses or approvals or granting pricing and/or reimbursement

approvals necessary for the marketing and sale of a Product in any country.

"Regulatory Documentation" means all applications, registrations, licenses, authorizations and approvals (including all 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.

"Research" means pre-clinical research including gene function, gene expression and target validation research, which may include small pilot toxicology studies but excludes IND-Enabling Studies, clinical development and commercialization.

"Research Plan" has the meaning set forth in Section 3.4.

"Research Program" has the meaning set forth in Section 3.1.

"Research Program Costs" has the meaning set forth in Section 3.5.

"Research Results" means all data, information, trade secrets, inventions and Know-How which are discovered, made, reduced to practice, identified or developed in whole or in part by Isis in the course of the performance of the Research Program.

"Research Term" will have the meaning set forth in Section 3.2.

"Research Year" means each 12 month period during the Research Term, with the first Research Year beginning on the Effective Date.

"Royalty Term" has the meaning set forth in Section 5.9.

"Senior Representatives" has the meaning set forth in Section 13.4.

"Term" has the meaning set forth in Section 9.1.

"Territory" means all countries and jurisdictions throughout the world.

"Third Party" means any Person other than Isis or BMS or their respective Affiliates.

"Valid Claim" means either (a) a claim of an issued and unexpired patent which has not been held permanently revoked, unenforceable or invalid by a decision of a court or other governmental agency of competent jurisdiction, unappealable or unappealed within the time allowed for appeal and that is not admitted to be invalid or unenforceable through reissue, disclaimer or otherwise (i.e., only to the extent the subject matter is disclaimed or is sought to be deleted or amended through reissue), or (b) a claim of a pending patent application that has not been abandoned, finally rejected or expired without the possibility of appeal or refiling, *provided however*, that (x) Valid Claim will exclude any such pending claim in an application that has not been granted within [***] following the [***] filing date for such application (unless and until such claim is granted) and (y) Valid Claim will exclude any such pending claim that does not have a reasonable bona fide basis for patentability (such reasonable bona fide basis to be determined by outside counsel selected by the parties the event that the parties disagree as to whether there is a reasonable bona fide basis for patentability for such a claim).

APPENDIX 2

PRODUCT-SPECIFIC PATENTS
(as of the Effective Date)

[***]

APPENDIX 3

ISIS CORE TECHNOLOGY PATENTS

[***]

APPENDIX 4

ISIS MANUFACTURING PATENTS

[***]

APPENDIX 5

CHARTER OF THE JOINT RESEARCH COMMITTEE

Purpose

The Joint Research Committee is established by Isis and BMS to oversee the Research Program under the Agreement.

Responsibilities

1. The JRC will, using the Research Plan initially attached to the Agreement, as a basis, continue to develop and refine the Research Plan, as needed, and will conduct a comprehensive review of the Research Plan on at least an annual basis.

2. The JRC will be responsible for the overall planning and execution of the Research Program and the approval and oversight of the Research Plan. The JRC will (i) evaluate the data generated by the Parties in the course of carrying out the Research Plan, (ii) discuss and resolve any overarching issues or significant changes in the Research Plan, (iii) recommend project prioritization within the Research Plan, (iv) make project progression decisions and resource allocation decisions in accordance with the Research Plan, (v) review and approve all patent filings covering the Research Results, and (vi) make revisions to the Research Plan as necessary. Except for amendments to the Research Plan (as adopted in accordance with this charter and the Agreement), in no event will the JRC have the power or authority to amend any provision of the Agreement.

3. The JRC will have the power to delegate its authority and duties to sub-committees as it deems appropriate.

Composition

4. The JRC will initially have six members, and will at all times have an equal number of members designated by each Party. Each Party may replace its appointed JRC representatives at any time upon written notice to the other Party. The size and composition of the JRC provided herein may not be changed without the consent of both Isis and BMS.

5. Each JRC member will have the requisite background, experience and training to carry out the duties and obligations of the JRC.

6. Each Party will designate one of its representatives as co-chairperson of the JRC. Each of the co-chairpersons will be responsible, on an alternating basis with the BMS co-chairperson having responsibility with respect to the initial meeting, for scheduling meetings, preparing and circulating an agenda in advance of each meeting, and preparing the minutes of each meeting.

Decisions

7. Each Party's JRC members will collectively have three votes, regardless of the number of its JRC members participating in any meeting. No votes will be taken unless there is at least one JRC member representing each of Isis and BMS participating in such meeting. Each Party may allocate its three votes among its attending JRC members in any manner, at such Party's discretion. If only one JRC member is attending on behalf of a given Party, such JRC member may cast all the votes allocated to such Party. Unless otherwise specified herein, all actions taken by the JRC as a committee will be by majority vote. If the JRC members reach a deadlock on any vote, then the deadlock will be resolved in accordance with Paragraph 8 below. Notwithstanding anything to the contrary, no decision by the JRC will require the other Party to: (i) breach any written agreement that such other Party may have with a Third Party (except where such agreement is entered into in breach of any representation, warranty, covenant or obligation of such Party under to this Agreement; (ii) perform any activities that are outside the scope of the Objective; or (iii) violate any Applicable Law or principles of scientific integrity.

8. If the JRC is unable to decide by a majority vote on any issue within the scope of its authority and duties, then the JRC will promptly raise such issue to each Parties co-chairperson on the JRC, and such co-chairs will have 10 days to mutually agree on how to resolve such issue. If the co-chairs are unable to resolve such issue within the 10 day period, then such issue will be brought to each Party's Senior Representatives, or their designees. The Senior Representatives will have ten days to mutually agree on how to resolve such issue. If the Senior Representatives are unable to resolve such issue within the ten day period, then, subject to the express limitations set forth in the Agreement and in Paragraph 9 below, such issue will be finally resolved by the Senior Representative of BMS, and such resolution will be binding on BMS and Isis.

9. Notwithstanding anything to the contrary, BMS will not have the final decision with respect to any dispute involving any of the following: (i) moving the performance of the Research Program away from the Objective; (ii) reducing the number of FTEs required by the Research Plan below [***] FTEs during the first [***] years of the Research Term; (iii) unilaterally changing the Research Plan in a manner that is

likely to produce data or results that are not reasonably consistent with the Objective; or (iv) changing the performance of the Research Plan to include new technology (e.g. assays, targets, capital equipment or animal models) for which Isis would bear the cost of obtaining.

Operations; Meetings

10. During the Research Term the JRC will initially meet once per month, unless and until the JRC determines that such meetings should occur once per Calendar Quarter (in either case, each a ***"Scheduled Meeting"***). Scheduled Meetings may be held in person or by audio or video teleconference when appropriate, but at a minimum, once each year in person (which in-person meeting will be held on an alternating basis in New Jersey and in San Diego). In addition, any two members of the JRC may jointly call for an *ad hoc* meeting of the JRC by teleconference at any time, by giving the other members of the JRC advance written notice of at least two Business Days (each, an "***Ad Hoc Meeting***"). An Ad Hoc Meeting may be called to address any time-sensitive matter.

11. Meetings of the JRC will be effective only if at least one JRC representative of each Party is present or participating. Each Party will be responsible for all of its own expenses of participating in the JRC meetings. The Parties will endeavor to schedule meetings of the JRC with at least 30 days advance notice.

12. Each Party may bring additional employees to each meeting as non-voting observers.

13. The co-chair responsible for each meeting (the ***"Responsible Chair"***) will, in consultation with other members of the JRC, develop and set the JRC's agenda for each Scheduled Meeting. The Responsible Chair will include on such agenda each item requested within a reasonable time in advance of such Scheduled Meeting by a JRC member. The agenda and information concerning the business to be conducted at each Scheduled Meeting will be communicated in writing to the members of the JRC within a reasonable time in advance of such Scheduled Meeting to permit meaningful review. No agenda is required for an Ad Hoc Meeting.

14. The Responsible Chair, or such person as the Responsible Chair may designate, will prepare, and distribute to all JRC members, draft committee minutes within 2 weeks following each Scheduled Meeting or Ad Hoc Meeting and such minutes shall be finalized by the JRC promptly thereafter. As part of the agenda of the first Scheduled Meeting, the JRC members will agree upon a standard procedure for review and approval of such draft committee minutes by the JRC.

APPENDIX 6

ISIS IN-LICENSE AGREEMENTS
AND
PRIOR THIRD PARTY AGREEMENTS

[***]

AMENDMENT NO. 1

This Amendment No. 1 (the "Amendment") amends the **MANUFACTURING, COMMERCIALIZATION AND DEVELOPMENT AGREEMENT** (the "Agreement") entered into as of July 31, 2006 between ISIS PHARMACEUTICALS, INC., a Delaware corporation, through its IBIS BIOSCIENCES division ("Ibis"), and BRUKER DALTONICS INC., a Delaware corporation ("Bruker") and is effective on the date both parties have signed below.

BACKGROUND

T5000 System: Over the past several months, Ibis has further refined, developed and replaced the Ibis T5000 System as described in the Agreement based on customer input and need. The instrument described and outlined in the Agreement was enhanced to include automation systems which allow the user to more easily run assays on the instrument. Therefore, this Amendment to the Agreement is agreed to, as the revenue sharing terms in Article 5 of the Agreement were based on the non-automated basic T5000 System.

Article 5 of the Agreement is therefore amended to fairly compensate each party for the enhancements included in this upgraded version of the Ibis T5000 System with a targeted average list price of $[***], targeted average selling price of $[***] and a targeted discount price of $[***].

Ibis Consumables: Some of the consumables for the T5000 System presently still require [***] and logistics. Ibis and Bruker agree that it will be a [***] to make all Ibis Consumables available in a [***] format by [***] or earlier, so that the expense and complexity of [***] and logistics can be eliminated.

Moreover, as Ibis Consumables are only becoming products over time in [***], it is clear that a major part of the early European market development in [***] will require Bruker to demonstrate the Ibis T5000 process and instrumentation in the applications laboratory in Bremen to potential European customers and collaborators. This Bruker applications lab itself will therefore be a significant consumer of Ibis Consumables, and needs access to Ibis Consumables [***] for potential customer demonstrations.

In consideration of the foregoing premises, the mutual covenants contained herein and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties hereto, intending to be legally bound, hereby agree to amend the Agreement, in accordance with Article 15.10 of the Agreement, as follows:

AMENDED OR NEW ARTICLES AND DEFINITIONS

Amended Definition: Exhibit A of the Agreement is amended as follows:

"T5000 Systems" means the fully integrated, automated system comprising a MicrOTOF, an Ibis Amplicon Desalting Module, the Ibis Analytical Systems, the Thermo CRS robot, mircotiter plate 'hotel' and related automation accessories, and other computers and hardware, as more fully described in Schedule 3, as updated from time to time by written agreement of the parties. "T5000 Systems" does not include Ibis Consumables. "T5000 Systems" includes new versions of the T5000 System as it exists as of the Effective Date, as well as successor products designed to perform mass spectrometry analysis of PCR products, but excluding any systems exclusively used for IVD Use.

The updated list of components representing the Ibis "T5000 Systems" described herein is an Attachment A to this Amendment.

Article 5.1 through and including 5.5 of the Agreement are replaced in their entirety by the following:

5.1 **Sales of T5000 Systems (Full Bruker Participation).** With respect to each sale of a T5000 System for which (a) Bruker sells, delivers and Installs, trains End Users on, services and supports and provides Updates for such T5000 System (all as contemplated by the Commercialization Plan) and (b) Ibis fulfills its obligations as contemplated by the Commercialization Plan with respect to such T5000 System, Bruker will pay Ibis the following amounts, which amounts will be cumulative and in addition to any other payments to be made to Ibis under this Agreement:

For Ibis T5000 System Sales in North America, Europe, and the Middle East: Bruker will receive the first $[***] of the total amount received from the sale of a T5000 System, for the manufacture, delivery, installation and warranty of the Ibis T5000 System. Then, to the extent available from the remainder of the amount received from such T5000 System sale, Bruker will pay Ibis $[***]. Finally, following such payments to Bruker and Ibis, for T5000 System sales in North America, Ibis and Bruker will [***] ([***]%) any remainder of the sale price received for such T5000 System, and for T5000 System sales in Europe and the Middle East, Ibis and Bruker will divide any remainder of the sale price received for such T5000 System by providing [***]% of such remainder to Ibis and [***]% of such remainder to Bruker, excluding shipping, taxes and other ancillary payments of revenue.

However, notwithstanding the foregoing, Bruker may negotiate sales of the T5000 System at its option provided Ibis receives the minimum amount of $[***] per system on Bruker negotiated sales, and Ibis may negotiate sales of the T5000 System at its option so long as Bruker receives the minimum amount of $[***] per system on Ibis negotiated sales.

For clarification, for purposes of Section 5.1(b), Ibis' obligations under the Commercialization Plan are not specific to particular sales or deployments of T5000

Systems, but rather require Ibis to provide Bruker generally with the Ibis Analytical Systems installed on a computer that will be integrated with each particular sale and deployment of a T5000 System.

5.2 **Sales of T5000 Systems (Other than Full Bruker Participation).** For each sale of a T5000 System for which Bruker does not perform all of the tasks assumable by Bruker as set forth in the Commercialization Plan, Ibis and Bruker, in accordance with Section 15.10, will determine an equitable allocation of System Revenues based on obligations assumed by Ibis (either directly or through a Third Party, including an Ibis Partner).

5.3 **Bruker Purchase of Ibis Consumables.** Solely in connection with satisfying its obligations under the Commercialization Plan, beginning on the Effective Date Bruker may purchase, and Ibis will sell, Ibis Consumables at [***]% of Ibis' then current list price for such Ibis Consumables in the United States. However, if Ibis discounts particular Ibis Consumables by more than [***]% from its current list price in the United States for purchases of the same or equivalent Ibis Consumables in the same or similar volume, then Bruker may purchase, and Ibis will sell, Ibis Consumables at [***]% of Ibis average selling price in the United States for purchases of the same or similar Ibis Consumables in the same or similar volume. Notwithstanding the foregoing, the parties understand and agree that Ibis may, from time to time, provide discounted Ibis Consumables to customers who will be supplying data to Ibis for marketing, regulatory or other valuable purposes or in connection with a significant relationship. Such discounted Ibis Consumables will not be included in calculating such average price; provided, however, that in any case not more than [***]% of Ibis Consumables sales will be excluded from the calculation of such average price.

During the start-up phase of the Ibis Consumables business, while the Ibis Consumables still require [***] and logistics, Ibis will replace consumables which are damaged due to loss of [***] during shipping. This replacement will be limited to a maximum of [***] kits for any customer or shipment. Bruker will use reasonable care in assuring shipments of consumbles requiring [***] are appropriately packaged and shipped. Any reimbursement to Bruker from the carrier for loss of consumables during shipment of [***] products will be remitted to Ibis.

Ibis will make Ibis Consumables available to the Bruker demonstration and applications laboratory for Bruker-internal use only as follows:

i) For customer demonstrations: at [***]% of Ibis' then current list price for such Ibis Consumables in the United States, limited to a maximum of [***] kit per demonstration.

5.4 **Extended Warranty.** (a) For each Extended Warranty sold to an End User located in the North American Territory, Bruker will pay Ibis [***]% of Extended Warranty Revenues, but in no event less than $[***] for each year of coverage under such Extended Warranty (unless specifically authorized in writing by the Ibis President for any particular End User or any particular defined business incentive) and (b) for each Extended Warranty sold to an End User located outside the North American Territory, Bruker will pay Ibis [***]%

of Extended Warranty Revenues, but in no event less than $[***] for each year of coverage under such Extended Warranty (unless specifically authorized in writing by the Ibis President for any particular End User or any particular defined business incentive). Bruker acknowledges and agrees that these payments are tied to each Extended Warranty sold to an End User for each T5000 System purchased by such End User for each year of coverage under such Extended Warranty. For clarification, (c) for purposes of Section 5.4(a), Ibis' obligations under the Commercialization Plan with respect to providing Bruker with Renewal Updates are not specific to particular sales of Extended Warranties, but rather require Ibis to provide Bruker generally with Renewal Updates that will be integrated with each particular sale of an Extended Warranty and (d) Bruker has no obligation to compensate Ibis for providing Renewal Updates other than as set forth in Section 5.4(a) and (b).

# # #

IN WITNESS WHEREOF, the parties have caused this Amendment to be executed by their duly authorized representatives.

Isis Pharmaceuticals, Inc.		**Bruker Daltonics, inc.**	
By:	*/s/ Michael J. Treble*	By:	*/s/ Gary Kruppa, Ph.D.*
Name:	Michael J. Treble	Name:	Gary Kruppa, Ph.D.
Title:	President, Ibis Biosciences, Inc.	Title:	Vice President, Bruker Daltonics,Inc.
Date:	May 15, 2007	Date:	May 22, 2007

Attachment A

List of Ibis T5000 System Components

Item

[***]
[***]
[***]
[***]

[***]
[***]
[***]
[***]
[***]
[***]

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: August 8, 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: August 8, 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 June 30, 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: August 8, 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.