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 September 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 November 5, 2007 was 86,950,330.

ISIS PHARMACEUTICALS, INC.
FORM 10-Q

INDEX

TRADEMARKS

Orasense™ is a trademark of Isis Pharmaceuticals, Inc.
Ibis Biosciences™ is a trademark of Ibis Biosciences, Inc.
Ibis T5000™ is a trademark of Ibis Biosciences, Inc.
Vitravene® is a registered trademark of Novartis AG.
Isis Pharmaceuticals® is a registered trademark of Isis Pharmaceuticals, Inc.
Regulus Therapeutics™ is a trademark of Regulus Therapeutics LLC.

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

	September 30, 2007 (Unaudited)	December 31, 2006
ASSETS		
Current assets:		
Cash and cash equivalents (including cash and cash equivalents held on behalf of Regulus Therapeutics LLC of $10.0 million at September 30, 2007 and $54.8 million held by Symphony GenIsis, Inc. at December 31, 2006)	$ 102,398	$ 114,514
Short-term investments	43,593	78,819
Contracts receivable	9,237	2,395
Inventories	1,930	861
Other current assets	4,229	9,614
Total current assets	161,387	206,203
Property, plant and equipment, net	6,583	7,157
Licenses, net	19,684	21,435
Patents, net	17,605	16,836
Debt issuance costs	4,938	1,400
Deposits and other assets	2,806	2,876
Total assets	$ 213,003	$ 255,907
LIABILITIES AND STOCKHOLDERS' EQUITY		

Current liabilities:		
Accounts payable	$ 4,507	$ 4,288
Accrued compensation	4,920	6,222
Accrued liabilities	5,278	6,071
Current portion of long-term obligations	7,457	7,514
Current portion of deferred contract revenue	7,804	1,044
Total current liabilities	29,966	25,139
5 1/2% convertible subordinated notes	—	125,000
2 5/8% convertible subordinated notes	162,500	—
Long-term obligations, less current portion	2,222	7,822
Long-term deferred contract revenue	8,131	44
Total liabilities	202,819	158,005
Noncontrolling interest in Symphony GenIsis, Inc.	—	29,339
Noncontrolling interest in Regulus Therapeutics LLC	9,952	—
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 86,610,243 and 82,283,693 shares issued and outstanding at September 30, 2007 and December 31, 2006, respectively	87	82
Additional paid-in capital	820,422	880,954
Accumulated other comprehensive income	511	4,278
Accumulated deficit	(820,788)	(816,751)
Total stockholders' equity	232	68,563
Total liabilities, noncontrolling interest and stockholders' equity	$ 213,003	$ 255,907

See accompanying notes.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2007	2006	2007	2006
Revenue:				
Research and development revenue under collaborative agreements	$ 11,921	$ 2,469	$ 17,404	$ 11,260
Licensing and royalty revenue	26,710	784	27,489	1,327
Total revenue	38,631	3,253	44,893	12,587
Expenses:				
Research and development	24,296	18,973	64,629	56,327
Selling, general and administrative	4,278	2,823	10,769	8,099
Restructuring activities	—	(279)	—	(457)
Total operating expenses	28,574	21,517	75,398	63,969
Income (loss) from operations	10,057	(18,264)	(30,505)	(51,382)
Other income (expense):				
Investment income	2,603	1,682	9,058	3,837
Interest expense	(1,488)	(2,256)	(6,132)	(6,816)
Gain on investments, net	—	—	3,510	2,263
Loss on early retirement of debt	—	—	(3,212)	—
Loss attributed to noncontrolling interest in Symphony GenIsis, Inc.	8,748	6,733	23,157	20,341
Loss attributed to noncontrolling interest in Regulus Therapeutics LLC	87	—	87	—
Net income (loss)	20,007	(12,105)	(4,037)	(31,757)
Excess purchase price over carrying value of noncontrolling interest in Symphony GenIsis, Inc.	(125,311)	—	(125,311)	—
Net loss applicable to common stock	$ (105,304)	$ (12,105)	$ (129,348)	$ (31,757)
Basic and diluted net loss per share	$ (1.25)	$ (0.16)	$ (1.57)	$ (0.44)
Shares used in computing basic and diluted net loss per share	83,942	73,588	82,650	72,934

See accompanying notes.

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

	Nine Months Ended September 30,	
	2007	2006
Net cash used in operating activities	$ (9,762)	$ (44,354)
Investing activities:		
Purchases of short-term investments	(61,052)	(38,468)
Proceeds from the sale of short-term investments	96,876	60,000
Purchases of property, plant and equipment	(1,452)	(1,103)
Acquisition of licenses and other assets	(2,407)	(1,293)
Proceeds from the sale of strategic investments	5,181	4,397
Acquisition of Symphony GenIsis, Inc.	(80,400)	—
Net cash (used in) provided by investing activities	(43,254)	23,533
Financing activities:		
Net proceeds from issuance of equity	6,522	9,021
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	(5,657)	(5,797)
Proceeds from purchase of noncontrolling interest in Symphony GenIsis, Inc, net of fees	—	70,950
Proceeds from capital contribution to Regulus Therapeutics LLC	10,000	
Net cash provided by financing activities	40,900	74,174
Net (decrease) increase in cash and cash equivalents	(12,116)	53,353
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 on behalf of Regulus Therapeutics LLC of $10.0 million at September 30, 2007 and $58.6 million held by Symphony GenIsis, Inc. at September 30, 2006) at end of period	$ 102,398	$ 104,238
Supplemental disclosures of cash flow information:		
Interest paid	$ 5,987	$ 4,653
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 25	$ 181
Common stock issued for Symphony GenIsis, Inc. acquisition	$ 51,093	$ —
Warrant issued in conjunction with Symphony GenIsis, Inc. transaction	$ —	$ 18,590

See accompanying notes.

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

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three and nine month periods ended September 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., Orasense, Ltd. and Symphony GenIsis, Inc. On September 27, 2007, Isis purchased all of the equity in Symphony GenIsis, Inc. On October 25, 2006, Isis dissolved its 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, Regulus Therapeutics LLC, 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*. Until the acquisition of Symphony GenIsis, Inc., in September 2007, Isis identified Symphony GenIsis as a variable interest entity for which Isis was the primary beneficiary. The condensed consolidated financial statements leading up to the acquisition date also include the financial condition and results of operations of Symphony GenIsis, Inc. 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 nine months 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 nine months 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 $550,000 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 nine months 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 includes $1.7 million of raw materials and $173,000 of work-in-process as of September 30, 2007, compared to $861,000 of raw materials as of December 31, 2006.

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 ten years, beginning with the date the patents are issued. For the first nine months of 2007 and 2006, Isis recorded a non-cash charge of $515,000 and $2.2 million, 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*.

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 September 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 September 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 September 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 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, mipomersen (formerly 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 treated Symphony GenIsis as a VIE for which Isis was 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. In September 2007, Isis purchased all of the equity of Symphony GenIsis at which point it became a wholly owned subsidiary of Isis and ceased being a VIE.

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.

In September 2007, Isis and Alnylam launched Regulus Therapeutics LLC, a joint venture focused on the discovery, development, and commercialization of microRNA therapeutics. Alnylam made an initial investment of $10 million to balance venture ownership; thereafter Isis and Alnylam will share funding of Regulus. Regulus will be operated as an independent company with a separate Board of Directors and management team. Alnylam and Isis will retain rights to develop and commercialize on pre-negotiated terms microRNA therapeutic products that Regulus decides not to develop either itself or with a partner. Isis treats Regulus as a VIE for which Isis is the primary beneficiary. As a result, beginning in the third quarter of 2007, Isis included the financial condition and results of operations of Regulus in its condensed consolidated financial statements. The creditors of Regulus do not have recourse to the general credit of Isis.

Comprehensive income (loss)

SFAS 130, *Reporting Comprehensive Income,* requires Isis to report, in addition to net income (loss), comprehensive income (loss) and its components. A summary follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2007	2006	2007	2006
Comprehensive income (loss):				
Unrealized gains (losses)	$ 93	$ (60)	$ (620)	$ (1,133)
Reclassification adjustment for net realized gains included in net income	—	—	(3,147)	(1,901)
Net income (loss)	20,007	(12,105)	(4,037)	(31,757)
Comprehensive income (loss)	$ 20,100	$ (12,165)	$ (7,804)	$ (34,791)

Stock-based compensation expense

Isis accounts for its stock-based compensation expense related to employee stock options, board of director 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 nine months 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 nine months ended September 30, 2007 and 2006, Isis used the following weighted-average assumptions in its Black-Scholes calculations:

Employee Stock Option Grants:

	September 30,	
	2007	2006
Risk-free interest rate	4.7%	4.9%
Dividend yield	0.0%	0.0%
Volatility	63.4%	68.7%
Expected Life	4.6 years	4.6 years

Board of Director Stock Option Grants:

	September 30,	
	2007	2006
Risk-free interest rate	4.9%	5.1%
Dividend yield	0.0%	0.0%
Volatility	65.5%	85.2%
Expected Life	7.4 years	7.0 years

ESPP:

	September 30,	
	2007	2006
Risk-free interest rate	5.1%	4.8%
Dividend yield	0.0%	0.0%
Volatility	51.1%	49.9%
Expected Life	6 months	6 months

Isis records stock options granted to non-employees at their fair value in accordance with the requirements of SFAS 123, *Accounting for Stock-Based Compensation*, then periodically remeasures them in accordance with EITF 96-18, *Accounting for Equity Instruments that are Issued to Other Than Employees for Acquiring, or in Conjunction with Selling, Goods or Services*, and recognizes them over the service period.

Stock-based compensation expense for the three and nine months ended September 30, 2007 and 2006 (in thousands, except per share data) was allocated as follows:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2007	2006	2007	2006
Research and development	$ 1,956	$ 1,091	$ 5,834	$ 3,348
Selling, general and administrative	499	326	1,374	842
Non-cash compensation expense related to stock options included in operating expenses	$ 2,455	$ 1,417	$ 7,208	$ 4,190
Basic and diluted net loss per share	$ (0.03)	$ (0.02)	$ (0.09)	$ (0.06)

As part of the Regulus joint venture, both Isis and Alnylam issued their own company's stock options to members of Regulus' Board of Directors and Scientific Advisory Board. These options are recorded on Regulus' books and treated as non-employee options. Since Isis is consolidating the financial results of Regulus, the non-cash stock based compensation expense associated with these options is included in Isis' consolidated expenses.

As of September 30, 2007, total unrecognized compensation cost related to non-vested stock-based compensation plans was $11.6 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 1.3 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.

In June 2007, the FASB ratified EITF No. 07-3, *Accounting for Nonrefundable Advance Payments for Goods or Services Received for Use in Future Research and Development Activities*. EITF No. 07-3 requires that nonrefundable advance payments for goods and services that will be used or rendered in future research and development activities pursuant to executory contractual arrangements be deferred and recognized as an expense in the period that the related goods are delivered or services are performed. EITF No. 07-3 is effective for fiscal years beginning after November 15, 2007 and, as such, Isis plans to adopt the provisions of EITF No. 07-3 as of January 1, 2008. Isis is currently evaluating the impact that the adoption of EITF No. 07-3 will have on its results of operations, financial position and cash flows.

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 2 5/8%, which is payable semi-annually. The 2 5/8% 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 2 5/8% 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 2 5/8% 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 2 5/8% notes being repurchased plus accrued interest and unpaid interest.

Isis used the net proceeds from the issuance of the 2 5/8% notes to repurchase its 5 ½% convertible subordinated notes due in 2009. In January 2007, Isis repurchased approximately $44.2 million aggregate principal amount of its 5 1/2% 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 nine months 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

National Institutes of Health

In September 2007, Isis received a multi-year Phase 2 Small Business Innovation Research (SBIR) grant by the National Institutes of Health ("NIH") for up to $1.5 million to design oligonucleotide drugs that can exploit the RNA interference (RNAi) antisense mechanism for disease treatment. The Phase 2

grant builds upon a successfully completed Phase 1 program that demonstrated the feasibility of using single-stranded antisense drugs to target the RNAi pathway.

The multi-year grant will fund research by Isis to improve the stability and tissue distribution of RNAi drugs. Much of the work will focus on optimizing the chemical properties of single-stranded oligonucleotides that trigger the RNAi pathway. In addition to demonstrating that compounds optimized with Isis' chemistries produce superior results in animal models when compared to unoptimized compounds, the grant funds the discovery of RNAi-based drugs. As of September 30, 2007, Isis has recognized revenue of $77,000 related to this grant.

Ortho-McNeil, Inc.

In September 2007, Isis entered into a collaboration with Ortho-McNeil ("OMI"), a Johnson & Johnson company, to discover, develop and commercialize antisense drugs to treat metabolic diseases, including Type 2 diabetes. As part of the collaboration, Isis granted OMI worldwide development and commercialization rights to two of its diabetes drugs, ISIS 325568 and ISIS 377131, which selectively inhibit the production of glucagon receptor (GCGR) and glucocorticoid receptor (GCCR), respectively. Additionally, OMI will provide funding to Isis to support a focused research program in metabolic disease. After the initial collaboration phase, Johnson & Johnson Pharmaceutical Research & Development, L.L.C. will continue development of these drugs.

Under the terms of the agreement, OMI paid Isis a $45 million upfront licensing fee which is amortized over the two year period of Isis' performance obligation based on the research plan included in the agreement. OMI will also provide Isis with research and development funding over the two year period of the collaboration. In addition to the licensing fee, Isis could receive over $225 million in milestone payments upon successful development and regulatory approvals of ISIS 325568 and ISIS 377131, as well as royalties on sales. Isis could also receive milestones and royalties on the successful development and regulatory approvals of additional drugs discovered as part of the collaboration.

In September 2007, Isis earned $5 million for achieving the first development milestone by initiating the Phase 1 clinical trial of ISIS 325568. Since the milestone was achieved before the contract was finalized, from an accounting perspective, it is treated as part of the upfront licensing fees and is amortized over the two year period of Isis' performance obligation. As of September 30, 2007, Isis has recognized revenue of $4.9 million related to the upfront licensing fee, the milestone payment and the initial research and development funding. Isis' balance sheet at September 30, 2007 does not include any deferred revenue since Isis had not received the cash payment for the upfront licensing fee and milestone payment as of September 30, 2007. Isis received these payments in October 2007, therefore Isis' balance sheet at December 31, 2007 will include deferred revenue reflecting the unamortized portion of these payments.

Regulus Therapeutics LLC

In September 2007, Isis and Alnylam launched Regulus, a joint venture focused on the discovery, development, and commercialization of microRNA therapeutics. Because microRNAs regulate whole networks of genes that can be involved in discrete disease processes, microRNA therapeutics represent a new approach to target the pathways of human disease. Regulus will combine the strengths and assets of Isis' and Alnylam's technologies, know-how, and intellectual property.

Both Isis and Alnylam granted Regulus exclusive licenses to their intellectual property for microRNA therapeutic applications, as well as certain early fundamental patents in the microRNA field including the "Tuschl III" patent. Alnylam made an initial investment of $10 million to balance venture ownership. Thereafter Isis and Alnylam will share funding of Regulus. Regulus is operated as an independent company with a separate Board of Directors and management team. Alnylam and Isis will retain rights to develop and commercialize on pre-negotiated terms microRNA therapeutic products that Regulus decides not to develop either itself or with a partner.

In accordance with FIN 46R, Isis has determined that Regulus is a variable interest entity for which Isis is the primary beneficiary. As a result, beginning in the third quarter of 2007, Isis included the financial condition and results of operations of Regulus in its condensed consolidated financial statements. Additionally, the condensed consolidated financial statements include line items called "Noncontrolling Interest in Regulus Therapeutics LLC." On the Condensed Consolidated Balance Sheet, this line reflects Alnylam's minority ownership of Regulus' equity. As the joint venture progresses, this line item will be reduced by Alnylam's share of Regulus' net losses, which were $87,000 in the third quarter, until the balance becomes zero. The reductions to the Noncontrolling Interest in Regulus will be reflected in Isis' Condensed Consolidated Statement of Operations using a similar line item and will provide a positive adjustment to Isis' net income (loss) equal to Alnylam's share of Regulus' losses.

Bristol-Myers Squibb Company

In May 2007, Isis entered into a collaboration agreement with Bristol-Myers Squibb ("BMS") to discover, develop and commercialize novel 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 obligation 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 September 30, 2007, Isis has recognized revenue of $3.3 million related to the upfront licensing fee and the research funding. Isis' balance sheet at September 30, 2007 includes deferred revenue of $12.9 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, mipomersen, and two novel drugs from Isis' metabolic disease program

ISIS 325568 and ISIS 377131. In addition to providing the financial support to move these three drugs forward, the transaction allowed Isis to continue to control and manage the development of these drugs through key development milestones.

Symphony Capital formed Symphony GenIsis, capitalized with $75 million, to provide funding for the development of these three drugs in collaboration with Isis. Isis licensed to Symphony GenIsis the intellectual property for its apoB-100, GCGR and GCCR programs. Isis received an exclusive purchase option from Symphony GenIsis' investors that allowed it to reacquire the intellectual property by purchasing all of Symphony GenIsis' equity at a predetermined price.

In September 2007, Isis purchased the equity of Symphony GenIsis for $120 million, $80.4 million in cash and the remaining amount in approximately 3.4 million shares of Isis' common stock. Isis granted OMI, as part of the collaboration agreement, worldwide development and commercialization rights to two of its diabetes drugs, ISIS 325568 and ISIS 377131 plus up to four antisense drugs. ISIS 325568 and ISIS 377131 were previously held by Symphony GenIsis. In addition, Isis has reaquired full ownership of mipomersen, its cholesterol-lowering drug targeting apolipoprotein B-100. The $125.3 million on Isis' Condensed Consolidated Statement of Operations in a line item called Excess Purchase Price over Carrying Value of Noncontrolling Interest in Symphony GenIsis, Inc. represents a deemed dividend to the previous owners of Symphony GenIsis. A portion of the $125.3 million reflects the significant increase in Isis' stock price used to calculate the value of the shares issued to Symphony Capital. This deemed dividend only impacts Isis' net loss applicable to common stock and its net loss per share calculations and does not affect Isis' net income (loss).

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 prior to the acquisition in September 2007, Symphony GenIsis was a variable interest entity for which Isis was the primary beneficiary. As a result, Isis included 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. From the inception of the collaboration to the acquisition of Symphony GenIsis on September 27, 2007, this line item was reduced by Symphony GenIsis' expenditures, which were $46.2 million. 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 nine months ended September 30, 2007, Isis' net loss was reduced by $8.7 million and $23.2 million, respectively, compared to $6.7 million and $20.3 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 resulting from 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. In addition to the collaboration agreement, Isis has entered into a target validation agreement with Pfizer. Under the terms of the collaboration agreement, Isis received an upfront technology access fee of $1.0 million and amortized this amount over the one year period of Isis' performance, which ended in April 2006, based on the research plan included in the agreement. There were no changes in Isis' period of performance. Isis' balance sheet as of September 30, 2007 and December 31, 2006 included deferred revenue of $60,000 and $0, respectively, related to Isis' agreements with Pfizer. As of September 30, 2007, Isis has earned milestone payments totaling $1.2 million under the collaboration agreement. Pfizer will also pay Isis additional milestone payments under the collaboration agreement 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, under the collaboration agreement, Isis will receive royalties on the sale of drugs resulting from the collaboration. For the nine months ended September 30, 2007 and 2006, Isis earned revenue of $385,000 and $533,000, respectively. Isis did not recognize any revenues for the three months ended September 30, 2007 and 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 inflammatory 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 to focus on a select number of targets. During the extension, Isis and Lilly will 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 September 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. Isis' balance sheet as of September 30, 2007 and December 31, 2006 included deferred revenue of $156,000 and $0, respectively. 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 nine months ended September 30, 2007, Isis earned revenue from its relationship with Lilly totaling $300,000 and $402,000, respectively, compared to $30,000 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 nine months 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 nine months 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' and ATL's joint antisense drug discovery and development collaboration, which Isis extended for an additional two years in January 2007. 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, 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. Isis' balance sheet as of September 30, 2007 and December 31, 2006 include deferred revenue of $250,000 and $0, respectively. For the three and nine months ended September 30, 2007, Isis recorded revenue of $3,000 and $58,000, respectively, related to this collaboration compared to $148,000 and $503,000 for the same periods in 2006. As of September 30, 2007, Isis' ownership percentage in ATL, including 10.3 million shares Isis purchased subsequent to shares it acquired in ATL's initial public offering, was less than 10%. Isis' balance sheet at September 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 nine months 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 $22.0 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 September 2007, Isis received a $1.25 million milestone payment in the form of equity securities in iCo which it has recognized a full valuation allowance for as the realization of this asset is uncertain. The milestone was related to the initiation of Phase 1 clinical trials of iCo 007.

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 September 30, 2007 and December 31, 2006. During the first nine months 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 nine months 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 September 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 September 30, 2007, OncoGenex had not triggered any of the milestone payments related to OGX-427.

For the three and nine months ended September 30, 2007, Isis earned revenue of $0 and $4,000, respectively, related to its collaboration with OncoGenex compared to $63,000 and $1.2 million for the same periods in 2006. Isis' balance sheet at September 30, 2007 and December 31, 2006 included 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 nine months 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's 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 September 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 September 30, 2007, Isis has earned a total of $31.5 million from Alnylam resulting from sublicenses of Isis' technology for the development of RNA interference therapeutics that Alnylam has granted to pharmaceutical partners, including $26.5 million resulting from Alnylam's sublicense of Isis' techonology to Roche, which Isis recognized in the third quarter of 2007.

As of September 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 nine months of 2007 and 2006, Isis sold portions of its Alnylam stock for cash proceeds of $5.2 million and $4.4 million, respectively. For the three and nine months ended September 30, 2007, Isis earned revenue of $26.5 million from Alnylam compared to $750,000 for the same periods in 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 nine months 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 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 September 30, 2007 and December 31, 2006, Isis' ownership interest in Santaris was less than 10%. Isis' balance sheet at September 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 nine months 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 sheet at September 30, 2007 and December 31, 2006 reflected a licensing asset, net of amortization, of $16.2 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 nine months ended September 30, 2007, Isis earned revenue of $0 and $10,000, respectively, 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. For the three and nine months ended September 30, 2007, Isis earned revenue of $0 related to its relationship with IDT compared to $0 and $20,000 for the same periods in 2006.

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 as of September 30, 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 nine months of 2007 and 2006, Isis did not recognize any revenue from its relationship with DRC. In October 2007, Isis received a total of $8 million as the final purchase price installment which was due under the agreement as a resolution for the various alleged competing breaches between Isis and DRC. DRC paid Isis $7 million subject to the terms of an amendment to the agreement and an unaffiliated third party paid Isis $1 million.

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 September 30, 2007, DRC has received $6.1 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.

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 nine months 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 nine months ended September 30, 2007, Isis recognized $700,000 and $1.8 million, respectively, relating to this contract, compared to $151,000 for the same periods in 2006. 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 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 September 2007, Ibis was awarded three new government contracts totaling up to $2.6 million to advance the detection and identification of microbial threat agents for biodefense applications. Two of these contracts are from the Department of Homeland Security Science and Technology Directorate ("DHS-S&T") and total up to approximately $1.7 million and a third contract, worth up to $0.9 million, is from the Defense Threat Reduction Agency ("DTRA"), an agency within the Department of Defense. As part of the contracts awarded by DHS-S&T, Ibis will continue to develop broad biological applications to identify and characterize important bacterial and viral agents that are considered crucial to maintain homeland security. Under the DTRA contract, Ibis will broaden its core technology in the area of biodefense through advances in sample preparation to allow detection of trace amounts of broad groups of microbial agents.

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 September 2007, Ibis received a new government contracts for up to $1.6 million from DHS-S&T to advance the application of the Ibis T5000 system in microbial forensics.

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 September 2007, Ibis received a grant for up to $1.2 million from the NIH to aid in influenza surveillance research through application of the Ibis T5000 Biosensor System. The NIH grant, applied for jointly by Ibis and the Lovelace Respiratory Research Institute ("LRRI") and subcontracted to Ibis by LRRI, provides funding for research studies, including assay development, and sample characterization in order to expand the understanding of transmission of influenza viruses, including the highly pathogenic H5N1 avian influenza viral strain.

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 was granted funding for the second and third phases of the grant, which included 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's 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.

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 September 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 September 30, 2007				
Revenue:				
Research and development	$ 7,283	$ 3,589	$ —	$ 10,872
Commercial revenue (1)	—	1,049	—	1,049
Licensing and royalty	26,710	—	—	26,710
Total segment revenue	$ 33,993	$ 4,638	$ —	$ 38,631
Income (Loss) from operations	$ 11,305	$ (1,248)	$ —	$ 10,057

	Drug Discovery and Development	Ibis	Corporate	Total
Three Months Ended September 30, 2006				
Revenue:				
Research and development	$ 330	$ 1,988	$ —	$ 2,318
Commercial revenue (1)	—	151	—	151
Licensing and royalty	784	—	—	784
Total segment revenue	$ 1,114	$ 2,139	$ —	$ 3,253
Income (Loss) from operations	$ (16,888)	$ (1,654)	$ 279	$ (18,264)
Nine Months Ended September 30, 2007				
Revenue:				
Research and development	$ 9,299	$ 5,615	$ —	$ 14,914
Commercial revenue (1)	—	2,490	—	2,490
Licensing and royalty	27,489	—	—	27,489
Total segment revenue	$ 36,788	$ 8,105	$ —	$ 44,893
Loss from operations	$ (23,253)	$ (7,252)	$ —	$ (30,505)
Nine Months Ended September 30, 2006				
Revenue:				
Research and development	$ 3,513	$ 7,596	$ —	$ 11,109
Commercial revenue (1)	—	151	—	151
Licensing and royalty	1,327	—	—	1,327
Total segment revenue	$ 4,840	$ 7,747	$ —	$ 12,587
Income (Loss) from operations	$ (48,185)	$ (3,654)	$ 457	$ (51,382)

(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 September 30,		Nine Months Ended September 30,	
	2007	2006	2007	2006
Partner A	69%	23%	59%	6%
Partner B	13%	0%	11%	0%
Partner C	5%	23%	7%	22%
Partner D	3%	28%	7%	17%
Partner E	1%	5%	1%	16%

For the three months ended September 30, 2007 and 2006, Isis derived approximately 12% and 66%, respectively, of its revenue from agencies of the United States Government compared to 18% and 62% for the nine months ended September 30, 2007 and 2006, respectively. For the first nine months of 2007, three of the five significant partners listed above represent revenue from agencies of the United States Government.

Contract receivables from three significant partners comprised approximately 53%, 21% and 10% of contract receivables at September 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., our Ibis Biosciences subsidiary and our Regulus Therapeutics joint venture. 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 SEC, and those identified within this Item entitled "Risk Factors" beginning on page 40 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 $109.8 million from our intellectual property licensing

program that helps support our internal drug discovery and development programs, included in this amount is the $26.5 million we received from Alnylam resulting from Alnylam's sublicense of our technology to Roche.

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 18 drugs in development. Our partners are licensed to develop, with our support, 14 of these 18 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 September 30, 2007, we had earned $65.1 million in revenue under our government contracts and grants, and we had an additional $6.9 million committed under our existing contracts and grants.

Recent Events

CHDI, Inc.

In November 2007, we announced that CHDI will provide up to $9.9 million in funding to us for the discovery and development of an antisense drug for the treatment of Huntington's Disease, a fatal neurodegenerative disease. CHDI's funding builds upon an earlier successful collaboration between us and

CHDI, in which CHDI funded proof-of–concept studies that demonstrated the feasibility of using antisense drugs to treat Huntington's Disease.

Altair Therapeutics Inc.

In October 2007, Altair, a new venture capital-funded biotechnology company, was created to focus on the discovery, development and commercialization of our antisense drugs to treat asthma and other respiratory conditions. We granted an exclusive worldwide license to Altair for the development and commercialization of ISIS 369645, an inhaled inhibitor of the IL-4/IL-13 signaling pathways for the treatment of asthma. We and Altair will also be collaborating to discover drugs directed to other promising targets for the treatment of respiratory conditions. We own 18 percent of Altair in the form of preferred stock. Furthermore, as ISIS 369645 and other drugs arising out of the research collaboration progress, Altair will pay us additional license fees and royalties.

Ibis Collaborations

In September 2007, Ibis was awarded four new government contracts totaling up to $4.2 million to advance the detection and identification of microbial threat agents for biodefense applications. Three of these contracts are from DHS-S&T and total up to approximately $3.3 million and a fourth contract, worth up to $0.9 million, is from DTRA. These contracts will fund Ibis' planned development of advanced sample preparation methodologies and validation of applications on the Ibis T5000 for broad biological weapon detection, the advancement of Ibis' microbial forensics applications, and the enhancement of Ibis' microbial database.

Additionally, in September 2007, Ibis received a grant for up to $1.2 million from the NIH to aid in influenza surveillance research through application of the Ibis T5000 Biosensor System. The NIH grant, applied for jointly by Ibis and the LRRI and subcontracted to Ibis by LRRI, provides funding for research studies, including assay development, and sample characterization in order to expand the understanding of transmission of influenza viruses, including the highly pathogenic H5N1 avian influenza viral strain.

iCo Therapeutics

In September 2007, we received a $1.25 million milestone payment in the form of equity securities in iCo. The milestone was related to the initiation of Phase 1 clinical trials of iCo 007, a drug licensed to iCo by us in 2005 for the treatment of various eye diseases, including diabetic macular edema.

National Institutes of Health

In September 2007, we received a multi-year Phase 2 SBIR grant by the NIH for up to $1.5 million to design oligonucleotide drugs that can exploit the RNAi antisense mechanism for disease treatment. The Phase 2 grant builds upon a successfully completed Phase 1 program that demonstrated the feasibility of using single-stranded antisense drugs to target the RNAi pathway.

The multi-year grant will fund research by us to improve the stability and tissue distribution of RNAi drugs. Much of the work will focus on optimizing the chemical properties of single-stranded oligonucleotides that trigger the RNAi pathway.

In addition to demonstrating that compounds optimized with our chemistries produce superior results in animal models when compared to unoptimized compounds, the grant funds the discovery of RNAi-based drugs.

Ortho-McNeil, Inc.

In September 2007, we entered into a collaboration with OMI, a Johnson & Johnson company, to discover, develop and commercialize antisense drugs to treat metabolic diseases, including Type 2 diabetes. As part of the collaboration, we granted OMI worldwide development and commercialization rights to two of our diabetes drugs, ISIS 325568 and ISIS 377131, which selectively inhibit the production of GCGR and GCCR, respectively. Additionally, OMI will provide funding to us to support a focused research program in metabolic disease. After the initial collaboration phase, Johnson & Johnson Pharmaceutical Research & Development, L.L.C. will continue development of these drugs.

Under the terms of the agreement, OMI paid us a $45 million upfront licensing fee, and will provide us with research and development funding over the period of the collaboration. In addition to the licensing fee, we could receive over $225 million in milestone payments upon successful development and regulatory approvals of ISIS 325568 and ISIS 377131, as well as royalties on sales. We could also receive milestones and royalties on the successful development and regulatory approvals of additional drugs discovered as part of the collaboration. In September 2007, we earned a milestone payment of $5 million for achieving the first development milestone by initiating the Phase 1 clinical trial of ISIS 325568.

In connection with this transaction, we purchased all of the equity in Symphony GenIsis, Inc. and reacquired the intellectual property related to the GCGR and GCCR programs as well as regaining full ownership of mipomersen, our lipid-lowering drug targeting Apolipoprotein B-100. As part of the $120 million Symphony GenIsis purchase price, we paid Symphony Capital $80.4 million in cash and the remaining amount in approximately 3.4 million shares of our common stock.

Regulus Therapeutics LLC

In September 2007, we and Alnylam launched Regulus, a joint venture focused on the discovery, development, and commercialization of microRNA therapeutics. Because microRNAs regulate whole networks of genes that can be involved in discrete disease processes, microRNA therapeutics represent a new approach to target the pathways of human disease. Regulus will combine the strengths and assets of Alnylam's and our technologies, know-how, and intellectual property with strong leadership from a focused management team and Scientific Advisory Board to be chaired by Nobel laureate David Baltimore and include key pioneers in the microRNA field.

Both we and Alnylam granted Regulus exclusive licenses to their intellectual property for microRNA therapeutic applications, as well as certain early fundamental patents in the microRNA field including the "Tuschl III" patent. Alnylam made an initial investment of $10 million to balance venture ownership; thereafter Alnylam and us will share funding of Regulus. Regulus is operating as an independent company with a separate Board of Directors and

management team. Alnylam and us will retain rights to develop and commercialize on pre-negotiated terms microRNA therapeutic products that Regulus decides not to develop either itself or with a partner.

Archemix

In August 2007, we entered into a new strategic alliance with Archemix 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 third quarter of 2007, we earned licensing revenue of $26.5 million resulting from Alnylam's sublicense of our technology for the development of RNA interference therapeutics to Roche. This payment is according to the terms of the 2004 strategic alliance agreement between Alnylam and us, under which Alnylam obtained an exclusive license to our intellectual property for double-stranded oligonucleotide therapeutics that mediate RNAi. Additionally, during the second quarter of 2007, 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.

Mipomersen Development Highlights

At the Drugs Affecting Lipid Metabolism (DALM) Symposium, we announced further data supporting the attractive profile of mipomersen:

- Mipomersen effectively reduces lipids in all patient populations tested. Data presented in heterozygous familial hypercholesterolemia patients at DALM adds to the previously presented data for homozygous familial hypercholesterolemia and routine high cholesterol in showing potent, dose dependent, linear decrease in lipids alone and in combination with other lipid lowering therapies.

- Mipomersen has a unique profile in lowering all atherogenic lipids. Adding to data previously presented showing statistically significant reductions of low-density lipoproteins, very low-density lipoproteins and triglycerides. Data presented at DALM showed statistically significant reductions of lipoprotein (a), an independent cardiovascular risk factor.

- We presented the first safety data from long-term treatment with mipomersen showing that, as predicted by long term studies in monkeys and mice, the drug continues to be well tolerated in patients treated for five months and longer.

- We presented preclinical data showing that inhibition of ApoB-100 (the target of mipomersen) results in changes in fat metabolism that reduce liver fat, adding additional mechanistic support for the mipomersen safety profile.

- We initiated a Phase 3 program for mipomersen in patients with familial hypercholesterolemia.

Issuance of 2 5/8% Convertible Subordinated Notes; Repurchase of 5 1/2% Convertible Subordinated Notes

In January 2007, we issued $162.5 million of 2 5/8% convertible subordinated notes due 2027. Using the net proceeds from the issuance of the 2 5/8 % notes, we repurchased our 5 1/2% convertible subordinated notes due 2009. The significantly lower interest rate of the 2 5/8% notes reduces our cash interest payments by approximately $2.6 million annually. In addition, the extended maturity date of the 2 5/8% 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., BMS, Lilly, OncoGenex, OMI 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. 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. Additionally, in September 2007, we earned a $5 million milestone payment for the initiation of a Phase 1 trial for ISIS 325568 under our recently announced collaboration with OMI. Since the milestone was achieved before the contract was finalized, the $5 million is treated as an upfront licensing fees and it will be amortized over the two year period of our performance obligation.

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 nine months 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 nine months 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 $550,000 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. We determined that there were no other-than-temporary declines in value of investments in the first nine months of 2007.

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 $515,000 and $2.2 million for the first nine months 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 nine months ended September 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 September 30, 2007, there was $11.6 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 1.3 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 nine months 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.

We record stock options granted to non-employees at their fair value in accordance with the requirements of SFAS 123, *Accounting for Stock-Based Compensation*, then periodically remeasure them in accordance with EITF 96-18, *Accounting for Equity Instruments that are Issued to Other Than Employees for Acquiring, or in Conjunction with Selling, Goods or Services*, and recognize them over the service period.

Results of Operations

Revenue

Total revenue for the three and nine months ended September 30, 2007 was $38.6 million and $44.9 million, respectively, compared to $3.3 million and $12.6 million for the same periods in 2006. Revenue was higher in 2007 compared to 2006 due to the $26.5 million licensing revenue that we earned from Alnylam in the third quarter of 2007 and revenue associated with our collaboration with BMS, which began in May 2007 and OMI, which began in September 2007.

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. For example, we recorded the $26.5 million of licensing revenue from Alnylam in the current quarter, without similar revenue in the third quarter of 2006.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2007	2006	2007	2006
Drug Discovery and Development:				

Research and development revenue	$ 7,283	$ 330	$ 9,299	$ 3,513
Licensing and royalty revenue	26,710	784	27,489	1,327
	$ 33,993	$ 1,114	$ 36,788	$ 4,840
Ibis Biosciences:				
Research and development revenue	$ 3,589	$ 1,988	$ 5,615	$ 7,596
Commercial revenue (1)	1,049	151	2,490	151
	$ 4,638	$ 2,139	$ 8,105	$ 7,747
Total Revenue:				
Research and development revenue	$ 10,872	$ 2,318	$ 14,914	$ 11,109
Commercial revenue (1)	1,049	151	2,490	151
Licensing and royalty revenue	26,710	784	27,489	1,327
	$ 38,631	$ 3,253	$ 44,893	$ 12,587

(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 nine months ended September 30, 2007 was $7.3 million and $9.3 million, respectively, compared to $330,000 and $3.5 million for the same periods in 2006. The increase reflects revenue associated with our collaboration with BMS and OMI offset by a decrease in revenue associated with our collaborations with Lilly and OncoGenex. 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 nine months ended September 30, 2007 was $26.7 million and $27.5 million, respectively, compared to $784,000 and $1.3 million for the same periods in 2006. The increase was primarily a result of the $26.5 million licensing revenue that we earned from Alnylam in the third quarter of 2007.

Ibis Biosciences, Inc.

Ibis' revenue for the three and nine months ended September 30, 2007 was $4.6 million and $8.1 million, respectively, compared to $2.1 million and $7.7 million for the same periods in 2006. Ibis earned commercial revenue of $1.0 million and $2.5 million for the three and nine months ended September 30, 2007, respectively, compared to $151,000 for each of the same periods in 2006, which consisted of revenue from sales of Ibis' T5000 Biosensor Systems and assay kits, as well as revenue from Ibis' assay services business. Because Ibis provides a full year of support for each Ibis T5000 Biosensor System following installation, Ibis is amortizing the revenue for each instrument sold over the period of this support obligation. Primarily as a result of the growing number of T5000 Biosensor System placements in 2007, commercial revenue in the third quarter of 2007 increased by 30% over the second quarter of 2007, building on a trend of increased commercial revenue quarter over quarter since the third quarter of 2006 when Ibis began earning commercial revenue. Additionally, Ibis generated revenue from its government contracts and grants of $3.6 million and $5.6 million, respectively, for the three and nine months ended September 30, 2007 compared to $2.0 million and $7.6 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. Recently Ibis received contracts and grants for up to $5.4 million to fund the development of a wide variety of applications for the Ibis T5000 Biosensor System. There was a transient decline in contract revenue for the nine months ended September 30, 2007 compared to the same period in 2006 as a

result of timing of the initiation of these new contracts. We expect that revenue from government contracts will continue to provide a solid revenue base going forward.

From inception through September 30, 2007, Ibis has earned $65.1 million in revenue from various government agencies to further the development of our Ibis T5000 Biosensor System and related assay kits. An additional $6.9 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

In 2007, with the successful progression of the drugs in our pipeline, we have expanded our clinical development programs. Additionally, we have built the manufacturing, marketing and sales infrastructure to commercialize the Ibis T5000 Biosensor System. These activities have led to an increase in operating expenses for the three and nine months ended September 30, 2007. Operating expenses for the three and nine months ended September 30, 2007 were $28.6 million and $75.4 million, respectively, compared to $21.5 million and $64.0 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 $2.5 million and $7.2 million for the three and nine months ended September 30, 2007, respectively, compared to $1.4 million and $4.2 million for the same periods in 2006, primarily reflecting the significant 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 September 30,		Nine Months Ended September 30,	
	2007	2006	2007	2006
Research and development expenses	$ 22,340	$ 17,882	$ 58,795	$ 52,979
Non-cash compensation expense related to stock options	1,956	1,091	5,834	3,348
Total research and development expenses	$ 24,296	$ 18,973	$ 64,629	$ 56,327

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2007	2006	2007	2006
Drug Discovery and Development	$ 19,738	$ 15,915	$ 52,623	$ 46,715
Ibis Biosciences	4,558	3,058	12,006	9,612
Total research and development expenses	$ 24,296	$ 18,973	$ 64,629	$ 56,327

For the three and nine months ended September 30, 2007, we incurred total research and development expenses, excluding stock compensation, of $22.3 million and $58.8 million, respectively, compared to $17.9 million and $53.0 million for the same periods in 2006. The increase is attributable to the expansion of the development of our key programs and the additional costs required to commercialize the Ibis T5000 Biosensor System.

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 $3.6 million and $10.1 million, respectively, for the three and nine months ended September 30, 2007 compared to $2.9 million and $9.1 million for the same periods in 2006. The higher expenses in 2007 were primarily due to increased activity levels which includes an increase in headcount and usage of lab supplies. We anticipate antisense drug discovery costs to increase in the near-term due to research efforts conducted by Regulus, which are consolidated into our financial results.

Antisense Drug Development

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2007	2006	2007	2006
Alicaforsen for Crohn's disease	$ —	$ 3	$ —	$ 5
Other antisense development products	6,567	4,565	16,446	13,993
Development overhead costs	1,850	617	4,177	2,745
Non-cash compensation expense related to stock options	693	361	2,033	1,076
Total antisense drug development	$ 9,110	$ 5,546	$ 22,656	$ 17,819

Antisense drug development expenditures were $8.4 million and $20.6 million, excluding non-cash compensation expense for the three and nine months ended September 30, 2007 compared to $5.2 million and $16.7 million for the same periods in 2006. The increase was primarily attributed to the expansion of our clinical development 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 mipomersen, which has led to an increase in development costs in 2007 compared to 2006. Development overhead costs were $1.9 million and $4.2 million, respectively, for the three and nine months ended September 30, 2007 compared to $617,000 and $2.7 million for the same periods in 2006. The increase in overhead costs was a result of the additional expenses needed to support the expansion of our clinical development programs.

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, 14 of our 18 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 nine months ended September 30, 2007 were $2.1 million and $5.0 million, respectively, compared to $1.4 million and $4.4 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. The increase was primarily due to the additional expenses required for the expansion of our key programs along with additional costs associated with the manufacturing of drug supplies for our corporate partners.

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 September 30,		Nine Months Ended September 30,	
	2007	2006	2007	2006
Research and development costs	$ 3,677	$ 2,315	$ 9,121	$ 7,198
R&D support costs	601	569	2,000	1,856
Non-cash compensation expense related to stock options	280	173	885	558
Total Ibis' research and development expenses	$ 4,558	$ 3,057	$ 12,006	$ 9,612

Ibis' research and development expenses, excluding non-cash compensation expense related to stock options, for the three and nine months ended September 30, 2007 were $4.3 million and $11.1 million, respectively, compared to $2.9 million and $9.1 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 September 30,		Nine Months Ended September 30,	
	2007	2006	2007	2006
Personnel costs	$ 1,602	$ 1,405	$ 4,606	$ 4,403
Occupancy	1,546	1,553	4,524	4,480
Depreciation and amortization	1,193	2,692	3,584	5,267
Insurance	227	255	715	775
Other	305	203	1,219	842
Non-cash compensation expense related to stock options	188	120	558	365
Total R&D support costs	$ 5,061	$ 6,228	$ 15,206	$ 16,132

R&D support costs excluding non-cash compensation expense for the three and nine months ended September 30, 2007 were $4.9 million and $14.6 million, respectively, compared to $6.1 million and $15.8 million for the same periods in 2006. The decrease from 2006 to 2007 was a result of a decrease in patent application costs that were abandoned and written-off during the first nine months of 2006 offset by an increase in additional expenses to support the continued development of our key programs.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2007	2006	2007	2006
Drug Discovery and Development	$ 4,460	$ 5,659	$ 13,206	$ 14,276
Ibis Biosciences	601	569	2,000	1,856
Total R&D support costs	$ 5,061	$ 6,228	$ 15,206	$ 16,132

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. Until the acquisition of Symphony GenIsis in September 2007, selling, general and administrative expenses also included Symphony GenIsis' general and administrative expenses.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2007	2006	2007	2006
Selling, general and administrative expenses	$ 3,779	$ 2,497	$ 9,395	$ 7,257
Non-cash compensation expense related to stock options	499	326	1,374	842
Total selling, general and administrative expenses	$ 4,278	$ 2,823	$ 10,769	$ 8,099

Selling, general and administrative expenses, excluding non-cash compensation expense related to stock options, for the three and nine months ended September 30, 2007 were $3.8 million and $9.4 million, respectively, compared to $2.5 million and $7.3 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 September 30,		Nine Months Ended September 30,	
	2007	2006	2007	2006
Drug Discovery and Development	$ 2,950	$ 2,087	$ 7,418	$ 6,310
Ibis Biosciences	1,328	736	3,351	1,789
Total selling, general and administrative expenses	$ 4,278	$ 2,823	$ 10,769	$ 8,099

Restructuring Activities

During the three and nine months ended September 30, 2006, we recorded a benefit of $279,000 and $457,000, 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 nine months ended September 30, 2006. Additionally in the third quarter of 2006, we negotiated a lease termination agreement with the landlord of a building that we vacated in 2005 as part of the restructuring activities. The early termination of the lease resulted in a benefit of approximately $350,000 over what was previously accrued. This benefit is reflected in the restructuring activities for the three and nine months ended September 30, 2006. There were no restructuring activities in the first nine months of 2007.

Investment Income

Investment income for the three and nine months ended September 30, 2007 totaled $2.6 million and $9.1 million, respectively, compared to $1.7 million and $3.8 million for the same periods in 2006. The increase in investment income was primarily due to a higher average cash balance during the first nine months of 2007 compared to the same period in 2006 as a result of the proceeds we received from the issuance of our 2 5/8% convertible subordinated notes, the $15 million upfront licensing fee that we received from our strategic partnership with BMS and the $26.5 million licensing fee received from Alnylam, offset by the repayment of our 5 ½% notes and the $80.4 million payment for the acquisition of Symphony GenIsis.

Interest Expense

Interest expense for the three and nine months ended September 30, 2007 totaled $1.5 million and $6.1 million, respectively, compared to $2.3 million and $6.8 million for the same periods in 2006. The decrease in interest expense is primarily because the 5 ½% notes were fully repaid in the first half of 2007 and the 2 5/8% notes issued in early 2007 have a lower interest rate.

Gain on Investments, net

Gain on investments for the first nine months ended September 30, 2007 was $3.5 million compared to $2.3 million for the same period in 2006. The 2007 gain on investments reflected a gain realized on the sale of the remaining equity securities of Alnylam that we owned compared to the 2006 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 nine months ended September 30, 2007 was $3.2 million. The loss on early retirement of debt reflected the early extinguishment of our 5 ½% convertible subordinated notes in the first half of 2007. As a result of the repayment of the 5 ½% 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 nine months of 2006.

Net income (loss)

Net income for the three months ended September 30, 2007 was $20.0 million and net loss for the nine months ended September 30, 2007 was $4.0 million compared to net loss of $12.1 million and $31.8 million for the same periods in 2006. We recognized a benefit of $8.7 million and $23.2 million for the three and nine months ended September 30, 2007, respectively, in the loss attributed to noncontrolling interest in Symphony GenIsis, Inc., resulting from our collaboration with

Symphony GenIsis. In 2006, the loss attributed to noncontrolling interest in Symphony GenIsis was $6.7 million and $20.3 million for the three and nine months ended September 30, 2006, respectively. Net loss for the first nine months of 2007 was lower compared to the same period in 2006 because of a decrease in loss from operations, higher interest income, a net gain on investments and benefit related to the loss attributed to noncontrolling interest in Symphony GenIsis, Inc. offset by the loss on early retirement of debt.

Net Loss Applicable to Common Stock

Net loss applicable to common stock for the three and nine months ended September 30, 2007 was $105.3 million and $129.3 million, respectively, compared to $12.1 million and $31.8 million for the same periods in 2006.

In September 2007, we purchased the equity of Symphony GenIsis at the pre-negotiated price of $120 million, which we paid with $80.4 million in cash and approximately 3.4 million shares of our common stock. The $125.3 million on our Condensed Consolidated Statement of Operations in a line item called Excess Purchase Price over Carrying Value of Noncontrolling Interest in Symphony GenIsis, Inc. represents a deemed dividend paid to the previous owners of Symphony GenIsis. A portion of the $125.3 million reflects the significant increase in our stock price used to calculate the value of the shares issued to Symphony Capital. This deemed dividend only impacts our net loss applicable to common stock and our net loss per share calculations and does not affect our net income (loss).

Net Loss Per Share

Net loss per share for the three and nine months ended September 30, 2007 was $1.25 per share and $1.57 per share, respectively, compared to $0.16 per share and $0.44 per share for the same periods in 2006. The increase in net loss per share was a result of the increase in net loss applicable to common stock discussed above.

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 September 30, 2007, we have earned approximately $552.6 million in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through September 30, 2007, we have raised net proceeds of approximately $735.3 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 September 30, 2007, we had cash, cash equivalents and short-term investments of $146.0 million, which included $10 million of cash and cash equivalents held on behalf of Regulus, consolidated working capital of $131.4 million and stockholders' equity of $232,000. Additionally, in the fourth quarter of 2007, we received approximately $52 million as payment for the $45 million upfront licensing fee, the $5 million milestone for the initiation of Phase 1 studies for ISIS 325568 and initial research and development funding associated with our recently announced collaboration with OMI. This $52 million is not reflected in our cash balance at September 30, 2007. 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 decrease in our cash, cash equivalents and short-term investments primarily reflects the $80.4 million payment for the acquisition of Symphony GenIsis and cash used in operations offset by the net cash received from the issuance of our 2 $^{5}/_{8}$% notes after repayment of the 5 $^{1}/_{2}$% notes, the $15 million upfront licensing fee from BMS for our strategic partnership and the $26.5 million licensing fee from Alnylam.

As of September 30, 2007, our debt and other obligations totaled $172.2 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 $^{5}/_{8}$% convertible subordinated notes offset by the repayment of the 5 $^{1}/_{2}$% notes and the declining balance on our Silicon Valley Bank term loan. The significantly lower interest rate of the 2 $^{5}/_{8}$% convertible subordinated notes from that of our recently repaid 5 $^{1}/_{2}$% 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 September 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**
2 5/8% Convertible Subordinated Notes	162.5	—	—	—	162.5
Silicon Valley Bank Term Loan	9.0	7.1	1.9	—	—
Capital Lease and Other Obligations	0.7	0.3	—	—	0.4
Operating Leases	21.2	2.9	5.5	3.4	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 7.0% at September 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 September 30, 2007 was $9.0 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 2 5/8%, which is payable semi-annually, and mature in 2027. The 2 5/8% 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 2 5/8% notes are also able to require us to repurchase the 2 5/8% 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 2 5/8% notes being repurchased plus accrued interest and unpaid interest. Using the net proceeds from the issuance of our 2 5/8% notes, we repaid the entire $125 million of our 5 1/2% convertible subordinated notes due 2009.

In addition to contractual obligations, we had outstanding purchase orders as of September 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 September 30, 2007, we had accumulated losses of approximately $820.8 million and stockholders' equity of approximately $232,000. 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, 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 mipomersen 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 Altair Therapeutics, Inc., Antisense Therapeutics Limited, Atlantic Healthcare, iCo Therapeutics, Inc., ImQuest Pharmaceuticals, Inc., Lilly, Merck & Co., Inc., OncoGenex Technologies Inc. and Ortho-McNeil, Inc. 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 September 30, 2007, the market price of our common stock ranged from $7.06 to $15.52 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.

The accounting method for our convertible debt securities may be subject to change.*

A convertible debt security providing for share and/or cash settlement of the conversion value and meeting specified requirements under EITF Issue No. 00-19, *Accounting for Derivative Financial Instruments Indexed to, and Potentially Settled in, a Company's Own Stock*, including our outstanding convertible debt securities, is currently classified in its entirety as debt. No portion of the carrying value of such a security related to the conversion option indexed to the issuer's stock is classified as equity. In addition, interest expense is recognized at the stated coupon rate. The coupon rate of interest for convertible debt securities, including our convertible debt securities, is typically lower than what an issuer would be required to pay for nonconvertible debt with otherwise similar terms.

The EITF recently considered whether the accounting for convertible debt securities that requires or permits settlement in cash either in whole or in part upon conversion ("cash settled convertible debt securities") should be changed, but was unable to reach a consensus and discontinued deliberations on this issue. Subsequently, in July 2007, the FASB voted unanimously to reconsider the current accounting for cash settled convertible debt securities, which includes our convertible debt securities. In August, the FASB exposed for public comment a proposed FASB Staff Position ("FSP") that would change the method of accounting for such securities and would require the proposed method to be retrospectively applied. The FSP, if issued as proposed, would become effective for calendar year end companies like us in the first quarter of 2008. Under this proposed method of accounting, the debt and equity components of our convertible debt securities would be bifurcated and accounted for separately in a manner that would result in recognizing interest on these securities at effective rates more comparable to what we would have incurred had we issued nonconvertible debt with otherwise similar terms. The equity component of our convertible debt securities would be included in the paid-in-capital section of stockholders' equity on our balance sheet and, accordingly, the initial carrying values of these debt securities would be reduced. Our net income for financial reporting purposes would be reduced by recognizing the accretion of the reduced carrying values of our convertible debt securities to their face amounts as additional non-cash interest expense. Therefore, if the proposed method of accounting for cash settled convertible debt securities is adopted by the FASB as described above, it would have an adverse impact on our past and future reported financial results.

We cannot predict the outcome of the proposed FSP. We also cannot predict any other changes in GAAP that may be made affecting accounting for convertible debt securities, some of which could have an adverse impact on our past or future reported financial results.

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 mipomersen 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 mipomersen 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 mipomersen and ISIS 113715. Failure to receive these approvals or delays in these approvals could prevent or delay commercial introduction of a product, including mipomersen 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 mipomersen 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 mipomersen 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 mipomersen and ISIS 113715. If any of our drugs in clinical studies mipomersen 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 mipomersen 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 mipomersen and ISIS 113715, could reduce the commercial viability of our drugs, including mipomersen and ISIS 113715.

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 mipomersen. 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 mipomersen.

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 nine months ended September 30, 2007 and 2006, we derived approximately 18% and 62%, 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 September 30, 2007. There

have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to September 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 asserted its right to terminate the sale and assignment agreement. Isis responded that in fact no breach had occurred and that DRC had no right to terminate the sale and assignment agreement. In October 2007, Isis and DRC agreed to resolve their disputes regarding various alleged competing breaches of their agreement. Isis received a total of $8 million as the final purchase price installment which was due under the assignment agreement. DRC paid Isis $7 million subject to the terms of an amendment to the agreement and an unaffiliated third party paid Isis $1 million.

On October 16, 2007 Idera Pharmaceuticals, Inc. (formerly Hybridon, Inc.) filed papers initiating an arbitration proceeding against the Company. Idera has alleged that the Company improperly sublicensed certain Idera patents which were the subject of a Collaboration and License Agreement by and between the Company and Hybridon, Inc. dated May 25, 2001. The Company has filed responsive papers and intends to vigorously defend this arbitration action. The Company believes that the Idera action is without merit and further believes that the potential for damages from this action is not probable or estimable at this time.

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

Not applicable

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

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

Not applicable

ITEM 5. OTHER INFORMATION

Not applicable

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Collaboration and License Agreement between the Registrant and Ortho-McNeil, Inc. dated September 12, 2007 (with

certain confidential information deleted).

10.2	License and Collaboration Agreement among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics LLC dated September 6, 2007 (with certain confidential information deleted).
10.3	Limited Liability Company Agreement of Regulus Therapeutics LLC dated September 6, 2007 (with certain confidential information deleted).
10.4	Retention Agreement dated September 21, 2007 between the Registrant and Mark K. Wedel.(1)
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.

(1) Filed as an exhibit to the Registrant's Current Report on Form 8-K dated September 27, 2007, and incorporated herein by reference.

Isis Pharmaceuticals, Inc.

(Registrant)

SIGNATURES

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

Signatures	Title	Date
/s/ Stanley T. Crooke Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	November 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)	November 8, 2007

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

ORTHO MCNEIL, INC.

COLLABORATION AND LICENSE AGREEMENT

THIS COLLABORATION AND LICENSE AGREEMENT (the ***"Agreement"***) is made and entered into this September 12, 2007 (the ***"Execution Date"***), by and between Ortho McNeil, Inc., a New Jersey Corporation (***"OMI"***) having a place of business at 1000 US Route 202, Raritan, New Jersey, 08869 and **Isis Pharmaceuticals, Inc.**, a Delaware Corporation (***"Isis"***) having a place of business at 1896 Rutherford Road, Carlsbad, California 92008. OMI 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 OMI each desire to collaborate (the ***"Collaboration"***) to conduct:

- a Development Program to advance ISIS 325568 and ISIS 377131 through human clinical trials and ultimately Commercialize them as Products; and

- a Research Program to (i) [***] and (ii) at OMI's option [***], in each case for OMI to advance into human clinical trials and ultimately Commercialize as Products.

WHEREAS, OMI will have exclusive rights to ISIS 325568 and ISIS 377131 and Products in the Research Program and (unless otherwise specified in the R&D Plan) 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, will 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 Grants to OMI.**

(a) **Exclusive License.** Subject to the terms and cond itions of this Agreement, Isis hereby grants to OMI a worldwide, exclusive license, with the right to grant sublicenses as set forth in Section 2.2(a) below, under the Product Specific Patents and Product Specific Know-How to research, develop, make, have made, use, gain regulatory approval, commercialize, sell, offer for sale, have sold, export and import Compounds and Products for all uses.

(b) **Nonexclusive License.** Subject to the terms and conditi ons of this Agreement and the limitations set forth in Section 2.4 below, Isis hereby grants to OMI a worldwide, nonexclusive license, with the right to grant sublicenses as set forth in Section 2.2 below, under the Isis Know-How, Isis Program Patents, the Isis Core Technology Patents and the Isis Manufacturing and Analytical Patents to research, develop, make, have made, use, gain regulatory approval, commercialize, sell, offer for sale, have sold, export and import Compounds and Products for all uses.

(c) **Nonexclusive License to Manufacturing Improvements**. Subject to the terms and conditions of this Agreement, the Parties grant to each a nonexclusive license to those Manufacturing Improvements provided in Sections 4.7.1 and 4.7.2, subject to the terms and restrictions set forth therein.

Section 2.2 **Sublicenses.**

(a) **All Subl icenses.** The licenses granted to OMI under Section 2.1 are sublicensable only in connection with a sublicense of a Compound or Product to any Affiliate of OMI or to any Third Party, in each case for the continued Research, Development and Commercialization of such Compound or Product in accordance with the terms of this Agreement.

(b) **Isis Manufacturing and Analytical Technology**. In addition, OMI (or its Affiliate or Licensee) may only sublicense the Isis Manufacturing and Analytical Technology, if OMI (or its Affiliate or Licensee) (i) uses appropriate precautions and includes provisions in such sublicense to protect the Isis Know-How or Product Specific Know-How such that the sublicensee will not use any Isis Know How or Product Specific Know-How to manufacture any other compounds or products for Third Parties and (ii) promptly notifies Isis in writing specifically identifying the Isis Manufacturing and Analytical Technology to be disclosed to such Third Party and identifying by name such Third Party. At Isis' reasonable request, OMI will enforce the provisions contemplated by clause (i) above against any sublicensee who is in breach of such provisions.

Section 2.3 **Exclusivity.** During the Collaboration Term and continuing thereafter so long as the exclusive license granted to OMI under Section 2.1(a) 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 whose primary mechanism of action is through its hybridization to Collaboration Gene Target mRNA or pre-mRNA or products containing such ASOs. Isis agrees that it will not work with a Third Party on research and development relating to (i) a Collaboration Gene Target or (ii) during the Research Term, a gene target that is part of the Target Pool, in each case, unless such work is conducted in performance of the R&D Plan.

Section 2.4 **License Conditions; Limitations.**

(a) During the Research Term, in order to maintain the license granted to OMI under Section 2.1, OMI must meet its obligations to fund and perform its obligations under the Research Program and Development Program in accordance with Section 3.5 and 6.2. If OMI fails to meet such obligations, Isis will have the right, consistent with and pursuant to the provisions of Section 10.3, to terminate the Agreement, including the licenses granted to OMI under Section 2.1.

(b) After the expiration of the Collaboration Term, in order to maintain the license granted to OMI under Section 2.1, on a Compound-by-Compound or Product-by-Product basis, OMI must meet its obligations to use Commercially Reasonable Efforts under Section 5.1 for the applicable Compound or Product. If OMI fails to meet its obligations to use Commercially Reasonable Efforts under Section 5.1 for a particular Compound or Product, Isis will have the right, consistent with and pursuant to the provisions of Section 10.4, to terminate the Agreement with respect to such Compound or Product, including the licenses granted to OMI under Section 2.1.

(c) The nonexclusive license and exclus ivity granted under Section 2.1(b) and 2.3 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.

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

ARTICLE 3 - COLLABORATION

Section 3.1 **Objective.** The Parties will collaborate in carrying out a program to Develop Compounds directed to the Collaboration Gene Targets and ultimately Commercialize them as Products. The Development Program is outlined in the R&D Plan and includes the conduct of the [***] for GCGR and the [***] for GCCR (the ***"Development Program"***). In addition, the Parties will collaborate in carrying out a research program to (i) [***] and (ii) at OMI's option, to [***] as provided for in the R&D Plan (the ***"Research Program"***).

Section 3.2 **R&D Plan.** The Collaboration will be carried out in accordance with a written research and development plan (the ***"R&D Plan"***) and corresponding written research and development budget (the ***"R&D Budget"***). The initial R&D Plan and R&D Budget, that have been agreed to by the Parties as of the Effective Date (as evidenced by separate signature of each Party on the cover page of the R&D Plan) are hereby incorporated by reference into this Agreement. The purpose of the R&D Plan is to detail the responsibilities and activities of Isis and OMI with respect to carrying out the Research Program and the Development Program. The R&D Plan will include a description of the specific activities to be performed by the Parties in support of the Collaboration, the estimated number of Isis FTEs to perform such activities and projected timelines for completion of such activities. The R&D Plan will include a list of subcontractors and consultants that Isis plans to use to fulfill its obligations under the R&D Plan. The R&D Budget will contain the estimated costs ([***]) associated with the tasks outlined in the R&D Plan. The R&D Plan and R&D Budget may only be amended with the unanimous approval of the R&D Committee (as permitted by the R&D Committee Charter). The R&D Plan and R&D Budget will be updated and amended from time to time, but at least annually. Therefore, [***] of each year of the Collaboration Term ([***]), the R&D Committee will review and update the R&D Plan and R&D Budget. In the event that the Parties cannot agree to updates or amendments to the R&D Plan and R&D Budget, the Parties will first pursue the dispute resolution provisions of the [***] **APPENDIX 5** and thereafter follow the provisions of section 14.4.1.

Section 3.3 **Collaboration Term.**

3.3.1 The Development Program will begin on the Effective Date and will end [***] from the Effective Date (the ***"Development Program Term"***). In the event that Isis has not completed its responsibilities under the Development Program within the Development Program Term, OMI, at its sole discretion, may elect to take sole responsibility for the Development of Compounds and Isis will cooperate fully in the transfer of data, protocols and the like to facilitate OMI's activities. The Research Program will be carried out during the period following the Effective Date and ending on the [***] of the Effective Date (the ***"Research Term"***).

3.3.2 OMI will have the option to extend the Research Term for [***] of the Effective Date unless extended per Section 3.3.4 or 3.6.2. For each extension of the Research Term, the Parties will negotiate in good faith a mutually agreed amendment and restatement of the R&D Plan and R&D Budget. For each extension, if the Parties fail to reach agreement on a mutually agreed amendment and restatement of the R&D Plan and R&D Budget by the end of the then effective Research Term, there will be no further extension to that Research Term.

3.3.3 In order to exercise its option to extend the Research Term, OMI must provide Isis a written notice exercising OMI's right to extend the Research Term at least [***]s prior to the scheduled expiration of the Research Term. If OMI does not provide such written notice, the Research Term will end when scheduled. In addition, no earlier than the [***] prior to the scheduled expiration of the Research Term, Isis may request in writing from OMI a nonbinding, good faith indication of whether or not OMI intends to extend the Research Term. In

such event, OMI will provide such nonbinding, good faith indication to Isis at least [***] prior to the scheduled expiration of the Research Term.

3.3.4 In addition, if a new gene target is designated a Selected Gene Target, as defined in Section 3.6 of this Agreement the Parties will negotiate in good faith an amendment and restatement of the R&D Plan and R&D Budget, including if necessary an extension of the Research Term to allow for completion of the planned Research on such new Selected Gene Target. If no agreement is reached on the amendment and restatement of the R&D Plan and R&D Budget under this Section 3.3.4 then the R&D Plan proposed by OMI will take effect; however, in no event will Isis be required to allocate resources from the current R&D Plan for the benefit of the amendment and restatement of the R&D Plan and R&D Budget. In any event, if Isis does not wish to participate in a Development Program for the Selected Gene Target, OMI may, at its sole option, continue to work on the Selected Gene Target through the end of the Development Program Term and proceed consistent with the provisions of Section 3.6.6.

Section 3.4 **R&D Committee.** The Parties will establish and maintain a joint research and development committee (the ***"R&D Committee"***) to oversee the conduct of the Collaboration, including, but not limited to approving any changes to the R&D Plan and R&D Budget. The R&D Committee will be established, operated and governed in accordance with the policies and procedures set forth in **APPENDIX 5** attached hereto [***] may be amended with the unanimous approval of the R&D Committee members.

As needed, the R&D Committee will establish subcommittees and working groups that will report to the R&D Committee to further the objectives of the Collaboration.

The R&D Committee and any subcommittees and working groups established by the R&D Committee will dissolve at the end of the Collaboration Term.

Section 3.5 **Collaboration Staffing; Funding; and Resources.**

3.5.1 **Staffing.** OMI will fund at the FTE Rate, and Isis will supply, Isis FTEs during the Collaboration Term to perform activities in support of and in accordance with the then-current R&D Plan.

3.5.2 **Funding; Expenses.**

(a) Within [***] of receipt of invoice from Isis in the form provided as **APPENDIX 7**, but not sooner than the Effective Date, OMI will pay Isis $[***] to reimburse Isis for the [***]. In addition, OMI will reimburse Isis for any [***] (such reimbursements to be added to and paid for under the invoice under Section 3.5.2(b) below).

(b) Within [***] of receipt of an invoice fro m Isis in the form provided as **APPENDIX 7**, but not sooner than the Effective Date, OMI will pay Isis for the OMI-funded Isis FTEs assigned to the R&D Plan in accordance with Section 3.5.1 for the period of time commencing on the Effective Date and ending on the last day of the Third Calendar Quarter of [***].

(c) Thereafter, no earlier than [***] b efore the [***] of any Calendar Quarter during the Collaboration Term, Isis will invoice OMI in the form provided as **APPENDIX 7**, and within [***] of receipt of such invoice from Isis, OMI will pay Isis for the OMI-funded Isis FTEs assigned to the R&D Plan in accordance with Section 3.5.1 for such Calendar Quarter (a prorated amount will be payable for any portion of a Calendar Quarter). Such FTE payment obligation of OMI will be subject to Isis providing such qualified FTE scientists. No later than [***] following the end of each Calendar Quarter, Isis will provide OMI with a report of the number of FTEs assigned to the Collaboration with a summary of their activities. Any overpayment by OMI may be applied by OMI to the funding of Isis FTEs in a subsequent Calendar Quarter.

(d) Isis will bear its own costs, including c osts related to research supplies, consumables and [***], in performing its obligations under the R&D Plan, *provided* that OMI will reimburse Isis for (i) [***] expenses identified in the R&D Budget (***"Program Costs"***) and

(ii) the costs of [***]. The Program Costs may include, for example, [***], but will not include routine laboratory supplies. For each project under the R&D Plan, the R&D Committee will set a budget for the Program Costs. At the end of each Calendar Quarter during the Research Term, Isis will invoice OMI in the form provided as **APPENDIX 7** for the Program Costs incurred during such Calendar Quarter, *provided, however*, that (x) for any particular item of such cost in excess of [***] of the amount allocated for such item in the budget will require the written approval of OMI prior to being incurred and (y) OMI will not be responsible for payment for those items of such cost in excess of [***] of the amount allocated for such item in the budget that are incurred by Isis without OMI's prior written consent (which consent can be made by the R&D Committee, as evidenced by written minutes). OMI will pay any correct invoices within [***] after receipt thereof. *Notwithstanding the foregoing*, in no event shall the R&D Budget exceed [***] of the budgeted costs in a Calendar Quarter without the R&D Committee's approval, *except* to the extent any Program Costs specifically allocated to a different Calendar Quarter in the R&D Budget are actually incurred in the Calendar Quarter in question.

Section 3.6 **Target Pool**. The Target Pool, as defined herein (***"Target Pool"***), identifies up to [***] gene targets including the gene targets selected for collaborative Research, Development and Commercialization under the Research Program (each such gene target is a ***"Selected Gene Target"***).

The number of Selected Gene Targets is initially limited to [***], but this limit may be increased as contemplated by clause (iii) of Section 3.6.2 below or upon mutual written agreement of the Parties. The gene targets that are part of the Target Pool (including which of such gene targets are the Selected Gene Targets and whether such gene target is in "Stage 1" or "Stage 2" under the R&D Plan) will be listed on **APPENDIX 12,** which may be updated from time to time by the Parties in accordance with this Agreement. OMI will have [***] following the Effective Date to designate the initial gene targets it wants to place in the Target Pool. In addition, OMI, at a minimum, must select the first [***] Selected Gene Targets on or before the Effective Date.

3.6.1 Target Substitution Procedures. At any time during the R esearch Term the Parties may mutually agree in writing to substitute and replace a gene target from the Target Pool for an existing Selected Gene Target. In addition, OMI can unilaterally (i.e. without Isis' agreement) substitute a gene target from the Target Pool for an existing Selected Gene Target at any time during the Research Term; *provided however*, that OMI is only allowed one such unilateral substitution in any [***] period unless OMI is making a substitution pursuant to an Inquiry Response under Section 3.6.2 below or OMI is substituting to replace a Selected Gene Target for which OMI has Designated a Clinical Candidate (collectively, the ***"Substitution Conditions"***). OMI will provide Isis with written notice of its intent to substitute, indicating which Selected Gene Target it wishes to substitute out and which new gene target from the Target Pool (the ***"Proposed Substitution Target"***) it wishes to substitute in. Provided OMI has satisfied the Substitution Conditions, at such time, the Proposed Substitution Target will become a Selected Gene Target and the gene target substituted out will no longer be considered part of the Target Pool or a Collaboration Gene Target, Isis' obligations (including but not limited to Section 2.3) and OMI's licenses under this Agreement with respect to such gene target and any ASOs targeting such gene targets will terminate. In such event, OMI will be able to add a new gene target to the Target Pool in accordance with Section 3.6.3 below.

3.6.2 Third Party Inquiries. If during the Research Term, Isis receives a [***] from a Third Party to obtain a license from or collaborate with Isis regarding a gene target that is in the Target Pool but is not a Selected Gene Target (a ***"Requested Target"***), Isis will promptly notify OMI in writing regarding such request (without any requirement to identify such Third Party) (an ***"Inquiry Notice"***). OMI will have [***] from receiving an Inquiry Notice to notify Isis in writing whether OMI wishes to (i) remove such Requested Target from the Target Pool, (ii) substitute out a Selected Gene Target for such Requested Target in accordance with Section 3.6.1 above, or (iii) mutually agree with Isis upon an appropriate expansion to the R&D Plan and

R&D Budget such that the R&D Plan includes such Requested Target as a [***] (or [***], as the case may be) Selected Target (each such notice, an ***"Inquiry Response"***). If OMI provides Isis with an Inquiry Response contemplated by subpart (i) above or fails to provide Isis with an Inquiry Response within [***] of receiving an Inquiry Notice, the Requested Target will no longer be part of the Target Pool, will no longer be considered a Collaboration Gene Target, Isis' obligations under this Agreement with respect to such Requested Target (including but not limited to Section 2.3) will terminate and OMI will be able to add a new gene target to the Target Pool in accordance with Section 3.6.3 below. If OMI provides Isis with an Inquiry Response contemplated by subpart (iii) above, Isis and OMI will mutually agree upon an appropriate expansion to the R&D Plan and R&D Budget such that the R&D Plan includes such Requested Target, in which event the Requested Target will be considered a Selected Gene Target.

3.6.3 Adding Targets to Target Pool. If during the Research Te rm and as a result of Sections 3.6.1 or 3.6.2 above or because OMI has Designated as a Clinical Candidate a Compound to a Selected Gene Target, the Target Pool has less than [***] gene targets, OMI may add a new gene target to the Target Pool by providing Isis with a written notice (the ***"Request Notice"***) of the gene target it wishes to add to the Target Pool (the ***"Proposed Target"***). The Request Notice will include the gene name, the NCBI accession number or nucleic acid sequence for the Proposed Target. Within [***] of receipt of the Request Notice, Isis will give OMI written notice (i) stating if any of the criteria set forth in clauses (a) through (c) below applied to such Proposed Target at the time of Isis' receipt of the Request Notice and (ii) fully disclosing all relevant Isis In-Licensed Agreements and prior Third Party Agreements and other potential encumbrances known by Isis and related to the Proposed Target (***"Target Encumbrances"***). If, at such time, the Proposed Target is (a) subject to Isis' own internal program pursuant to which Isis has identified a lead compound, (b) encumbered by a contractual obligation between Isis and a Third Party that would preclude Isis from collaborating with OMI under this Agreement or from granting a license under Section 2.1 with respect to the Proposed Target, or (c) the subject of a [***] Isis has received from a Third Party regarding a potential license or collaboration, then, in each case, the Proposed Target will be rejected and will not become a part of the Target Pool. If the Proposed Target is rejected, OMI can request another gene target in accordance with the terms of this Section 3.6.3. If the Proposed Target is not rejected, the Proposed Target will become a member of the Target Pool; *provided, however*, that if the Proposed Target has any Target Encumbrances (and Isis has fully disclosed such Target Encumbrances to OMI), before such Proposed Target can become a Selected Gene Target, OMI must agree in writing (within [***] of receiving from Isis the description of such Target Encumbrances) to assume all applicable Target Encumbrances for such Proposed Gene Target. Target Encumbrances assumed by OMI under this Section will be considered Isis Third Party Payments under Section 6.5.2. In addition, whenever a gene target becomes part of the Target Pool, the R&D Committee will agree whether a Compound targeting such gene target is in [***] as set forth in the R&D Plan.

3.6.4 Lapse of Third Party Interest. Notwithstanding the provi sions of Section 3.6.2 and 3.6.3, if any gene target is either removed from the Target Pool pursuant to clause (i) of Section 3.6.2 or not included in the Target Pool pursuant to clause (c) of Section 3.6.3 and the proposed transaction/negotiation has not, within [***] of such removal or rejection resulted in a signed agreement preventing Isis from including such gene target in the Target Pool, Isis will notify OMI in writing. In such event, but within the [***] following receipt of such notice, OMI will have the right to include such gene target in the Target Pool in addition to the gene targets already in the Target Pool even if it increases the size of the Target Pool above [***] gene targets.

3.6.5 Confidentiality. The fact that OMI has included a partic ular gene target in the Target Pool or has selected a gene target as a Selected Gene Target is Confidential Information of OMI.

3.6.6 End of Research Term. Upon the expiration of the Research Term, any gene targets in the Target Pool that are not Selected Gene Targets will no longer be considered a Collaboration Gene Target and Isis' obligations under this Agreement with respect to such gene

targets (including but not limited to Section 2.3) will terminate. In addition, within [***] following the end of the Research Term, if a Research Compound targeting a Selected Gene Target has not satisfied the Designation of a Compound as Clinical Candidate, then such Selected Gene Target will no longer be considered a Collaboration Gene Target. Isis' obligations (including but not limited to Section 2.3) and OMI's licenses under this Agreement with respect to such gene target and any ASOs targeting such gene target will then terminate, and, subject to Article 11, Isis will own any data generated under the R&D Plan for such gene target and any ASOs targeting such gene target. OMI will have the right to use any data generated under the R&D Plan for its own internal research purposes that are unrelated to any Discontinued Products.

Section 3.7 **Collaboration Records.** Each Party and its contractors will maintain complete and accurate records of all work conducted in the performance of the Collaboration and all results, data, inventions and developments made in the performance of the Collaboration. Such records will be in sufficient detail and in good scientific manner appropriate for patent and regulatory purposes. Isis will maintain appropriate records sufficient to document the work performed by each of the individuals comprising the FTEs working in support of the Collaboration and the time such individuals spent working in support of the Collaboration. Upon reasonable prior written notice, Isis will provide OMI the right to inspect such records, and will provide copies of all requested records, to the extent reasonably required for the performance of OMI's rights and obligations under this Agreement. Upon reasonable prior written notice, and solely with respect to Discontinued Products, OMI will provide Isis the right to inspect such records, and will provide copies of all requested records, to the extent reasonably required for the performance of Isis' rights and obligations under this Agreement. In each case, each Party will maintain such records and the information it receives from the other Party in confidence in accordance with Article 8 hereof and will not use such records or information except to the extent otherwise permitted by this Agreement.

Section 3.8 **Disclosure of Results of Research Program and Development Program.** The results of all work performed by the Parties as part of the Collaboration will be promptly disclosed to the other Party in a reasonable manner as such results are obtained. In addition, Isis will periodically provide OMI with written reports of the work performed under the Collaboration and the results achieved by Isis. Isis and OMI will provide reports and analyses at each R&D Committee meeting, and more frequently on reasonable request by the R&D Committee, detailing the current status of the Research Program and Development Program. In addition, on reasonable request by a Party, the other Party will make presentations of its activities in the performance of the Collaboration to inform such Party of the details of the work done in the performance of the Collaboration. The results, reports, analyses and other information regarding the Collaboration 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 OMI, Isis will provide OMI with additional data, results and other information with respect to the work performed by Isis in the performance of the Collaboration. Any reports required, excluding reports needed for submission to a Regulatory Agency, under this Section 3.8 may take the form of and be recorded in minutes of the R&D Committee that will contain copies of any slides relating to the results and presented to the R&D Committee. Reports needed to support regulatory submissions and updates to a Regulatory Agency will be provided [***] and in a format as agreed upon by the R&D Committee or designated sub committee.

In addition, within [***] of OMI's request, Isis will transfer to OMI copies of 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 3.9 **Research Efforts; Resources, Scientific Manner.** Each Party will use Commercially Reasonable Efforts to perform the Collaboration, including its responsibilities under the R&D Plan.

3.9.1 Throughout the Collaboration Term, Isis will assign no less than the number of FTE qualified scientists specified in the R&D Plan to perform the work set forth in the then-applicable R&D Plan. The mixture of skills and levels of such FTEs will be appropriate to the scientific objectives of the Research Program or Development Program (as applicable).

3.9.2 Each Party will maintain laboratories, offices, administrative support and all other facilities at its own expense and risk necessary to carry out its responsibilities under the Collaboration pursuant to the R&D 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 Collaboration. OMI and Isis will cooperate with each other in carrying out the Collaboration, and each Party will contribute its relevant know-how and experience necessary to carry out the Collaboration.

3.9.3 The Collaboration will be conducted by each Party in good scientific manner, and in compliance with all applicable GCP, GLP and GMP, and applicable legal requirements, to attempt to achieve efficiently and expeditiously the Objectives of the Collaboration. Each Party will comply with all Applicable Laws, in the performance of work under this Agreement.

3.9.4 Isis will not perform any of its obligations under the R&D Plan through one or more subcontractors or consultants, without the prior written approval of OMI, such approval not to be unreasonably withheld. OMI will promptly notify Isis regarding any Third Party OMI uses to conduct research under the R&D Plan or that OMI transfers Compounds or Products to, including identifying such Third Party.

Section 3.10 **Materials Transfer.** In order to facilitate the Collaboration, either Party may provide to the other Party certain materials for use by the other Party in furtherance of the Collaboration. All such materials will 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 will not transfer such materials to any Third Party unless expressly contemplated by this Agreement or upon the written consent of the supplying Party. Any materials provided by OMI to Isis in support of the Collaboration, including but not limited to any biological materials with respect to screening assays, including any progeny, expression products, mutants, replicates, tissue samples, cells, derivatives and modifications thereof, (such materials being individually and collectively referred to as the ***"OMI Materials"***) will be used by Isis solely for purposes of performing the Collaboration and for no other purpose, and any remaining OMI Materials (including, as applicable, any progeny, expression products, mutants, replicates, tissue samples, cells, derivatives and modifications thereof) will be returned to OMI (or destroyed as may be requested by OMI in writing) promptly following the end of the Research Term or earlier upon request by OMI. All information related to such OMI Materials will be OMI 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. Isis recognizes that OMI's obligations under the R&D Plan will necessarily involve the transfer of materials to Third Party contractors and that is expressly contemplated by this Agreement.

Section 3.11 **Safety Database**

3.11.1 OMI shall establish the global safety database of adverse events and pregnancy reports for the Compound/Product that will be used for regulatory reporting and responses to safety queries from Regulatory Authorities. Isis shall promptly transfer all clinical adverse event and drug exposure during pregnancy data that it has regarding the Compounds or Products to OMI for entry into the global safety database upon request from OMI.

3.11.2 [***] a database that includes information regarding the safety and tolerability of [***] drug compounds, individually and as a class, including information discovered during pre-clinical and clinical development (the ***"[***] Database"***).

(a) In an effort to maximize understand ing of the [***] will cooperate in connection with populating the [***] Database. In accordance with Applicable Law and any applicable informed consents or other Third Party obligations, [***] with copies of [***] serious adverse event final reports related to [***]. In addition, in connection with any reported serious adverse event (including any follow-up or amended reports), in accordance with Applicable Law and any applicable informed consents or other Third Party obligations and to the extent [***] has collected such data, [***], the following [***] All such information [***] in connection with this Section will be [***] Confidential Information; *provided, however*, that [***] any Third Party so long as [***] does not disclose to any Third Party the [***] in connection with any such disclosure.

(b) From time to time, [***] the information in the [***] Database to conduct analyses to keep [***] informed regarding class generic properties of [***], including with respect to safety. As such, if and when [***] that may be relevant to a Compound or Product (including potential class-related toxicity liabilities), [***] of such issues, and if requested, provide the data supporting [***] regarding such issues.

(c) [***]

(d) In addition, each Party will notify the o ther Party in writing if such Party confirms that a serious adverse event with respect to a Product has occurred. Such notice will be provided within [***] of confirming the serious adverse event.

ARTICLE 4 - MANUFACTURING

Section 4.1 **Supply of ASO for Research Program**. Isis agrees to manufacture and supply all ASOs for use in support of the Research Program. [***] will bear its own costs for the manufacture of all ASO needed for research through the [***] under the R&D Plan. Once a Selected Gene Target has [***] under the R&D Plan, OMI will order additional quantities of API for Research Compounds directed to such Selected Gene Target in [***] increments. Isis agrees to supply such quantities which will be supplied outside the Clinical Manufacturing & Supply Agreement; *provided, however*, that Isis will not charge for API used to [***]. The cost to manufacture such additional quantities of ASOs will be negotiated and agreed to in good faith by the Parties, but will not exceed $[***] per [***] for MOE Gapmers.

Section 4.2 **Supply of Existing Development Compounds.** Within [***] of receipt of invoice from Isis in the form provided as **APPENDIX 7**, the invoice received no sooner than the Effective Date, OMI will pay Isis $[***] for the [***] that is in Isis' possession on [***]. The $[***] represents Isis' out-of-pocket expenses incurred in connection with manufacturing such [***]). Such API and drug product will be used as outlined in the R&D Plan. The Parties acknowledge and agree that such API and drug product may be used between [***] to conduct activities outlined in the R&D Plan. Isis shall deliver such API as governed by the R&D Plan or as otherwise requested by OMI within a reasonable period of time after such request.

Section 4.3 **Clinical Supply of API Through Completion of [***].** Isis and OMI will enter into a manufacture and supply agreement(s) for the [***] (a ***"Clinical Supply Agreement"***) for each Designation of a Compound as a Clinical Candidate. Each Clinical Supply

Agreement will include customary terms and conditions to be negotiated in good faith and the Clinical Supply Agreement is attached hereto as **APPENDIX 8** for ISIS 325568 and ISIS 377131, which will serve as a template for future Clinical Supply Agreements.

Section 4.4 **Option to Supply GCGR and GCCR Compounds.** At any time (including, but not limited to if OMI determines that Isis is unable or unlikely to meet Isis' supply obligations), at OMI's written request and consistent with the Supply Agreement, Isis will transfer to OMI or a Third Party manufacturer selected by OMI all documentation and information, including Isis Manufacturing and Analytical Technology and permit OMI to reference and use any regulatory filings, and otherwise fully cooperate with OMI to enable OMI to make or have made API for use by OMI 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 OMI will be solely responsible for the manufacturing of Compound and Product for [***] and commercial supply, including management of the overall manufacturing strategy and tactics, formulation, internal or contract manufacturer selection for API and finished Product, associated audits, stability testing, pricing, relationship with contract manufacturer(s) and any work proposals or contract negotiations or contracts themselves.

4.5.2 Clinical Supply of ISIS 325568 and ISIS 377131 API for [***]. Solely at the discretion of OMI, OMI will notify Isis of OMI's intent to require Isis to supply quantities of ISIS 325568 and ISIS 377131 as is necessary to fulfill OMI's Product requirements for [***] Studies. OMI will notify Isis of its intent, leaving a reasonable time to permit the Parties to negotiate a [***] Clinical Supply Agreement, such that the supply agreement is in place no later than [***] prior to the planned delivery date for such API.

4.5.3 Transfer of Manufacturing and Analytical Technology.

(a) As soon as is practicable after Isi s receives a written request from OMI to transfer any Isis Manufacturing and Analytical Technology to OMI, but not later than 30 days after receipt of such request, Isis will initiate transfer to OMI, or at OMI's option, to such Third Party Manufacturer, the Isis Manufacturing and Analytical Technology. For such purpose, Isis will transfer to OMI or such Third Party Manufacturer all documentation and information, and permit OMI to reference and use any regulatory filings, and otherwise fully cooperate with OMI to enable OMI to make or have made API and finished drug Product for use by OMI in accordance with this Agreement at no cost to OMI. In addition, upon request by OMI, Isis will provide OMI with a reasonable level of technical assistance and consultation in connection with the transfer of such manufacturing and analytical technology to help enable OMI or such Third Party manufacturer (as applicable) to manufacture and release such API and finished drug Product. For such

purpose Isis will provide OMI with reasonable access by teleconference or in-person at Isis' facilities to Isis personnel involved in the manufacturing and release of API and finished drug Product, *provided* that if OMI requests such technical assistance in excess of [***] of technical assistance, [***]. Such payment will be made to Isis within [***] after OMI's receipt of an invoice by Isis in the form provided as **APPENDIX 7** reasonably detailing Isis' time expended, together with reasonable substantiation of any out-of-pocket expenses incurred.

(b) OMI and/or its Third Party manufacturer w ill use any Isis Know-How or Product Specific Know-How and other documentation and information transferred pursuant to Section 4.4 and Article 4.5 solely for the purpose of manufacturing API and Product for OMI's (or its Affiliate's or Licensee's) benefit pursuant to the exercise of OMI's rights under this Agreement, and for no other purpose. OMI acknowledges and agrees that any such transfer of such manufacturing technology to a Third Party manufacturer must satisfy the conditions set forth in Section 2.2(b) and will be subject to a written agreement between such Third Party

manufacturer and OMI that contains obligations of confidentiality substantially equivalent to those of this Agreement.

Section 4.6 **Supply of Finished Drug Product.** Except as otherwise specified in the R&D Plan or Clinical Manufacturing and Supply Agreement, the Parties acknowledge and agree that [***] will be solely responsible for the manufacturing, stability testing and supply of finished drug Product.

Section 4.7 **Manufacturing Improvements.**

4.7.1 The entire right, title, and interest in and to all Manufacturing Improvements developed or invented solely by employees, or consultants of OMI during the Term will be the sole and exclusive property of OMI. OMI hereby grants Isis a [***] license to practice under OMI's rights to any Know-How or Patent claiming Manufacturing Improvements to [***] and to the extent that such Manufacturing Improvements are under the control of OMI. Notwithstanding the foregoing, Isis recognizes that OMI may not own or control Manufacturing Improvements developed or invented by a contract manufacturer. The license granted under this Section 4.7.1 falls within the restrictions [***].

4.7.2 The entire right, title, and interest in and to all Manufacturing Improvements developed or invented solely by employees, or consultants of Isis during the Term will be the sole and exclusive property of Isis. Isis hereby grants OMI [***] license to practice under Isis' rights to any Know-How, Product Specific Know-How or Patent claiming such Manufacturing Improvements to make and have made Products. The license granted under this Section 4.7.2 will be sublicensable by OMI solely in connection with the grant of a license to develop, make, use, import, offer for sale and sell a Product.

4.7.3 The entire right, title, and interest in and to all Manufacturing Improvements developed or invented jointly by employees or consultants of Isis and OMI during the Term will be the joint property of Isis and OMI. Each Party will have an undivided joint ownership interest in such Manufacturing Improvements, and may license its rights under such Manufacturing Improvements for its own account and without the consent of the other Party, subject to the exclusivity granted to OMI under Section 2.3.

4.7.4 During the first [***], if requested by a Party, the Parties will meet annually to review Manufacturing Improvements developed by either of the Parties [***] of the Collaboration. At such time, the Parties will disclose all such Manufacturing Improvements Controlled by such Party in reasonable detail as to enable the other Party to [***] will have the right to [***] with respect to the commercialization of one or more [***]

Section 4.8 **Isis Regulatory Inspections.** Isis will cooperate in good faith with respect to the conduct of any inspections by any Regulatory Authority of an Isis site or a contractor's site and facilities if such inspection concerns work being performed under the R&D Plan and the Clinical Manufacturing and Supply Agreement. OMI shall be given the opportunity to attend any inspections by any Regulatory Authority of Isis' or Isis' contractor's site and facilities if such inspections concern work being performed under the R&D Plan and the Clinical Manufacturing and Supply Agreement, and the summary (or wrap up) meeting with a Regulatory Authority at the conclusion of such site inspection. In the event that during an inspection of the Isis facilities, the facilities are found by a Regulatory Authority to be non-compliant with one or more GLP, GMP, GCP or current standards for pharmacovigilance practice compliance standards and such facilities are being used to conduct work under the R&D Plan and the Clinical Manufacturing and Supply Agreement, Isis will promptly notify OMI of such finding and will submit a proposed recovery/corrective action plan, including a time line for implementation of the plan, within [***] of such notification of non-compliance.

Section 4.9 **Quality Agreement.** A quality agreement (the ***"Quality Agreement"***) will be negotiated simultaneously with the present Agreement and is attached hereto as **APPENDIX 9**.

ARTICLE 5 - DEVELOPMENT & COMMERCIALIZATION

Section 5.1 **Development, Commercialization and Regulatory Responsibilities.** Other than Isis' responsibilities under the R&D Plan, OMI will 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. OMI hereby assumes all regulatory responsibilities in connection with Compounds and Products, including sole responsibility for all Regulatory Documentation and for obtaining all Approvals. OMI will comply with all Applicable Laws in connection with the Development and Commercialization of Compounds and Products. OMI (by itself or through its Affiliates, Licensees, (sub)contractors or agents, as applicable) will use Commercially Reasonable Efforts to Develop and Commercialize at least one Compound or Product for each Collaboration Gene 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 will be owned by OMI. In addition, upon reasonable notice by OMI and during normal business hours, Isis will provide OMI 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 OMI requests such assistance in excess of [***]

of assistance, [***] after receipt by OMI of an invoice by Isis in the form provided as **APPENDIX 7** reasonably detailing Isis' time expended, together with reasonable substantiation of any out-of-pocket expenses incurred.

Section 5.2 **Reports by OMI after the Collaboration Term.** After the Collaboration Term with respect to any Compound or Product that OMI is developing, at Isis' request, OMI will provide a report to Isis summarizing OMI's activities over the [***] with respect to the identified Compound or Product and an appropriate number of representatives from each Party will meet at least [***] to review Development activities. OMI will consider Isis' input regarding such activities. The reports provided by OMI under this Section 5.2 will contain sufficient information to allow Isis to reasonably determine whether OMI is in compliance with its obligations to use Commercially Reasonable Efforts under Section 5.1.

Section 5.3 **Product Development Plans; Integrated Product Plans.** For each Product that OMI is clinically developing under this Agreement, OMI will prepare a development plan outlining key aspects of the clinical development of such Product through Approval. Each development plan will contain information customarily contained in OMI's development plans for its similar products at similar stages of development (each a ***"Product Development Plan")***. In addition, prior to the launch of a Product, OMI will prepare a global integrated Product plan outlining the key aspects of market launch and commercialization (the ***"Integrated Product Plan"*** or ***"IPP"***). The Integrated Product Plan will contain information customarily contained in OMI's commercialization plans. Each Product Development Plan and IPP will be updated annually by OMI. OMI will provide to Isis a copy of the final draft of the Product Development Plans and IPPs (original and updates) for each of the [***], if available. OMI and Isis will meet on [***] to discuss the draft of each Product Development Plan and IPP and OMI will consider, in its sole discretion, any proposals and comments made by Isis for incorporation in the final

Product Development Plan or IPP (as the case may be). Furthermore, to the extent OMI intends to make any claims in a Product label that are class generic to MOE Gapmers, OMI will provide such claims to Isis in advance and will consider, in its sole discretion, any proposals and comments made by Isis.

ARTICLE 6 - FINANCIAL PROVISIONS

Section 6.1 **Up-Front Payment.** In partial consideration for the licenses and other rights granted under this Agreement, within [***] following the Effective Date, OMI will pay Isis [***] $45,000,000.

Section 6.2 **Collaboration Funding.** OMI will provide Collaboration funding to Isis as set forth in Section 3.5.2.

Section 6.3 **Milestone Payments by OMI.** OMI will give Isis notice promptly upon achievement of each Milestone Event provided in Table 1. Upon receipt of an invoice, as set forth in **Appendix** 7, OMI will pay Isis the following milestone payments within [***] after receipt of such notice, with the proviso that with respect to the [***] Milestone for GCGR, payment shall be due [***] after notice and invoice by Isis of achievement of such Milestone.:

6.3.1 Development Milestones.

(a) For each Selected Gene Tar get, the milestone payments under Column 1 of Table 1 below will be payable by OMI to Isis for the first achievement of the specified milestone events by OMI, its Licensees or their Affiliates for the first Research Compound or Research Product that targets such Selected Gene Target to reach the specified milestone event.

(b) The milestone payments under Col umn 2 of Table 1 below will be payable as set forth below for the first achievement of the specified milestone events by OMI, its Licensees or their Affiliates for the first GCGR Compound or GCGR Product to reach the specified milestone event.

(c) The milestone payments und er Column 3 of Table 1 below will be payable as set forth below after the first achievement of the specified milestone events by OMI, its Licensees or their Affiliates for the first GCCR Compound or GCCR Product to reach the specified milestone event.

Table 1

Milestone Event	Column 1 Payment for First Research Compound Per Selected Gene Target	Column 2 Payment for First GCGR Compound	Column 3 Payment for First GCCR Compound
[***]			
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]

[***]

6.3.2 Approval Milestones.

(a) For each Selected Gene Target, the milestone payments under Column 1 of Table 2 below will be payable by OMI to Isis for the first achievement of the specified milestone events by OMI, its Licensees or their Affiliates for the first Research Compound or Research Product that target such Selected Gene Target to reach the specified milestone event.

(b) The milestone payments under Column 2 of Table 2 below will be payable as set forth below after the first achievement of the specified milestone events by OMI, its Licensees or their Affiliates for the first GCGR Compounds or GCGR Products to reach the specified milestone event.

(c) The milestone payments under Column 3 of Table 2 below will be payable as set forth below after the first achievement of the specified milestone events by OMI, its Licensees or their Affiliates for the first GCCR Compounds or GCCR Products to reach the specified milestone event.

Table 2

Milestone Event	Column 1 Payment for First Research Compound Per Selected Gene Target	Column 2 Payment for First GCGR Compound	Column 3 Payment for First GCCR Compound
[***]			
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]			
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]

In the event that an original Compound or Product for a Collaboration Gene Target fails in development and is replaced by OMI with a back-up Compound or Product targeting the same Collaboration Gene Target, any milestone payments previously paid with respect to such original Compound or Product shall be fully creditable toward the same milestone due with respect to the back-up Compound or Product, and OMI shall notify Isis in writing of the selection of the back-up Compound or Product. The Parties acknowledge that, after the approval milestone payments for a Second Indication are paid to Isis, OMI shall not be obligated to make any additional approval milestone payments with respect to a Product comprising the same Compound or Product or its back-up Compound or Product, regardless of the number of additional indications for which such Compound or Product is developed. The Parties also acknowledge that different formulations (e.g., dosage strength, delivery forms) of a Compound or Product (back-up Compound or Product) or bioequivalents therefore (i.e., salts, esters, polymorphs) shall be deemed the same Compound or Product, and all milestones due shall be payable one time only per Compound or Product.

[remainder of page intentionally left blank]

Section 6.4 **Royalty Payments by OMI.** In consideration of the licenses granted to OMI by Isis hereunder and the assignments made pursuant to Section 9.2.3 (b) OMI will pay Isis royalty payments on Products as follows: Subject to the other provisions of this Agreement, OMI will pay to Isis the royalty rate under Column 1 of Table 3 below for each Research Product. Subject to the other provisions of this Agreement, OMI will pay to Isis the royalty rate under Column 2 of Table 3 below for each GCGR Product. Subject to the other provisions of this Agreement, OMI will pay to Isis the royalty rate under Column 3 of Table 3 below for each GCCR Product. The royalty rate payable with respect to each particular Product will be based on the level of annual worldwide Net Sales of such Product in a given Calendar Year period by OMI, its Affiliates and Licensees, with the royalty rate tiered based upon the level of such worldwide Net Sales in such Calendar Year period as set forth in the table below.

Table 3

Column 1 Royalty Rate Research Product	Column 2 Royalty Rate GCGR Product	Column 3 Royalty Rate GCCR Product	
			Annual Worldwide Net Sales
[***]%	[***]%	[***]%	of annual worldwide Net Sales less than or equal to $[***]
[***]%	[***]%	[***]%	of annual worldwide Net Sales greater than $[***] and less than or equal to $[***]
[***]%	[***]%	[***]%	of annual worldwide Net Sales greater than $[***]

For example, in the instance of a full Calendar Year, if annual OMI Net Sales of GCGR Product in such Calendar Year worldwide are $[***], the amount due will be $[***] ([***]% of the [***] (or $[***]) in the first increment, plus [***]% of the next $[***] (or $[***]) in the second increment, plus [***]% of the remaining $[***] (or $[***]) in the third increment).

Section 6.5 **Third Party Payment Obligations.**

6.5.1 **Isis In-License Agreements.**

(a) Certain of the Isis Patent Rights Controlled by Isis as of the Effective Date that are licensed to OMI 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 OMI 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 payment becomes payable by Isis to such Third Party licensor depends on the terms and conditions of the Isis In-License Agreement.

(b) Isis will b e responsible for paying [***]% of the Isis Supported Payments as they apply to any Compound or Product.

6.5.2 **Additional Third Party Agreements.**

(a) After the E ffective Date, Isis may wish to in-license or acquire rights to Know-How or Third Party Patents (such a Third Party in-license or acquisition agreement being an ***"Additional Third Party Agreement"***) which, if so licensed or acquired, may be included in the Isis Patent Rights licensed to OMI under Section 2.1. In such event (and to the extent permitted by Isis' confidentiality agreement with the applicable Third Party), Isis will notify OMI regarding the nature of the technology and status of negotiations related to the Additional Third Party Agreement through the R&D Committee. Once Isis has executed such Additional Third

Party Agreement, Isis will offer such Third Party Patents or Know-How to OMI (including a description of the payments paid or potentially payable by Isis thereunder). At such time, if OMI wishes to include such Third Party Patents under the licenses granted under Section 2.1, OMI will notify Isis of its desire to do so [***], if appropriate. As part of this [***], Isis will share with OMI, in reasonable detail, the [***]. If OMI does not [***], and to [***] as set forth below, then [***] will not be [***] under this Agreement.

(b) In the even t that a milestone payment or a payment on net sales of Product becomes payable by Isis to a Third Party under an Additional Third Party Agreement, and such milestone or payment obligation is based on [***]. (such milestone and/or payments being the ***"Isis Third Party Payment"***), then [***] will be responsible for the payment of such Isis Third Party Payment obligation as long as [***]. In the event that a milestone payment or a royalty payment on net sales of Product becomes payable by Isis to a Third Party under an Additional Third Party Agreement, and such milestone or royalty payment obligation is based on [***], then as long as [***] will be responsible for the payment of such Isis Third Party Payment obligation. In both cases [***] under this Agreement.

(c) Any Pass Th rough Obligations OMI is responsible for paying under this Section 6.5.2 will be [***] and OMI will satisfy such obligation by paying Isis directly.

6.5.3 **OMI Third Party Licenses.** OMI will be responsible for ne gotiating and entering into any Third Party licenses that OMI determines may be necessary or useful or may relate to the Development or Commercialization of Products. If OMI, in its reasonable judgment, is required to obtain a license from any Third Party under any patent covering technology necessary or useful for the Development or Commercialization of a Product, and the infringement of such patent cannot reasonably be avoided by OMI, and if OMI is required to pay to such Third Party in consideration for such license for a Product any royalty payment calculated on sales of a Product (such royalty payments collectively being a ***"OMI Third Party Royalty Payment"***) then OMI may reduce the royalty payable to Isis under Section 6.4 by up to [***]% of the amount of the OMI Third Party Royalty, subject to the limitation set forth in Section 6.5.4. *Notwithstanding* the foregoing, no reduction of the royalties payable to Isis under Section 6.4 will be permitted with respect to OMI Third Party Payments with respect to any Third Party patent covering (x) methods or materials used in the [***], (y) any [***] which is not a Compound (i.e., a non-Compound active ingredient in a Combination Product) or (z) [***].

6.5.4 For any additional royalty rate payments payable by OMI under Section 6.5.2 or 6.5.3, OMI may reduce its obligation to pay Isis royalty payments under Section 6.4 by [***]% of the amount of such additional payments payable by OMI as set forth in Sections 6.5.2 and 6.5.3; *provided, however* that no such reduction(s) in the aggregate will reduce the royalty payments payable to Isis under Section 6.4 in any given Calendar Quarter period below [***] of Isis' [***] royalty under Section 6.4 (i.e. [***]% multiplied by [***] of the applicable royalty rate under Section 6.4 [***] the royalty payments payable by Isis under Section 6.5.1(b)). For example, royalty payments payable for GCGR may not be reduced below [***]% (in the first increment) [***]% (hypothetical example of Isis Supported Payments under Section 6.5.1(b)) multiplied by [***]%, or [***]% ([***]% - [***]% = [***]% x [***]% = [***]%). In this instance, royalty payments payable in the first increment for GCGR would not be reduced below [***]% ([***]% + [***]% = [***]%).

Section 6.6 **[***].** If the portion of [***] (calculated in accordance with **Appendix 16** attached hereto) for the [***] sold in the US and EU (the ***"[***]"***) exceeds [***]% of annual Net Sales in the U.S. and EU in a given year, then the royalty rate provided in Section 6.4, Table 3 payable for worldwide sales of such Product for such year will be [***]. *Notwithstanding the foregoing*, at no time will, as the result of this calculation and allowance, the Royalty Rate provided in Section 6.4, Table 3 be reduced below [***]. The parties will use Commercially Reasonable Efforts and work in good faith to [***]

Section 6.7 The royalty rates under Section 6.4 will be subject to the following conditions:

(a) that only one royalty rate will be due to Isis hereunder with respect to the same unit of Product;

(b) that no royalty payment will be due upon the sale or other transfer of a Product among OMI, its Affiliates or Licensees, but in such cases a royalty payment will be due and calculated upon OMI'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**;

(c) no royalty payments will be due on the disposition of Product in reasonable quantities by OMI, its Affiliates or Licensees as part of an Expanded Access Program to include compassionate use, named patients or other similar use or as part of Phase 4 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 OMI, its Affiliate or Licensees receives any payment or other in-kind consideration for such Product;[***]

(d) a Product will only be eligible for the full royalty rate designated under Section 6.4 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 that country is [***];

(e) if, as of the date of the First Commercial Sale of a Product in a given country, the making, using or selling of such Product (or the Compound contained in such Product) in that country is either (i) *not* [***] or (ii) *only* [***], then the Net Sales in that country will be reduced by [***]% before adding such Net Sales to the Net Sales of all of the other countries used in arriving at the aggregate annual Net Sales upon which the royalty is based;

(f) If no royalty payment is due in a country on a Product but a royalty payment is still payable by Isis under the Isis Supported Payments or as the result of any Target Encumbrance under 3.6.3, then OMI will pay Isis a royalty equal to the amount the applicable royalty under the Isis Supported Payments and Target Encumbrances for so long as and in the amount that such royalty payment is owing. Once a Product is determined to be eligible for the applicable base royalty payment under part (d) or (e) above, it will continue to be eligible at such base rate for the applicable Royalty Term, subject to the other terms and conditions of this Agreement (including but not limited to any applicable adjustment under Section 6.5, 6.6 or 6.8).

Section 6.8 **Generic Competition.** Solely with respect to Products for which the full royalty applies under part (d) of Section 6.6 above, if there are one or more unauthorized Third Parties selling a Generic Product, then the Net Sales in that country will be reduced by [***]% before adding such

Net Sales to the Net Sales of all of the other countries used in arriving at the aggregate annual Net Sales upon which the royalty is based ; *provided, however*, that, in no event will the royalties payable to Isis under 6.4 above be reduced below [***].

Section 6.9 **Royalty Term.** Royalties payable under Section 6.4 (subject to and including any reduction set forth in Sections 6.5, 6.6 and 6.7) 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) [***] 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 9.6 for the Product in the applicable country. 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 6.10 **Royalty Report and Payment.** During the Term following the First Commercial Sale of any Product, within [***] after the end of each Calendar Quarter, OMI will 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 OMI, its Licensees and their respective Affiliates during such Calendar Quarter reporting period; and

(b) the royalties which will have accrued hereunder with respect to such Net Sales.

In addition, during the Term following the First Commercial Sale of any Product, within [***] after the end of each Calendar Quarter, OMI will provide Isis a preliminary non-binding quarterly royalty report showing the total Net Sales of Product and royalty payable for such Calendar Quarter. Furthermore, OMI agrees to supply Isis the information Isis reasonably requires to comply with any Pass Through Obligations.

If no royalty or payment is due for any royalty period hereunder, OMI will so report. OMI will keep, and will require its Licensees and their respective Affiliates to keep (all in accordance with GAAP, 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 (but no more frequently than once in any 12-month period), OMI will report to Isis the quantity of Product not subject to royalties distributed by OMI, its Affiliates or Licensees as part of an Expanded Access Program to include compassionate use, named patients or other similar use or as part of Phase 4 Trials or as bona fide samples or as donations to non-profit institutions or government agencies for non-commercial purposes. All information disclosed by OMI to Isis under this Section 6.9 will be OMI Confidential Information.

Section 6.11 **Manner of Payment and Exchange Rate.** All payments to be made by OMI to Isis hereunder will be made by deposit of [***] by wire transfer in immediately available funds in the requisite amount to such bank account Isis may from time to time designate by notice to OMI. [***]

Section 6.12 **Audits, including Audits of Royalty Reports.**

6.12.1 Audits of Royalty Reports. Upon the written request of Isis and not more than once in each Calendar Year, OMI will permit an independent certified public accounting firm of nationally recognized standing selected by Isis and reasonably acceptable to OMI, at Isis' expense and upon execution of a confidentiality agreement with OMI, to have access during normal business hours to such records of OMI 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 [***] 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 will terminate [***] after the end of any such Calendar Year. Isis will provide OMI with a copy of the accounting firm's written report within [***] of completion of such report.

If such accounting firm concludes that an overpayment or underpayment was made, then the owing Party will pay the amount due within [***] of the date Isis delivers to OMI such accounting firm's written report so correctly concluding. Isis will bear the full cost of such audit unless such audit correctly discloses that the additional payment payable by OMI for the audited period is more than [***]% of the amount of the royalties paid for that audited period, in which case OMI will pay the reasonable fees and expenses charged by the accounting firm. However, if the result of the audit is contested, then the Parties agree to retain a mutually acceptable independent certified public accounting firm or equivalent thereof within [***] to review the relevant books and records and to submit to the Parties its written determination as to the amount in dispute and the basis for its determination. The determination by the accounting firm will be binding on the Parties absent manifest error. If such accounting firm determines that

the result of the original audit was correct (within a margin of error of [***]%) then the Party who contested the original audit will pay the fees and expenses of the accounting firm for such determination and *vice versa*.

OMI will 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 OMI's independent accountant to the same extent and under the same obligations as required of OMI under this Agreement. OMI will advise Isis in advance of each audit of any Licensee with respect to Product sales. OMI 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. OMI will pay the reasonable fees and expenses charged by the accounting firm, except that Isis will pay for all additional services requested exclusively by Isis from OMI'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 will be OMI Confidential Information and will 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 OMI 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.

6.12.2 Audit by OMI. OMI shall have the right to audit Isis' books and records, and the records of any successors hereto for the purpose of accurate accounting and compliance with the terms of this agreement including its activities under the R&D Plan. Isis shall maintain complete and accurate records in accordance with GAAP, which are relevant to costs, expenses and payments under this Agreement and such records shall be made available to OMI upon its reasonable request but no more than [***], during reasonable business hours for a period of [***] from creation of individual records, for examination at OMI's expense by an independent certified public accounting firm selected by OMI and acceptable to Isis for the sole purpose of verifying the correctness of calculations or such costs, expenses or payments made under this Agreement. In the absence of material discrepancies (in excess of [***] percent ([***]%) in any audit period resulting from such audit, the accounting expense shall be paid by OMI. If such material discrepancies do result, Isis shall bear the reasonable audit expense and shall promptly pay the amount of discrepancy. All financial information subject to review under this Section will be Isis Confidential Information and will be treated in accordance with the confidentiality provisions of this Agreement.

Section 6.13 **Taxes.**

(a) OMI will make all payments to Isis under this Agreement without deduction or withholding for taxes except to the extent that any such deduction or withholding is required by law in effect at the time of payment.

(b) Any tax required to be withheld on amounts payable under this Agreement will promptly be paid by OMI on behalf of Isis to the appropriate governmental authority, and OMI will furnish Isis with proof of payment of such tax. Any such tax required to be withheld will be an expense of and borne by Isis.

(c) OMI and Isis will cooperate with respect to all documentation required by any taxing authority or reasonably requested by OMI to secure a reduction in the rate of applicable withholding taxes.

If OMI had a duty to withhold taxes in connection with any payment it made to Isis under this Agreement but OMI failed to withhold, and such taxes were assessed against and paid by OMI, then Isis will indemnify and hold harmless OMI from and against such taxes (including interest but excluding any penalties).

Section 6.14 **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 6.15 **Sublicenses.** In the event OMI grants licenses or sublicenses to a Licensee to sell Products which are subject to royalties under Section 6.4, 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 OMI.

Section 6.16 **Interest.** If OMI fails to make any payment due to Isis under this Agreement, then interest will accrue on a [***]; *provided, however*, that if OMI cures such late payment as provided for in Article 10 and OMI has not been late with respect to any other payment under this Agreement in the same Calendar Year, then no such interest will accrue during the applicable cure period for such first late payment.

ARTICLE 7 -
PRESS RELEASES & PUBLICATIONS

Section 7.1 **Press Releases; Public Disclosure.**

7.1.1 Upon execution of this Agreement, the Parties may issue a press release announcing the existence of this Agreement in a form and substance mutually agreed to in writing, in advance of the Execution Date, 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 will not be unreasonably withheld or delayed, *provided however*, that each Party may make disclosures permitted by, and in accordance with, Article 8. 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 will provide the other with an advance copy of any such announcement at least [***] prior to its scheduled release. Each Party will have the right to expeditiously review and recommend changes to any such announcement and, except as otherwise permitted by Article 8, the Party whose announcement has been reviewed will 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, approved and released by the reviewing Party can be re-released by either Party without a requirement for re-approval. Notwithstanding the foregoing and subject to Article 8, the Parties agree that such Public Disclosures shall minimize the disclosure of financial information.

7.1.2 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 7.1.1 above, any press release or other similar public communication by either Party related to a Product's efficacy or safety data and/or results, will be submitted to the other Party for review and approval at least [***] [***] in advance of such proposed public disclosure. Except as permitted by Article 8, such public disclosures shall be permitted at the sole discretion of OMI.

Section 7.2 **Publication of Research Results.** During the Collaboration Term, neither Party will publish, present or otherwise disclose to the public the Research Results exclusively licensed to OMI hereunder or information relating to Collaboration Gene Targets, except as specifically approved by the R&D Committee. The R&D Committee will agree upon the form and timing of any publication or presentation or other disclosure (such as an abstract, manuscript or presentation) to the public of the Research Results exclusively licensed to OMI hereunder or information relating to Collaboration Gene Targets. For clarification, this Section 7.2 will not apply with respect to the use and disclosure of Confidential Information as specifically provided for in

Section 7.1 or Article 8 (i.e., a disclosure expressly permitted and made in accordance with Section 7.1 or Article 8). At the termination of the Collaboration Term and solely with respect to Selected Gene Targets for which OMI has Designated a Compound as a Clinical Candidate, OMI may publish, present or otherwise disclose Research Results to the public at its sole discretion subject to Article 8; however, OMI will notify Isis [***] in advance of the publication.

ARTICLE 8 - CONFIDENTIALITY

Section 8.1 **Disclosure and Use Restriction.** Each Party agrees that, for so long as this Agreement is in effect and for a period of [***] thereafter, a Party (the ***"Receiving Party"***) receiving Confidential Information of the other Party (the ***"Disclosing Party"***) will (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, or Affiliates of the Receiving Party 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 will be permitted to use the OMI Confidential Information solely for purposes of performing the Research Program in accordance with the R&D Plan and for no other purpose. Upon completion of the Research Program or earlier upon written request by OMI, Isis will return to OMI or destroy any OMI Confidential Information.

Section 8.2 **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) communicating with 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, and including any marketing or promotional information related to the Product; *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 8.3 or 8.4 as applicable; and

(e) disclosure, in connection with the performance of this Agreement and solely on a need-to-know basis, 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 8; *provided, however*, that the Receiving Party will remain responsible for any failure by any Person who receives Confidential Information pursuant to this Article 8 to treat such Confidential Information as required under this Article 8.

If and whenever any Confidential Information is disclosed in accordance with this Section 8.2, such disclosure will 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 8.3 and 8.4, the Receiving Party will notify the Disclosing Party of the Receiving Party's intent to make such disclosure pursuant to clauses (a) through (d) of this Section 8.2 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 8, during the Collaboration Term, the Research Results will be treated as Confidential Information of both Parties. After the expiration of the Collaboration Term, the Research Results will be treated as Confidential Information of OMI (unless such Research Results are transferred to Isis under Article 11).

Section 8.3 **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 will 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 will 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 8.4 **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 will notify the other Party of such intention and will 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 will be provided not less than 5 business days prior to such filing) (and any material 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 will 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 will only disclose Confidential Information which it is advised by counsel is legally required to be disclosed. No such notice will be required under this Section 8.4 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 8.5 **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 8.4 will 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 8.6 **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 8 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 may be entitled to seek injunctive relief by a court of competent jurisdiction against any action that constitutes any such breach of this Article 8.

ARTICLE 9 - PATENTS

Section 9.1 **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 and Development Program under this Agreement (collectively, the ***"Program Inventions"***) and any Patents claiming such Program Inventions (***"Program Patents"***), 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 will 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. OMI will own Program Inventions, including those inventions described in Section 4.7.1, invented solely by employees, consultants and/or (sub)contractors of OMI (the ***"OMI Inventions"***) and any Patents claiming such Program Inventions (the ***"OMI Program Patents"***). Isis will own Program Inventions, including those inventions described in Section 4.7.2, invented solely by employees, consultants and/or (sub)contractors of Isis (the ***"Isis Inventions"***) and any Patents claiming such Program Inventions (the ***"Isis Program Patents"***). Isis and OMI will own jointly such Program Inventions, including those inventions described in Section 4.7.3, invented jointly by employees, consultants and/or (sub)contractors of Isis and OMI (the ***"Joint Inventions"***) and any Patents claiming such Program Inventions (the ***"Joint Patents"***). Isis will promptly disclose to OMI any such Isis Invention or Joint Invention, and OMI will promptly disclose to Isis any OMI 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 will 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).

Section 9.2 **Filing, Prosecution and Maintenance of Patents.**

9.2.1 **Solely Owned Patents.** Subject to the other sections of this Article 9, including the other subsections of this Section 9.2 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 and Analytical Patents.

9.2.2 **Filing, Prosecution and Maintenance of Isis Core Technology Patents and Isis Manufacturing and Analytical Patents.**

(a) As between Isis and OMI, Isis will 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 and Analytical Patents, and Isis will 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 and Analytical Patents. At OMI's reasonable request, Isis, or its outside counsel, will promptly provide OMI with an update of the filing, prosecution and maintenance status for each of the Isis Core Technology Patents and Isis Manufacturing and Analytical Patents, including without limitation an update of **APPENDIX 3** and **4**.

9.2.3 **Filing, Prosecution and Maintenance of Product Specific Patents.**

(a) [***]. In accordance with th is Section 9.2.3 and subject to Section 9.2.4, for Product Specific Patents related to Selected Gene Targets that OMI has [***] Isis will have lead responsibility (using internal or outside counsel selected by Isis) for preparing, filing, prosecuting (including, without limitation, any interferences, reissue proceedings, oppositions and reexaminations) and maintaining such Product Specific Patents at Isis' expense. In addition, within [***], for each Selected Gene Target, Isis will have filed a patent application claiming at a minimum the specific composition of matter of the Research Compound(s) targeting such Selected Gene Target. OMI will cooperate with Isis in the filing and prosecution of such patent applications, including consulting with and assisting Isis and its patent counsel in drafting patent applications and responses. At OMI's reasonable request, Isis, or its outside counsel, will promptly provide OMI with an update of the filing, prosecution and maintenance status for each of the Product Specific Patents [***].

(b) [***]. In accordance with this Sec tion 9.2.3, for Product Specific Patents related to Selected Gene Targets that OMI [***], Isis will assign to OMI, in the form provided as provided in **Appendix 17,** all of Isis' rights, title and interest in all Product Specific Patents, Research Results and data from the R&D Plan that relate to such Compound or Product.

(c) Cooperation. In each case under Section 9.2.3 subparagraph (a) or (b) above, upon request by the Party prosecuting Product Specific Patents (the ***"Prosecuting Party"***), the other Party will provide such assistance and execute such documents as are reasonably necessary to

permit the filing, prosecution and/or maintenance of such Product Specific Patents or the issuance, maintenance and/or extension of any resulting patent or permit enforcement of such patent application or any such patent. At the request of the other Party, the Prosecuting Party, or its outside counsel, will provide the other Party with an update of the filing, prosecution and maintenance status for each of the Product Specific Patents on a periodic basis for which the Prosecuting Party assumes lead responsibility and will reasonably consult with and cooperate with the other Party with respect to the preparation, filing, prosecution and maintenance of such Product Specific Patents. If requested in writing by the other Party, the Prosecuting Party, or its outside counsel, will provide to the other Party copies of any papers relating to the filing, prosecution and maintenance of such Product Specific Patents promptly upon their being filed or received.

(d) Election Not to File, Prosecute, or Ma intain Product Specific Patents. In the event that the Prosecuting Party elects not to pursue or continue the filing, prosecution (including any material reduction in claim scope) or maintenance of any Patents or subject matter included in such Product Specific Patents in any country, it will provide the other Party with an opportunity to assume responsibility and costs for such filing, prosecution or maintenance of such Product Specific Patents as set forth in this Section 9.2.3. The Prosecuting Party will not 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 the other Party's written consent or the other Party otherwise first being given an opportunity to assume full responsibility (at the assuming Party's expense) for the continued prosecution and maintenance of such Product Specific Patents, or the filing of such new patent application. Accordingly, the Prosecuting Party, or its outside counsel, will, to the extent that it is able, provide the other Party 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 the other Party will provide the Prosecuting Party with prompt notice as to whether the other Party desires the Prosecuting Party to file any such new patent application.

(e) National Phase Filing Decisions for Product Specific Patents. At the time that a Product Specific Patent is ready to enter National Phase outside of the United States, the Prosecuting Party shall provide notice to the other Party at least 30 Business Days prior to the National Phase deadline that an election of countries is required. OMI will provide notice to Isis of the countries it intends to elect and OMI shall bear the reasonable costs of such election.. At a minimum, OMI must elect the countries in which OMI typically enters National Phase for OMI's products (collectively, the ***"Minimum OMI Countries"***). The Minimum OMI Countries as of the Execution Date are set forth in **APPENDIX 13** attached hereto. Isis shall have the right and option to elect other countries for National Phase entry in writing with notice to OMI. Upon such notice to Isis, Isis shall promptly notify OMI of its election and OMI will use Commercially Reasonable Efforts to comply with Isis' election. Each Party shall bear the costs of their respective elections and prosecution. In the case where a Party wishes to pursue subject matter the Prosecuting Party (under subparagraph (a) or (b) above as the case may be) has deleted from a claim (where such Prosecuting Party has elected to not otherwise pursue the subject matter of such claim in the same or another application), the other Party may pursue at its own cost (including costs associated with transfer, filing, prosecution or maintenance) such subject matter in a corresponding continuation or divisional application (where permissible under law) in accordance with and subject to this Section 9.2.3.

(f) Filing, Prosecution and Maintenance of Product Specific Patents by OMI.. For so long as OMI retains lead responsibility under this Section 9.2.3 with respect to a particular Product Specific Patent, OMI will 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 result in claims that no longer cover the Product. In the case where OMI assumes responsibility, under subsection (b) of this section, 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 9.2.3, OMI 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.

(g) Filing, Prosecution and Maintenance of Product Specific Patents by Isis. For so long as Isis retains lead responsibility under Section 9.2.3 with respect to a particular Product Specific Patent, Isis will 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 OMI written notice and information as set forth above. In the case where Isis assumes responsibility, under subsection (a) of this section, 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 9.2.3, Isis will not be liable to OMI 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.

9.2.4 Filing, Prosecution and Maintenance of Certain Program Patents, including Joint Patents.

(a) This Section 9.2.4 will apply to Program Patents that are not Product Specific Patents (the preparation, filing, prosecution and maintenance of the Program Patents that are Product Specific Patents are governed by Section 9.2.3) and to Joint Patents under Section 9.1(a). Each Party will have lead responsibility for Program Patents invented solely by its own

employees as provided in Section 9.1(a), and OMI will cooperate fully, with respect to the preparation, filing, prosecution (including, without limitation, any interferences, reissue proceedings, oppositions and reexaminations) and maintenance of the Program Patents with respect to Joint Patents claiming Program Inventions for the Term. Each Party will be responsible for all of its own out-of-pocket costs with respect to such preparation, filing, prosecution and maintenance of Program Patents that are not Product Specific Patents.

(b) With respect to Joint Inventions claming Program Patents that are not Product Specific Patents, pursuant to 9.1(a), OMI will promptly disclose to Isis such Joint Inventions, and Isis will have the right, and bear the costs, in accordance with this Section 9.2.4 to file and prosecute any new patent application claiming such inventions. OMI will cooperate with Isis in the filing and prosecution of such patent applications, including consulting with and assisting Isis and its patent counsel in drafting patent applications and responses. In addition, upon request by Isis, OMI 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. Isis, or its outside counsel, will provide

OMI with an update of the filing, prosecution and maintenance status for each of the Program Patents on a periodic basis for which Isis assumes lead responsibility and will reasonably consult with and cooperate with OMI with respect to the preparation, filing, prosecution and maintenance of such Joint Patents, including providing OMI with drafts of proposed filings in sufficient time to allow OMI's review and comment before such filings are due. Isis, or its outside counsel, will provide to OMI copies of any papers relating to the filing, prosecution and maintenance of such Joint Patents promptly upon their being filed or received. In the event that Isis elects not to pursue or continue the filing, prosecution or maintenance of any Joint Patents in any country, Isis will provide OMI with an opportunity to assume responsibility for such filing, prosecution or maintenance of such Patents to the same manner and under the same conditions that Isis is able to assume responsibility for Product Specific Patents from OMI as provided in Section 9.2.3, such that such Program Patent Rights will be treated in the same manner as Product Specific Patents under Section 9.2.3. In the case where either Party assumes responsibility for the preparation, filing, prosecution or maintenance of any patent or patent application as set forth above, and has used good faith, reasonable efforts to comply with its obligations to provide notice and information as set forth is this Section 9.2.4, that Party will not be liable to the other Party 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.

9.2.5 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 9.3 **Patent Term Extension.** Isis and OMI will each cooperate with one another and will use Commercially Reasonable Efforts in obtaining patent term restorations and/or 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 OMI hereunder. If elections with respect to obtaining such patent term extensions or supplemental protection are to be made, OMI will 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 9.4 **Enforcement of Patents**

9.4.1 Enforcement by OMI of Product Specific Patents. In the event that Isis or OMI becomes aware of a suspected infringement 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 will notify the other Party promptly, and following such notification, the Parties will confer. OMI will have the right, but will not be obligated, to defend any such action or proceeding or bring an infringement action with respect to such infringement to the extent relevant to OMI'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 will reasonably assist OMI in any action or proceeding being defended or prosecuted if so requested, and will lend its name to such actions or proceedings if reasonably requested by OMI or required by Applicable Law. OMI will reimburse Isis for the documented out-of-pocket costs Isis reasonably incurs in providing such assistance as specifically requested in writing by OMI. In the event Isis is a required party to the proceeding or action, Isis will have the right to be represented by its own counsel (such selection to be subject to OMI's approval, such approval not to be unreasonably withheld), and OMI will reimburse Isis for the documented external costs Isis reasonably incurs that are reasonably related to the proceeding or action, including attorneys fees, *provided* that OMI will 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 will have the right to participate and be represented in any such suit by its own counsel at its own expense, *provided* that OMI will 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 OMI without the prior written consent of Isis, which consent will not be unreasonably withheld, delayed or conditioned.

9.4.2 Enforcement by Isis. If OMI elects not to settle, defend or bring any action for infringement described in Section 9.4.1 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 OMI's request based on OMI's good faith reasonable determination, the basis for which will 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 will apply. OMI will reasonably assist Isis in any action or proceeding being defended or prosecuted if so requested, and will lend its name to such actions or proceedings if requested by Isis or required by Applicable Law. Isis will reimburse OMI for the documented external costs OMI reasonably incurs, including attorneys fees, in providing such assistance as specifically requested in writing by Isis. OMI will have the right to participate and be represented in any such suit by its own counsel at its own expense, *provided* that Isis will 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, or which could be reasonably expected to have a material adverse financial impact on OMI, may be entered into by Isis without the prior written consent of OMI, which consent will not be unreasonably withheld, delayed or conditioned. In addition, if OMI elects not to settle, defend or bring any action for infringement against an infringing Third Party described in Section 9.4.1, then any infringing products sold by

such Third Party will not be included in the calculation of sales of Generic Products under Section 6.7.

9.4.3 Withdrawal. In addition to Section 9.4.2, if either Party brings an action or proceeding under this Section 9.4 and subsequently ceases to pursue or withdraws from such action or proceeding, it will 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 9.4 (including but not limited to the proviso in the first sentence of Section 9.4.2).

9.4.4 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 9.2.5 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.

9.4.5 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.

9.4.6 Damages. In the event that either Party exercises the rights conferred in this Section 9.4 and recovers any damages or other sums in such action, suit or proceeding or in settlement thereof, such damages or other sums recovered will 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 9.4, 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 will be shared pro rata in proportion to the total of such costs and expenses incurred by each Party. If after such reimbursement any funds will remain from such damages or other sums recovered, such funds will be divided as follows: (i) as to ordinary damages based on lost sales or profit, OMI will retain such funds and such funds will be treated as Net Sales and royalties will be payable by OMI 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 will receive [***]% of the amount of such special or punitive damages and the other Party will receive [***]% of the amount of such special or punitive damages.

9.4.7 Enforcement of Isis Core Technology Patents and Isis Manufacturing and Analytical Patents by OMI. In the event that Isis or OMI becomes aware of a suspected infringement of any Isis Core Technology Patents and Isis Manufacturing and Analytical Patents by a Third Party where such infringement involves the manufacture, use or sale of an ASO targeting a Collaboration Gene Target (including but not limited to infringement which is the subject of a notice under Section 9.5), the Parties will confer and discuss in good faith an enforcement strategy with respect to such Isis Core Technology Patents and Isis Manufacturing and Analytical Patents against such Third Party, and Isis will consider in good faith and not unreasonably deny or delay OMI's request to enforce such Isis Core Technology Patents and Isis Manufacturing and Analytical Patents in the same manner as a Product Specific Patent as set forth above in this Article 9.

Section 9.5 **Notification of Patent Certification.** Isis will notify and provide OMI 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 will be

provided to OMI by Isis as soon as practicable and at least within five (5) days after Isis receives such certification, and will be sent by facsimile and overnight courier to the address set forth below:

Ortho McNeil, Inc.
1000 US Route 202
Raritan, New Jersey, 08869
Attention: President
Facsimile: 908-707-9757

With copy to:

Johnson & Johnson Chief Patent Counsel
Johnson & Johnson
1 Johnson & Johnson Plaza
New Brunswick, NJ 08933
Facsimile: 732-524-5575

Section 9.6 **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), OMI will 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 OMI 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 OMI, Isis will provide reasonable cooperation to OMI in filing and maintaining any such listing and filings. All listing and filing decisions shall be at the sole discretion of OMI; *provided ,however* that OMI will 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 will Isis withhold or delay such consent where the listing of such Isis Core Technology Patent is required under applicable law.

Section 9.7 **Further Actions.** Each Party will, 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 9; *provided however*, that neither Party will be required to take any action pursuant to Article 9 that such Party reasonably determines in its sole judgment and discretion conflicts with or violates any applicable court or government order or decree.

Section 9.8 **Infringement Claims; Oppositions.** OMI and Isis will 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 will become aware. The Parties will confer on the handling of such matter. Isis will not acknowledge to a Third Party the validity of any such allegation or admit liability without the prior written consent of OMI, and OMI will 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. OMI and Isis will 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 will 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.

OMI and Isis will 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 will confer on the handling of such matter and such matters will be handled in accordance with Section 9.2.3 and 9.2.4 above.

Section 9.9 **Records Regarding Isis Patents.** Each Party will assign patent counsel representatives who will be responsible for coordinating activities between the Parties in accordance with this Article 9. Such representatives will use Commercially Reasonable Efforts to maintain a report listing the Isis Patents that are subject to the license granted to OMI under Section 2.1. Such report will be used to facilitate the identification and tracking of the Isis Patents licensed under this Agreement, but will 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 Patents licensed under this Agreement.

ARTICLE 10 - TERM AND TERMINATION

Section 10.1 **Term.** The term of this Agreement (the ***"Term"***) commences upon the Execution Date and, unless earlier terminated in accordance with the provisions of this Article 10 or Article 11, will continue until (i) the expiration of all obligations to pay royalties on all Products to Isis (including any Pass Through Royalties) and (ii) the making, using or selling of a Compound or Product is not covered by a Valid Claim within any Isis Patent Right, provided, however, that in accordance with Section 14.13, certain provisions of this Agreement will only become effective and binding on the Parties as of the Effective Date upon the satisfaction of the conditions set forth in Section 14.13(c).

Section 10.2
OMI Right to Terminate.

(a) At any time prior to the Effective Date, OMI may terminate this Agreement in accordance with the terms of Section 14.13(f) of this Agreement.

(b) After the expiration of the Collaboration Term, OMI may terminate this Agreement (including its license rights under this Agreement) in full (but not in part), effective upon [***] prior written notice. For purposes of clarification, milestone and royalty payments will be due on milestones achieved and Products sold during the period between notice of termination and the effective date of termination.

(c) At any time During the Collaboration Term, but following payment by OMI of the technology access fee under Section 6.1, OMI shall be entitled to terminate this Agreement (including its license rights under this Agreement) in full (but not in part) in the event of the detection in a test population of adverse experiences associated with the administration of MOE Gapmers as a generic class of compounds that are significant, serious or life threatening to the patient or demonstrate significant toxicological effect(s) of MOE Gapmers as a generic class on one or more body tissues that are not balanced by a countervailing benefit to the patient. The safety of MOE Gapmers will be determined by OMI in view of the risk to benefit relationship of such MOE Gapmers in the relevant patient population.

(d) OMI shall be entitled to terminate this license at any time on a Product by Product basis for safety reasons, including the detection in a test population of adverse experiences associated with the administration of the Product that are significant, serious or life threatening to the patient or demonstrate significant toxicological effect(s) of such Product on one or more body tissues that are not balanced by a countervailing benefit to the patient. The safety of a Product will be determined by OMI in view of the risk to benefit relationship of such Product in the relevant patient population.

Section 10.3 **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 OMI's obligations under Section 5.1, which is governed by Section 10.4), then the non-breaching Party may deliver notice of such breach to the other Party. In such notice the non-breaching Party will identify the actions or conduct that it wishes such Party to take for an acceptable and prompt cure of such breach (or will otherwise state its good faith belief that such breach is incurable); *provided* that such identified actions or conduct will not be binding upon the other Party with respect to the actions that it may need to take to cure such breach. If the breach is curable, the allegedly breaching Party will have [***] 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 [***] following such notice) or, if a cure cannot be reasonably effected within such [***] period, to deliver to the non-breaching Party a plan for curing such breach which is reasonably sufficient to effect a cure within a reasonable period. If the breaching Party fails to (i) cure such breach within the [***] period or (ii) use Commercially Reasonable Efforts to carry out the plan and cure the breach, the non-breaching Party may terminate this Agreement on a Product-by-Product basis by providing written notice to the breaching Party.

(b) Notwithstanding the foregoing, if the allegedly breaching Party disputes in good faith the existence, materiality, or failure to cure of any such breach which is not a payment breach, and provides notice to the non-breaching Party (the ***"Other Party"***) of such dispute within such [***] period, the Other Party will not have the right to terminate this Agreement in accordance with this Section 10.3 unless and until it has been determined in accordance with Section 14.4 that this Agreement was materially breached by the allegedly breaching Party and

that Party fails to cure such breach within [***] 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 will remain in effect and the Parties will continue to perform all of their respective obligations hereunder.

(c) This Section 10.3 will be subject to and will not limit the provisions of Section 10.4 and Section 10.5.

Section 10.4 **Termination by Isis For Failure of OMI to Use Commercially Reasonable Efforts.**

(a) Subject to Section 10.4(b) and 10.4(c), at any time after the expiration of the Collaboration Term, Isis will have the right to terminate the License granted under Section 2.1 on a country-by-country basis, if OMI is in breach of its obligations to use Commercially Reasonable Efforts as set forth in Section 5.1, *provided however*, that the Agreement will not so terminate unless (i) OMI is given [***] prior written notice by Isis of Isis's intent to terminate, stating the reasons and justification for such termination and recommending steps which OMI should take, and (ii) OMI, or its Licensee, has not used good faith Commercially Reasonable Efforts during the [***] period following such notice to diligently pursue the Development and/or Commercialization of at least one Compound or Product for each Collaboration Gene Target. Any such termination will be limited in force and effect to the country or countries and Products 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 OMI (by itself or through its Affiliates or Licensees) uses Commercially Reasonable Efforts to Develop a Product in each and every Major Market Country, OMI will be deemed to be in compliance with its obligation under Section 5.1 to use Commercially Reasonable Efforts to Develop a Product with respect to all countries in the world. Termination under this Section 10.4 will apply to all Compounds and Products that target the applicable Collaboration Gene Target, but only for the affected country or countries.

(c) If OMI disputes in good faith the existence or materiality of an alleged breach specified in a notice provided by Isis pursuant to Section 10.4(a), and provides notice to Isis of such dispute within the [***] following such notice provided by Isis, Isis will not have the right to terminate this Agreement unless and until the existence of such material breach or failure by OMI has been determined in accordance with Section 14.4 and OMI fails to cure such breach within [***] 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 will remain in effect and the Parties will continue to perform all of their respective obligations hereunder.

Section 10.5 **Consequences of Termination.**

10.5.1 **Licenses.** Upon termination of this Agreement in its entirety by either Party pursuant to this Article 10, the licenses granted by Isis to OMI hereunder will terminate.

10.5.2 **Return of Information and Materials.** Upon termination of this Agreement in its entirety by either Party pursuant to this Article 10, the Parties will return (or destroy, as directed by the other Party) all data, files, records and other materials containing or comprising the other Party's Confidential Information. Notwithstanding the foregoing, the Parties will be permitted to retain one copy of such data, files, records, and other materials for archival purposes.

Section 10.6 **Accrued Rights; Surviving Obligations.**

10.6.1 **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 will be payable by OMI 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.

10.6.2 **Survival.** Articles 7, 8, 9, 10, 11, 12 and 14, and Section 6.11, 6.15 and Section 13.4 of this Agreement will survive expiration or termination of this Agreement for any reason. Furthermore, Isis hereby grants to OMI a worldwide non-exclusive license, with the right to grant sublicenses under Section 2.2, to Isis Know-How existing now or in the future and disclosed to OMI during the Term, solely for the further manufacture and sale of Compounds and Products after the expiration of the Term. Isis further acknowledges and agrees that upon the expiration of the Term, (i) OMI will no longer have an obligation to pay royalties to Isis on any Product, and (ii) the making, using or selling of a Compound or Product will not be covered by a Valid Claim within any Isis Patent Right.

Section 10.7 **Rights in Bankruptcy.** All rights and licenses granted under or pursuant to this Agreement by Isis or OMI are, and will 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, will 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, will be promptly delivered to it upon the non subject Party's written request therefor. Any agreements supplemental hereto will be deemed to be "agreements supplementary to" this Agreement for purposes of Section 365(n) of the U.S. Bankruptcy Code.

ARTICLE 11 - ISIS REVERSION RIGHT

Section 11.1 **Isis Reversion Rights.**

11.1.1 If (i) OMI terminates the Agreement under Section 10.2, (ii) OMI makes a substitution under Section 3.6.1, or (iii) Isis terminates the Agreement under Section 10.3 or 10.4, Isis may elect to continue to Develop and Commercialize any Compound or Product that is the subject of such termination or substitution (a ***"Discontinued Product"***) by notice in writing to OMI within [***] of such termination (an ***"Election Notice"***) that Isis is exercising its rights under this Section 11.1, in which case OMI will (x) grant to Isis a fully-paid, sublicensable, worldwide license or sublicense, as the case may be, to [***] as of the date of the Election Notice solely as they are [***] to make, have made, use, sell, offer for sale, have sold and import Discontinued Products, and (y) transfer to Isis, for Isis' use with respect to the Development and Commercialization of the Discontinued Products, any data, results, regulatory information and files in the possession of OMI as of the date of the Election Notice that relate to such

Discontinued Products. Further, any Product Specific Patents assigned to OMI pursuant to 9.2.3 (c) shall be reassigned back to Isis.

11.1.2 In consideration for the rights granted by OMI to Isis under parts (x) and (y) of Section 11.1.1, Isis will pay a royalty on net sales of each Discontinued Product by Isis, its Affiliates and licensees as follows: (i) [***]% of net sales of such Discontinued Product if the Election Notice occurs after the applicable Compound or Product achieved the [***] milestone, and OMI makes the corresponding payment to Isis under Section 6.3, (ii) [***]% of net sales of such Discontinued Product if the Election Notice occurs after the applicable Compound or Product achieved the [***] milestone, and OMI makes the corresponding payment to Isis under Section 6.3. Such royalty payment obligation will be governed by Sections 6.8 through 6.15 (and the definition of Net Sales) which shall apply to Isis in the same way as they applied to OMI prior to such termination of the Agreement.

ARTICLE 12 -

INDEMNIFICATION, INSURANCE AND LIMITATION OF LIABILITY

Section 12.1 **Indemnification of Isis.** OMI 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 will 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 attorneys' 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) the Development, manufacture, use, handling, storage, sale or other Commercialization or disposition of any Compound or Product in the Territory by OMI or its Affiliates, Licensees or contractors, (b) any breach by OMI of any of its representations or warranties pursuant to this Agreement or any of the agreements or covenants in this Agreement that contemplate performance or compliance by OMI on or prior to the Effective Date or (c) to the extent resulting from the negligence or willful misconduct of OMI or any OMI Affiliate or Licensee in connection with this Agreement; *except* in any such case to the extent such Losses result from: (i) the 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 12.2 **Indemnification of OMI.** Isis agrees to defend OMI, its Affiliates, Licensees and their respective directors, officers, employees and agents, and their respective successors, heirs and assigns (collectively, the ***"OMI Indemnitees"***), and will indemnify and hold harmless the OMI Indemnitees, from and against any Losses and Third Party Claims brought against any OMI Indemnitee and resulting from or occurring as a result of: (a) any breach by Isis of any of its representations or warranties pursuant to this Agreement or any of the agreements or covenants in this Agreement that contemplate performance or compliance by Isis on or prior to the Effective Date or (b) to the extent resulting from the negligence or willful misconduct of any Isis Indemnitee or any (sub)contractor of OMI in connection with this Agreement; *except* in any such case to the extent such Losses result from: (i) the negligence or willful misconduct of any OMI Indemnitee or (sub)contractor of OMI, (ii) any breach by OMI 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 OMI Indemnitee or (sub)contractor of OMI.

Section 12.3 **Notice of Claim.** All indemnification claims provided for in Sections 12.1 and 12.2 will be made solely by such Party to this Agreement (the ***"Indemnified Party"***). The Indemnified Party will 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 12.1 or 12.2, but in no event will 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 will furnish promptly to the indemnifying Party copies of all papers and official documents received in respect of any Losses and Third Party Claims.

Section 12.4 **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 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 will 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 will 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 will 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 12.4(b), the Indemnified Party will 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 will 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 12.4(a), any Indemnified Party will 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 will 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 12.4(a) (in which case the Indemnified Party will 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 will 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 will 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 will have

acknowledged in writing the obligation to indemnify the Indemnified Party hereunder, the indemnifying Party will 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, will 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 12.4(a), the indemnifying Party will 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 will not be unreasonably withheld). The indemnifying Party will 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 will 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 will, and will cause each other Indemnified Party to, cooperate in the defense or prosecution thereof and will 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 will 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 will 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 12.4, the costs and expenses, including attorneys' fees and expenses, incurred by the Indemnified Party in connection with any claim will 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 12.5 **Insurance.** OMI will maintain at its cost and expense, adequate liability insurance (including product liability insurance covering OMI's products undergoing clinical trials and commercialized products) to protect against potential liabilities and risk arising out of activities to be performed by OMI 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 OMI under this Agreement. OMI will promptly notify Isis of any material change in insurance or self-insurance coverage or lapse in coverage in that regard. Furthermore, OMI will provide Isis the information Isis reasonably requests to allow Isis to maintain Isis' clinical trial insurance covering the clinical trials for Compounds or Products conducted by OMI. Isis agrees to procure and maintain in full force and effect during the Term, valid and collectible insurance policies as outlined in **Appendix 14**. Upon written request, Isis shall provide OMI with certificates of insurance evidencing the required coverage.

ARTICLE 13 -
REPRESENTATIONS AND WARRANTIES

Section 13.1 **Representations, Warranties and Covenants.** Each Party hereby represents and warrants as of both the Execution Date and 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; and

(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.

Section 13.2 **Isis Representations, Warranties, and Covenants**. Isis' representations and warranties under this Agreement regarding gene targets are limited to GCCR, GCGR on both the Execution Date and Effective Date and the gene targets that are part of the Target Pool on the Execution Date. Similarly, Isis' representations and warranties under this Agreement regarding Compounds are limited to (i) Compounds that inhibit GCCR and GCGR Compounds identified and known by Isis both on the Execution Date and Effective Date and (ii) Compounds that inhibit the gene targets that are part of the Target Pool on the Execution Date. As such, Isis hereby represents and warrants as of the Execution Date and, where indicated, as of the Effective Date and covenants to OMI 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 Patents as is necessary to fulfill its obligations under this Agreement and further, that, with respect to the Compounds, the grant of the licenses (or sublicenses as the case may be) to OMI pursuant to this Agreement does not, and as of the Effective Date will not, violate any right known to Isis of any agreement Isis has with a Third Party;

(b) with respect to agreements between Isis and any Third Party existing on the Execution Date, the only financial Pass Through Obligations for ISIS 325568 and ISIS 377131 are the Isis Supported Payments and further that Isis is not aware of any other Third Party Patents that are necessary for OMI to make, use or sell ISIS 325568 and ISIS 377131 other than those provided in **Appendix 6**. Any existing Pass Through Royalties encumbering the Compounds or gene targets in the Target Pool are listed in **Appendix 6**;

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

(d) subject to the limitations set forth in **Appendix 6**, it has, and as of the Effective Date, will have, the ability to grant to OMI the licenses granted or to be 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, and as of the Effective Date will not be, 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 OMI the licenses granted by Isis under this Agreement on the terms set forth herein or the right of OMI to exercise such license rights;

(f) it has not granted, or permitted to be attached, and it will not grant or permit to be attached during the Term, 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 OMI hereunder;

(g) during the Term, Isis will 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 OMI under this Agreement; as of the Execution Date, Isis is in compliance in all material respects with any aforementioned agreements with Third Parties;

(h) it has not granted, as of the Effective Date will not have granted, any license, option or other rights to any other Third Party with respect to any Product Specific Patents (with the exception of the material transfer agreements listed as numbers 20-29 in **Appendix 6**);

(i) subject to the limitations set forth in **Appendix 6**, it has not granted, and as of the Effective Date will not have 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 OMI hereunder that is in conflict with the rights or licenses granted or to be granted to OMI under this Agreement;

(j) 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 R&D Plan (together with any associated potential Pass Through Obligations) are included in the list of agreements identified in **Appendix 6**;

(k) Isis owns or possesses adequate licenses or other rights to use all existing research tools that it uses or has used to identify the Compounds;

(l) unless disclosed in writing between the Parties to this Agreement or their respective agents, to Isis' knowledge, (i) there are no issued patents of a Third Party that would be infringed by OMI's manufacture, use or sale of the Compounds and (ii) no Third party is currently infringing any Product Specific Patents licensed hereunder;

(m) the license and/or transfer of any data related to the Compounds that is part of the Isis Know-How and Product Specific Know-How under this Agreement will not violate the terms of any agreement Isis has with a Third Party;

(n) Isis has written evidence that [***];

(o) Isis is not aware of any Third Party Patents, apart from those encompassed in the licenses listed in **Appendix 6** that are necessary for OMI to make, use or sell ASOs directed to gene targets that are part of the Target Pool; and

(p) on or prior to the Effective Date, Isis will have exercised the Purchase Option, consummated the Purchase Option Closing and terminated the Technology License Agreement (as such terms are defined in Section 14.13 herein) and re-acquired Isis' GCCR Program and GCGR Programs pursuant to the Purchase Option Agreement such that neither Symphony GenIsis Inc. nor Symphony GenIsis Holdings LLC will have any rights that would prevent or encumber or otherwise limit the licenses granted by Isis to OMI under this Agreement or Isis' ability to perform its obligations under the R&D Plan.

Section 13.3 **OMI Representation and Covenant.** OMI hereby represents and warrants as of both the Execution Date and the Effective Date and covenants to Isis that:

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

(b) OMI's 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) OMI, 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.

(d) certain OMI Affiliate employee(s) were previously employed by Isis and may work on the subject matter of this Agreement; therefore OMI represents that, while the employee(s) Know-How learned at Isis may be employed to the benefit of this Collaboration, such information shall remain Confidential pursuant to Article 8 herein.

Section 13.4 **DISCLAIMER OF WARRANTY.** EXCEPT FOR THE EXPRESS WARRANTIES SET FORTH IN THIS ARTICLE 13, OMI 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 OMI AND ISIS EACH SPECIFICALLY DISCLAIM ANY OTHER WARRANTIES, WHETHER WRITTEN OR ORAL, OR EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF QUALITY, MERCHANTABILITY OR FITNESS FOR A PARTICULAR USE OR PURPOSE OR ANY WARRANTY AS TO THE VALIDITY OF ANY PATENTS OR THE NON-INFRINGEMENT OF ANY INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES.

ARTICLE 14 - MISCELLANEOUS

Section 14.1 **Assignment; OMI Affiliates.** 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 6 (but no liabilities) to a Third Party in connection with a royalty factoring transaction. Any purported assignment or transfer in violation of this Section 14.1 will be void *ab initio* and of no force or effect. Isis acknowledges and agrees that certain of OMI's responsibilities and obligations may be performed by one or more of OMI's Affiliates; *provided, however*, that OMI will continue to be liable to Isis for any breach of this Agreement by any of OMI's Affiliates.

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

Section 14.3 **Governing Law; 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 will be governed by and construed and enforced in accordance with the patent laws of the applicable jurisdiction.

Section 14.4 **Dispute Resolution**.

14.4.1 **Resolution by Senior Representatives.** The Parties will seek to settle amicably any and all disputes, controversies or claims arising out of or in connection with this Agreement. Any dispute within the R&D Committee's decision-making authority will be finally decided as set forth in **Appendix 5**. Any dispute between the Parties which is outside the R&D Committee's decision-making authority will be promptly presented to each Party's respective co-chair of the R&D Committee for resolution, and if the co-chairs of the R&D Committee are unable to resolve such dispute, such dispute will then be presented to the President, R&D of OMI and the Executive Vice President and CFO 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. Any dispute within the R&D Committee's decision-making authority will not be subject to arbitration.

14.4.2 **Arbitration and Mediation.** If after negotiating in good faith pursuant to Section 14.4.1, after good faith discussions undertaken within reasonable promptness, to reach an amicable agreement within 90 days, then either Party may upon written notice to the other submit to mediation and binding arbitration pursuant to Sections 14.4.2.2 and 14.4.2.3 below. No statements made by either Party during such discussions will be used by the other Party or admissible in arbitration or any other subsequent proceeding for resolving the dispute.

14.4.2.1 Arbitration.

a. Any dispute, claim or controversy arising from or related in any way to this Agreement or the interpretation, application, breach, termination or validity thereof, including any claim of inducement of this Agreement by fraud or otherwise, not resolved under the provisions of Sections 14.4.1 and 14.4.2.3 will be submitted for resolution to arbitration pursuant to the rules then pertaining of the CPR Institute for Dispute Resolution for Non-Administered Arbitration (available at www.cpradr.org/arb-rules.htm), or successor ("CPR"), except where those rules conflict with these provisions, in which case these provisions control. The arbitration will be held in Chicago, Illinois.

b. The arbitration panel shall consist of three arbitrators chosen from the CPR Panels of Distinguished Neutrals (or, by agreement, from another provider of arbitrators). Unless otherwise agreed by the Parties, each of the arbitrators will be a lawyer with at least 15 years experience with a law firm or corporate law department of over 25 lawyers or who was a judge of a court of general jurisdiction. In the event the aggregate damages sought by the claimant Party are stated to be less than $[***], and the aggregate damages sought by the counterclaimant Party are stated to be less than $[***], and neither side seeks equitable relief, then a single arbitrator shall be chosen, having the same qualifications and experience specified above. Each arbitrator shall be neutral, independent, disinterested, and impartial and shall abide by The CPR-Georgetown Commission Proposed Model Rule for the Lawyer as Neutral available at www.cpradr.org/cpr-george.html.

c. The Parties agree to cooperate (1) to attempt to select the arbitrator(s) by agreement within 45 days of initiation of the arbitration, including jointly interviewing the final candidates, (2) to meet with the arbitrators within 45 days of selection, and (3) to agree at that meeting or before upon procedures for discovery and as to the conduct

of the hearing which will result in the hearing being concluded within no more than nine (9) months after selection of the arbitrators and in the award being rendered within 60 days of the conclusion of the hearings, or of any post-hearing briefing, which briefing will be completed by both sides within 45 days after the conclusion of the hearings.

d. In the event the Parties cannot agree upon selection of any arbitrators, the CPR will select arbitrators as follows: CPR shall provide the Parties with a list of no less than 25 proposed arbitrators (15 if a single arbitrator is to be selected) having the credentials referenced above. Within 25 days of receiving such list, the Parties shall rank at least 65% of the proposed arbitrators on the initial CPR list, after exercising cause challenges. The Parties may then interview the five candidates (three if a single arbitrator is to be selected) with the highest combined rankings for no more than one hour each and, following the interviews, may exercise one peremptory challenge each. The panel will consist of the remaining three candidates (or one, if one arbitrator is to be selected) with the highest combined rankings. In the event these procedures fail to result in selection of the required number of arbitrators, CPR shall select the appropriate number of arbitrators from among the members of the various CPR Panels of Distinguished Neutrals, allowing each side challenges for cause and three peremptory challenges each.

e. In the event the Parties cannot agree upon procedures for discovery and conduct of the hearing meeting the schedule set forth in paragraph (c) above, then the arbitrators shall set dates for the hearing, any post-hearing briefing, and the issuance of the award in accord with the paragraph (c) schedule. The arbitrators shall provide for discovery according to those time limits, giving recognition to the understanding of the Parties that they contemplate reasonable discovery, including document demands and depositions, but that such discovery be limited so that the paragraph (c) schedule may be met without difficulty. In no event will the arbitrators, absent agreement of the Parties, allow more than a total of ten days for the hearing or permit either side to obtain more than a total of 20 hours of deposition testimony from all witnesses, including both fact and expert witnesses, or serve more than 10 individual requests for documents, including subparts, or 10 individual requests for admission or interrogatories, including subparts. Multiple hearing days will be scheduled consecutively to the greatest extent possible.

f. The arbitrators must render their award by application of the substantive law of Illinois, except regarding any patent disputes or other such issues where state law is preempted by federal law, in which event US federal law shall apply, and are not free to apply “amiable compositeur” or “natural justice and equity.” The arbitrators shall render a written opinion setting forth findings of fact and conclusions of law with the reasons therefor stated. A transcript of the evidence adduced at the hearing shall be made and shall, upon request, be made available to either Party. The arbitrators shall have power to exclude evidence on grounds of hearsay, prejudice beyond its probative value, redundancy, or irrelevance and no award shall be overturned by reason of such ruling on evidence. To the extent possible, the arbitration hearings and award will be maintained in confidence.

g. In the event the panel’s award exceeds $[***] in monetary damages or includes or consists of equitable relief, or rejects a claim in excess of that amount or for that relief, then the losing Party may obtain review of the arbitrators’ award or decision by a single appellate arbitrator (the “Appeal Arbitrator”) selected from the CPR Panels of Distinguished Neutrals by agreement or, failing agreement within seven working days, pursuant to the selection procedures specified in paragraph d above. If CPR cannot provide such services, the Parties will together select another provider of arbitration services that can. No Appeal Arbitrator shall be selected unless he/she

can commit to rendering a decision within forty-five days following oral argument as provided in this paragraph. Any such review must be initiated within thirty (30) days following the rendering of the award referenced in f above.

h. The Appeal Arbitrator will make the same review of the arbitration panel’s ruling and its basis that the U.S. Court of Appeals of the Circuit where the arbitration hearings are held would make of findings of fact and conclusions of law rendered by a district court after a bench trial and then modify, vacate or affirm the arbitration panel’s award or decision accordingly, or remand to the panel for further proceedings. The Appeal Arbitrator will consider only the arbitration panel’s findings of fact and conclusions of law, pertinent portions of the hearing transcript and evidentiary record as submitted by the Parties, opening and reply briefs of the Party pursuing the review, and the answering brief of the opposing Party, plus a total of no more than four (4) hours of oral argument evenly divided between the Parties. The Party seeking review must submit its opening brief and any reply brief within seventy-five (75) and one hundred thirty (130) days, respectively, following the date of the award under review, whereas the opposing Party must submit its responsive brief within one hundred ten (110) days of that date. Oral argument shall take place within five (5) months after the date of the award under review, and the Appeal Arbitrator shall render a decision within forty-five (45) days following oral argument. That decision will be final and not subject to further review, except pursuant to the Federal Arbitration Act.

i. The Parties consent to the jurisdiction of the State or Federal District Court for the district in which the arbitration is held for the enforcement of these provisions and the entry of judgment on any award rendered hereunder (including after review by the Appeal Arbitrator where such an appeal is pursued). Should such court for any reason lack jurisdiction, any court with jurisdiction shall act in the same fashion.

j. Each Party has the right before or, if the arbitrator(s) cannot hear the matter within an acceptable period, during the arbitration to seek from the appropriate court provisional remedies such as attachment, preliminary injunction, replevin, etc., to avoid irreparable harm, maintain the status

quo, or preserve the subject matter of the arbitration.

k. EACH PARTY HERETO WAIVES ITS RIGHT TO TRIAL OF ANY ISSUE BY JURY.

l. EACH PARTY HERETO WAIVES ANY CLAIM TO PUNITIVE, EXEMPLARY OR MULTIPLIED DAMAGES FROM THE OTHER. EACH PARTY HERETO WAIVES ANY CLAIM OF CONSEQUENTIAL, INDIRECT OR INCIDENTAL DAMAGES FROM THE OTHER. EACH PARTY HERETO WAIVES ANY CLAIM FOR ATTORNEYS' FEES AND COSTS AND PREJUDGMENT INTEREST FROM THE OTHER. IN ADDITION, THE RIGHTS OF TERMINATION BY ISIS UNDER SECTION 10.4 AND THE EFFECT OF SUCH TERMINATION AS SET FORTH IN SECTIONS 10.5 AND 11.1 WILL BE ISIS' ONLY REMEDY AND OMI'S ONLY LIABILITY WITH RESPECT TO OR RESULTING FROM OMI'S BREACH OF ITS OBLIGATIONS AS SET FORTH IN SECTION 5.1.

14.4.2.2 Mediation.

a. Any dispute, controversy or claim arising out of or related to this Agreement, or the interpretation, application, breach, termination or validity thereof, including any claim of inducement by fraud or otherwise, which claim would, but for this provision, be submitted to arbitration shall, before submission to arbitration, first be mediated through non-binding mediation in accordance with The CPR Mediation Procedure then in effect of the CPR Institute for Dispute Resolution (CPR) available at www.cpradr.org/m_proced.htm, except where that procedure conflicts with these provisions, in which case these provisions control. The mediation shall be conducted

in Chicago, Illinois and shall be attended by a senior executive with authority to resolve the dispute from each of the Parties.

b. The mediator shall be neutral, independent, disinterested and shall be selected from a professional mediation firm such as ADR Associates or JAMS/ENDISPUTE or CPR.

c. The Parties shall promptly confer in an effort to select a mediator by agreement. In the absence of such an agreement within 10 days of initiation of the mediation, the mediator shall be selected by CPR as follows: CPR shall provide the Parties with a list of at least 15 names from the CPR Panels of Distinguished Neutrals. Each Party shall exercise challenges for cause, two peremptory challenges, and rank the remaining candidates within 5 working days of receiving the CPR list. The Parties may together interview the three top-ranked candidates for no more than one hour each and, after the interviews, may each exercise one peremptory challenge. The mediator shall be the remaining candidate with the highest aggregate ranking.

d. The mediator shall confer with the Parties to design procedures to conclude the mediation within no more than 45 days after initiation. Under no circumstances may the commencement of arbitration under Section 14.3.4.2 above be delayed more than 45 days by the mediation process specified herein absent contrary agreement of the Parties.

e. Each Party agrees not to use the period or pendency of the mediation to disadvantage the other Party procedurally or otherwise. No statements made by either side during the mediation may be used by the other or referred to during any subsequent proceedings.

f. Each Party has the right to pursue provisional relief from any court, such as attachment, preliminary injunction, replevin, etc., to avoid irreparable harm, maintain the status quo, or preserve the subject matter of the arbitration, even though mediation has not been commenced or completed.

14.4.3 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 10.3 (or 10.2, as applicable). If the material breach is not cured within the time period provided pursuant to Section 10.3 (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 14.5 **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 OMI, to:

Ortho McNeil, Inc.
1000 US Route 202
Raritan, New Jersey, 08869 Attention: President
Facsimile: 908-707-9757

With copy to:

Chief Patent Counsel
Johnson & Johnson
One Johnson & Johnson Plaza

New Brunswick, New Jersey 08933
Facsimile: (732) 524-5575

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 14.5 is not intended to govern the day-to-day business communications necessary between the Parties in performing their duties, in due course, under the terms of this Agreement.

Section 14.6 **Entire Agreement; Modifications**. This Agreement (including the attached Appendices and the R&D 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 14.7 **Headings.** The headings of Articles and Sections of this Agreement are for ease of reference only and will not affect the meaning or interpretation of this Agreement in any way.

Section 14.8 **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 14.9 **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 14.10 **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 14.11 **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 14.12 **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 14.13 **HSR Act Filing; Symphony GenIsis Purchase Option Closing and Technology License Termination; Effective Date.**

(a) The Parties will each, prior to or as promptly as practicable after the Execution Date, file or cause to be filed with the U.S. Federal Trade Commission and the U.S. Department of Justice (requesting early termination of the waiting period) any notifications required to be filed under the HSR Act with respect to the transactions contemplated hereby; *provided* that the Parties will each file the notifications required to be filed under the HSR Act no later than five (5) Business Days after the Execution Date of this Agreement. Each Party will be responsible for its own costs in connection with such filing. The Parties will use commercially reasonable efforts to respond promptly to any requests for additional information made by either of such agencies, and to cause the waiting periods under the HSR Act and any applicable foreign equivalent thereof to terminate or expire at the earliest possible date after the date of filing.

Notwithstanding the foregoing or any other provision of this Agreement, neither OMI nor any of its affiliates shall be required to agree to any sale, transfer, license, separate holding, divestiture or other disposition of, or to any prohibition of, or any limitation on, the acquisition, ownership, operation, effective control or exercise of full rights of ownership of (a "Divestiture"), any asset or assets of OMI or its affiliates.

(b) Isis will, upon receipt of notice of the expiration or earlier termination of the waiting period under the HSR Act in the United States with respect to the transactions contemplated hereby (***"HSR Clearance"***), immediately (i) exercise the Purchase Option pursuant to the Purchase Option Agreement, dated April 7, 2006 (the ***"Purchase Option Agreement"***), among Isis, Sympony GenIsis Holdings LLC (***"Holdings"***) and Symphony GenIsis Inc. (***"Symphony GenIsis"***), (ii) consummate the Purchase Option Closing and re-acquire the rights to Isis' GCCR Program and GCGR Program pursuant to the Purchase Option Agreement, and (iii) terminate the Novated and Restated Technology License Agreement, dated April 7, 2007 (the ***"Technology License Agreement"***), between Isis, Holdings and Symphony GenIsis.

(c) Notwithstanding anything in this Agreement to the contrary, Articles 2, 3, 4, 5, 6, 9, and 11 of this Agreement will not become effective and binding on the Parties until (i) receipt of HSR Clearance (ii) the consummation of the Purchase Option Closing and the termination of the Technology License Agreement, and (iii) receipt by OMI of a Confirmation of Closing, in the form set forth in **Appendix 15** hereto, executed by Isis and Holdings, a Confirmation of Termination, in the form set forth in Appendix 15 hereto, executed by Isis and Symphony GenIsis, and other evidence reasonably satisfactory to OMI that the Purchase Option Closing has been consummated and the Technology License Agreement has been terminated. The date of satisfaction of the conditions set forth in this Section 14.13(c) is referred to in this Agreement as the ***"Effective Date."***

(d) At OMI's request, Isis will deposit into escrow with legal counsel mutually agreeable to both Parties, all documents that are necessary to exercise the Purchase Option and required by Isis to consummate the Purchase Option Closing and terminate the

Technology License Agreement, with instructions to deliver such documents to Symphony GenIsis and Holdings and declare such documents automatically effective upon receipt of HSR Clearance.

(e) Defined terms used in this Section 14.13, but not otherwise defined in this Agreement, will have the meaning ascribed to them in the Purchase Option Agreement.

(f) If the conditions set forth in Section 14.13(c)(ii) and (iii) above shall not have been satisfied within 10 (ten) Business Days of receipt of HSR Clearance, OMI shall have the unilateral right to terminate this Agreement without any prior notice to Isis.

(g) In the event of a termination of this Agreement under part (f) above, notwithstanding the provisions of Section 10.6.2 herein, only Articles 7, 8, 10, 12 and 14 and Section 13.4 of this Agreement shall survive such termination.

Section 14.14 **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 14.15 **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 will be construed as if drafted jointly by the Parties and no presumption or burden of proof will arise favoring or disfavoring any Party by virtue of the authorship of any provisions of this Agreement.

(b) The definitions of the terms herein will apply equally to the singular and plural forms of the terms defined. Whenever the context may require, any pronoun will include the corresponding masculine, feminine and neuter forms. The words "include", "includes" and "including" will be deemed to be followed by the phrase "without limitation". The word "will" will be construed to have the same meaning and effect as the word "will". The word "any" will 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 will 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 will be construed as referring to such Applicable Laws as from time to time enacted, repealed or amended, (iii) any reference herein to any person will be construed to include the person's successors and assigns, (iv) the words "herein", "hereof" and "hereunder", and words of similar import, will 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, will 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 will 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

ORTHO MCNEIL, INC.

By: /s/ Michael J. Grissing

List of Appendices

APPENDIX 1

DEFINITIONS

"Additional Third Party Agreement" has the meaning set forth in Section 6.5.2.

"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, the R&D Plan and the R&D Budget as the same may be amended or supplemented from time to time in accordance with the terms of this Agreement.

"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 OMI (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 GMP for a Product. References to the weight of a quantity of API refer to the gross mass of the API after lyophilization.

"**ASO**" [***]

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

"Calendar Quarter" means a Johnson & Johnson Calendar Quarter of the Johnson & Johnson Calendar Year, based on the Johnson & Johnson Universal Calendar for that year, a copy of which, for 2007is attached hereto as Appendix 10, and which is used for OMI's internal business purposes; *provided, however*, that wherever this Agreement refers to the timing of when Isis will provide an invoice to OMI, any reference to Calendar Quarter will mean the respective periods of three consecutive calendar months ending on March 31, June 30, September 30 and December 31.

"Calendar Year" shall mean a calendar year based on the J&J Universal Calendar for that year.

"Clinical Supply Agreement" has the meaning set forth in 4.2 and attached in Appendix 8.

"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 4 Trials for, marketing, promoting, distributing, importing or selling a Product.

"Collaboration" has the following meaning. A Development Program to advance ISIS 325568 and ISIS 377131 through human clinical trials and ultimately Commercialize them as Products; and A Research Program to (i) [***] and (ii) at OMI's option [***] in each case for OMI to advance into human clinical trials and ultimately Commercialize as Products.

"Collaboration Gene Targets" means GCGR, GCCR or a Selected Gene Target. For purposes of clarification, once a Collaboration Gene Target has been returned to Isis pursuant to Section 3.6 or Article 11, such gene target will no longer be considered a Collaboration Gene Target.

"Collaboration Term" means, the period of time beginning on the Effective Date and ending on the later to expire of the Research Term and the Development Program Term.

"Commercially Reasonable Efforts" means, with respect to a Compound and Product, the carrying out of discovery, research, Development or Commercialization activities 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 a Research Compound, a GCGR Compound and/or a GCCR Compound.

"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; R & D Plans 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 OMI has rights hereunder) will be treated as being Confidential Information of both Parties. Accordingly, each Party will be considered the Receiving Party with respect to the Research Results and will 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. Nothwithstanding the foregoing, upon the transfer of the ownership of relevant Research Results and data pursuant to Section 9.2.3 of this Agreement, such Research Results and data will be the sole property of OMI and Isis will continue to maintain their confidential nature pursuant to the terms of Article 8 of this Agreement.

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, *provided*, Confidential Information shall not be deemed to have entered the public domain merely by reason of its having been filed with any Regulatory Authority;

(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.

"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.

"Designation of a Compound as a Clinical Candidate" means the designation by an appropriate committee of OMI of a Compound as ready for the initiation of IND-Enabling Studies. The initiation of IND-Enabling studies for a Compound for which a Product Specific Patent filing has been made will together be conclusive evidence that "Designation of a Compound as a Clinical Candidate" has occurred for such Compound.

"Development" means non-clinical (such as, but not limited to, IND-enabling toxicology and production of GMP quality Product) and clinical development activities reasonably related to the development and submission of information to a Regulatory Authority, including, without limitation, chemical synthesis, toxicology, pharmacology, 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.

"Development Compound" means ISIS 377131 and ISIS 325568.

"Development Program" has the meaning set forth in 3.1.

"Development Program Term" has the meaning set forth in 3.3.1

"Disclosing Party" has the meaning set forth in Section 8.1.

"Discontinued Product" has the meaning set forth in 11.1.

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

"Effective Date" has the meaning set forth in Section 14.13 of this Agreement.

"Election Notice" has the meaning set forth in 11.1.

"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.

"Execution Date" has the meaning set forth in the opening paragraph of this Agreement.

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

"First Commercial Sale" means the first sale of a Product by OMI, 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 with appropriate professional scientific and/or technical or managerial experience, 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 R&D Plan, carried out by an Isis employee, or Third Party mutually agreed upon by the R&D Committee and expressly stated in the R&D Plan. 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 will be treated as an FTE on a pro-rata basis, based upon the actual number of hours worked divided by [***].

"FTE Rate" means the rate that OMI will fund Isis FTEs which is $[***] per FTE for the year ending December 31, 2007. For the year ending December 31, 2008 and each year thereafter such FTE rate will increase by a factor that reflects the [***] for such year.

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

"GCCR" means glucocorticoid receptor (GenBank accession #NM_000176), or any alternate splice variants, mutants, polymorphisms and fragments thereof.

"GCCR Compound" means (i) ISIS 377131 or [***]

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

"GCGR" means glucagon receptor (GenBank accession #NM_000160), or any alternate splice variants, mutants, polymorphisms and fragments thereof.

"GCGR Compound" means (i) ISIS 325568 or [***]

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

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

"**Good Clinical Practice**" or "**GCP**" shall mean the then current standards for clinical trials for pharmaceuticals, as set forth in the United States Code of Federal Regulations, ICH guidelines and applicable regulations, laws or rules as promulgated thereunder, as amended from time to time, and such standards of good clinical practice as are required by the European Union and other organizations and governmental agencies in countries in which a Licensed Product is intended to be sold to the extent such standards are not less stringent than United States GCP.

"**Good Laboratory Practice**" or "**GLP**" shall mean the then current standards for laboratory activities for pharmaceuticals, as set forth in the FDA's GLP regulations and/or ICH guidelines and applicable regulations.

"**Good Manufacturing Practice(s)**" or "**GMP**" shall mean the regulatory requirements for current good manufacturing practices promulgated in the United States Code of Federal Regulations including those rules promulagated by the United States Food and Drug Administration under the U.S. Food, Drug and Cosmetic Act, 21 C.F.R. § 210 et seq. ("FD&C Act") and ICH Guidelines and applicable regulations, as the same may be amended from time to time.

"**Holdings**" has the meaning set forth in Section 14.13.

"HSR Act" means the U.S. Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended from time to time, and the rules, regulations, guidance and requirements promulgated thereunder as may be in effect from time to time.

"**HSR Clearance**" has the meaning set forth in 14.13.

"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.

"Indemnified Party" has the meaning set forth in 12.3.

"Indemnification Claim Notice" has the meaning set forth in 12.3.

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

"**Initiation of Phase 1 Trial"** means the dosing of the [***] human subject in a Phase 1 Trial.

"**Initiation of Phase 2b Trial"** means the dosing of the [***] human patient in the first Phase 2b Trial.

"Initiation of Phase 3 Trial" means the dosing of the [***] human patient in a Phase 3 Trial. In the case where a Phase 2b/3 Trial precedes any Phase 3 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 2b/3 Trial in order to provide sufficient evidence of safety and efficacy to be included as a Phase 3 Trial in filings with Regulatory Authorities will be deemed to be the "start of Phase 3 Trial" for such Product.

"Inquiry Notice" has the meaning set forth in Section 3.6.2.

"Inquiry Response" has the meaning set forth in Section 3.6.2.

"Integrated Product Plan or IPP" has the meaning set forth in Section 5.3

"ISIS 325568" means the compound known as ISIS 325568 as specifically set forth in Appendix 11.

"ISIS 377131" means the compound known as ISIS 377131 as specifically set forth in Appendix 11.

"**Isis Core Technology Patents**" means Patents Controlled by Isis or its Affiliates on the Effective Date and/or at any time thereafter, in each case that are useful or necessary 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 6.5 will govern whether such Patent will be included as an Isis Core Technology Patent. In addition, Isis Core Technology Patents will exclude the Product Specific Patents and the Isis Manufacturing and Analytical Patents. A representative list of the Isis Core Technology Patents as of the Effective Date is 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.

"Isis Database" has the meaning set forth in Section 3.11.

"Isis In-License Agreements" has the meaning set forth in Section 6.5.1.

"**Isis Inventions"** has the meaning set forth in Section 9.1.

"**Isis Know-How"** means all Know-How Controlled by Isis or its Affiliates as of the Effective Date and/or at any time thereafter that is useful for the Research, discovery, Development, manufacturing and Commercialization of MOE Gapmers. The Isis Know-How shall not include Product Specific Know-How.

"**Isis Manufacturing and Analytical Patents"** means Patents Controlled by Isis or its Affiliates on the Effective Date and/or or at any time through the period ending on the [***] anniversary of the expiration of the Collaboration Term, 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 6.5 will govern whether such Patent will be included as an Isis Manufacturing Patent. A representative list of Isis Manufacturing and Analytical Patents is attached hereto as Appendix 4. Isis Manufacturing and Analytical Patents will 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 and Analytical Technology"** means the Isis Know-How, Product Specific Know-How and Isis Manufacturing and Analytical 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 OMI (or its Affiliate or Licensee).

"**Isis Patents"** means the Isis Core Technology Patents, the Product Specific Patents and the Isis Manufacturing and Analytical Patents (including patents licensed to Isis under an Isis In-License Agreement in accordance with Section 6.5.1).

"**Isis Program Patent"** has the meaning set forth in Section 9.1.

"**Isis Supported Payment"** means the royalty or milestone obligations of Isis, if any, applicable with respect to a Compound or Product under Isis' agreement with [***].

"**Isis Technology"** means collectively the, Product Specific Know-How and the Isis Patent.

"**Isis Third Party Payments"** has the meaning set forth in Section 6.5.2.

"Johnson & Johnson Universal Calendar" means the universal calendar Johnson & Johnson uses as part of its financial reporting system, as provided to Isis from time to time and as consistent with the 2007 universal calendar attached hereto as Appendix 10.

"Joint Invention" has the meaning set forth in Section 9.1

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

"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.

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

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

"Manufacturing Improvements" means any and all scientific and technical data, information, methods, techniques, protocols, inventions, and processes that are useful in the manufacture of MOE Gapmer ASO compounds developed by or coming under Control of a Party after the Collaboration Term. Manufacturing Improvements will exclude any proprietary or patented methods employed by a contract manufacturer under contract with OMI to manufacture ASO or Products.

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

"Major Market Country" means Canada, France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States.

"MAA Approval" will 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 all of the backbone linkages are modified by substituting a sulfur at the non-bridging oxygen (phosphorothioate) and (ii) having a gap region of unsubstituted 2' deoxy nucleotides positioned between two wing regions each composed entirely of 2'-O-(methoxyethyl) substituted nucleotides.

"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 OMI, an Affiliate of OMI, 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 will be determined in accordance with OMI's standard accounting procedures and in accordance with GAAP. In the event that OMI, its Affiliates or Licensees make any adjustments to such deductions after the associated Net Sales have been reported pursuant to this Agreement, the adjustments will 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 will 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 will 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 will in good faith, determine Net Sales for such Combination Product by mutual agreement.

In the event, in a particular country, OMI 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 OMI or its Affiliates any additional amount related to such sale, then OMI will adjust such selling price for purposes of calculating Net Sales so as to bring it to an arm's length basis.

Net Sales will not include (x) any payments among OMI, 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.

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

"OMI Third Party Payment" has the meaning set forth in 6.5.3.

"OMI Third Party Royalty Payment" has the meaning set forth in 6.5.3.

"OMI Indemnitees" has the meaning set forth in 12.2.

"OMI Inventions" has the meaning set forth in 9.1.

"OMI Product Specific Patent" means any Patents (including all claims and the entire scope of claims therein) Controlled by OMI or its Affiliates on the Effective Date and/or at any time thereafter, in each case claiming (a) the sequence or a portion thereof corresponding to the GCCR, GCGR or Selected Gene Target gene sequence or a portion thereof, (b) the specific composition of matter of a Product, (c) methods of using a Compound or Product as a therapeutic or (d) methods of using a Compound as a therapeutic).

"OMI Program Patents" has the meaning set forth in 9.1.

"Other party" has the meaning set forth in 10.3.

"Objective" means the objective of the R&D Plan set forth in Section 3.1.

"Party (ies)" has the meaning set forth in the opening paragraph of this Agreement.

"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 OMI under this Agreement, where such royalty obligation is based on the manufacture, use or sale of the Product being Covered by an Isis Patent licensed to OMI under Section 2.1 which Isis Patent Right is licensed to Isis under such Isis In-License Agreement and includes any Target Encumbrances assumed by OMI under Section 3.6.3.

"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 OMI 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 OMI 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).

"Permitted License" means a license granted by Isis to a Third Party (i) under the Isis Core Technology Patents or the Isis Manufacturing and Analytical 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 and Analytical Patents (but not under the Isis Core Technology Patents or Product Specific Patents) to enable such Third Party to broadly manufacture or formulate ASOs, where such Third Party is primarily engaged in providing contract manufacturing or services and is not engaged in drug discovery, development or commercialization.

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

"Phase 1 Trial" means the initial clinical testing of a Product in humans (first-in-humans study) with the intention of gaining a preliminary assessment of the safety of such Product.

"Phase 2 Clinical Supply" has the meaning set forth in Section 4.3.

"Phase 2 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 2b Trial" means a Phase 2 Trial, designed to support and immediately precede the initiation of a Phase 3 Trial program without any further Phase 2 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 2b/3 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 3 Trials, and which itself provides sufficient evidence of safety and efficacy to be included as a Phase 3 Trial in filings with Regulatory Authorities.

"Phase 3 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 4 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 4 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 Development Plan" has the meaning set forth in Section 5.3

"Product Specific Know-How" means all chemical, biological and structure activity relationship information, technical information and materials, including without limitation, technology, software, instrumentation, devices, data, biological materials, assays, constructs, unpatented inventions, practices, methods, knowledge, know-how, trade secrets, skill and experience solely related to the Compounds or Products, existing as of the effective date and anytime thereafter.

"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 thereafter, including those patents assigned to OMI pursuant to Article 9 in each case claiming (a) the sequence or a portion thereof corresponding to the GCCR, GCGR or Selected Gene Target gene sequence or a portion thereof, (b) the specific composition of matter of a Product, (c) methods of using a Compound or 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 6.5 will govern whether such Patent will be included as an Product Specific Patent 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, will be considered to be Isis Core Technology Patents (or Isis Manufacturing and Analytical Patents, as applicable). For clarification, any Isis Program Patent 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.

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

"Program Inventions" has the meaning set forth in Section 9.1.

"Program Patents" has the meaning set forth in Section 9.1.

"Proposed Substitution Target" has the meaning set forth in Section 3.6.1

"Proposed Target" has the meaning set forth in Section 3.6.3

"**Purchase Option Agreement**" has the meaning set forth in Section 14.13

"R&D Budget" has the meaning set forth in Section 3.2.

"R&D Committee Charter" has the meaning set forth in Section 3.4.

"R&D Committee" has the meaning set forth in Section 3.4.

"R&D Plan" has the meaning set forth in Section 3.2.

"R&D Budget" has the meaning set forth in Section 3.2

"R&D Year" means each 12 month period during the Collaboration Term, with the first R&D Year beginning on the Effective Date.

"Receiving Party" has the meaning set forth in Section 8.1.

"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.

"Request Notice" has the meaning set forth in Section 3.6.3.

"Requested Target" has the meaning set forth in Section 3.6.2.

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

"Research Compound" means any MOE Gapmer that modulates the expression of a Selected Gene Target where its primary mechanism of action is through its hybridization to such Selected Gene Target mRNA or pre-mRNA and that is identified by Isis as of the Effective Date or during the Collaboration.

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

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

"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 and Development Program.

"Research Term" has the meaning set forth in Section 3.3.1.

"Royalty Term" has the meaning set forth in Section 6.8.

"sNDA" means a Supplemental New Drug Application filed with the FDA after the first NDA Approval for a Product in the U.S.

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

"Selected Gene Target" has the meaning set forth in Section 3.6.

"Senior Representatives" has the meaning set forth in Section 14.4.

"Substitution Conditions" has the meaning set forth in Section 3.6.1

"**Symphony GenIsis**" has the meaning provided in Section 14.13.

"Target Encumbrances" has the meaning set forth in Section 3.6.3

"Target Pool" has the meaning set forth in Section 3.6.

"Technology License Agreement" has the meaning set forth in Section 14.13.

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

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

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

"Third Party Claims" has the meaning set forth in 12.1.

"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 [***] 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)

GCCR Applications

[***]

GCGR Applications

[***]

APPENDIX 3

ISIS CORE TECHNOLOGY PATENTS

[***]

Also includes (x) all U.S. patents and patent applications, (y) any substitutions, divisions, continuations, continuations-in-part, reissues, renewals, registrations, confirmations, re-examinations, extensions, supplementary protection certificates and the like, and any provisional applications, of any of the above listed patents or patent applications, and (z) any foreign or international equivalent of any of the above to the extent they satisfy the definition of Isis Core Technology Patent as set forth in Appendix 1 of the Agreement.

APPENDIX 4

ISIS MANUFACTURING & ANALYTICAL PATENTS

[***]

APPENDIX 5

[***]

Purpose

The Joint Research Committee is established by Isis and OMI to oversee the Collaboration under the Agreement.

Responsibilities

[***]***Composition***

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

2. Each R&D Committee member will have the requisite background, experience and training to carry out the duties and obligations of the R&D Committee.

3. Each Party will designate one of its representatives as co-chairperson of the R&D Committee. Each of the co-chairpersons will be responsible, on an alternating basis with the OMI 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

4. Each Party's R&D Committee members will collectively have 4 votes, regardless of the number of its R&D Committee members participating in any meeting. No votes will be taken unless there is at least one R&D Committee member representing each of Isis and OMI participating in such meeting. Each Party may allocate its 4 votes among its attending R&D Committee members in any manner, at such Party's discretion. If only one R&D Committee member is attending on behalf of a given Party, such R&D Committee member may cast all the votes allocated to such Party. Unless otherwise specified herein, all actions taken by the R&D Committee as a committee will be by majority vote. If the R&D Committee 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 R&D Committee will require the other Party to: (i) [***]; (ii) perform [***]; or (iii) violate any Applicable Law or principles of scientific integrity.

5. If the R&D Committee is unable to decide by a majority vote on any issue within the scope of its authority and duties, then the R&D Committee will promptly raise such issue to each Parties co-chairperson on the R&D Committee, and such co-chairs will have [***] to mutually agree on how to resolve such issue. If the co-chairs are unable to resolve such issue within the [***] period, then such issue will be brought to each Party's Senior Representatives, or their designees. The Senior Representatives will have [***] to mutually agree on how to resolve such issue. If the Senior Representatives are unable to resolve such issue within the [***] 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 OMI, and such resolution will be binding on OMI and Isis.

6. [***]

Operations; Meetings

7. During the Collaboration Term the R&D Committee will initially meet once per month, unless and until the R&D Committee 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 Spring House, PA and in Carlsbad, CA). In addition, any two members of the R&D Committee may

jointly call for an *ad hoc* meeting of the R&D Committee by teleconference at any time, by giving the other members of the R&D Committee 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.

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

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

10. The co-chair responsible for each meeting (the ***"Responsible Chair"***) will, in consultation with other members of the R&D Committee, develop and set the R&D Committee'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 R&D Committee 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 R&D Committee within a reasonable time in advance of such Scheduled Meeting to permit meaningful review. No agenda is required for an Ad Hoc Meeting.

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

APPENDIX 6

ISIS IN-LICENSE AGREEMENTS
AND
PRIOR THIRD PARTY AGREEMENTS

[***]

APPENDIX 7

[***]

APPENDIX 8

SUPPLY AGREEMENT
CLINICAL MANUFACTURING AND SUPPLY AGREEMENT

This Clinical Manufacturing and Supply Agreement (the ***"Supply Agreement"***) is entered into as of the ___th day of _____, 2007 (the "Effective Date") by and between **Isis Pharmaceuticals, Inc.** ("Isis") and **Ortho McNeil, Inc.** ("OMI"). OMI and Isis may each be referred to herein as a "Party" or together as the "Parties". Capitalized terms not defined herein will have the meaning given to such terms in the Collaboration and License Agreement between the Parties dated _____, 2007 (the "License Agreement"). The Parties agree as follows:

WHEREAS, the Parties have signed the License Agreement contemporaneous with the present Clinical Manufacturing and Supply Agreement;

WHEREAS, the License Agreement provides that Isis shall be responsible for the manufacture of Compound through [***];

WHEREAS, the Parties agree that the terms of this Supply Agreement will apply to all manufactured lots of active pharmaceutical ingredient (API) made and supplied under this Supply Agreement and further that this Supply Agreement will be construed in a manner consistent with the License Agreement, including its defined terms.

NOW, THEREFORE in consideration of the premises and mutual covenants herein contained, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties hereto agree to this Agreement as follows:

1. **Scope** — Isis will produce under cGMP conditions and in accordance with the Quality Agreement between the Parties and referencing this Supply Agreement (the "Quality Agreement"), the bulk API for the Compounds and in the amount specified in the applicable Firm Order for use in preclinical and clinical Development through the completion of [***]. Isis will use Commercially Reasonable Efforts to maintain available capacity of facilities and equipment to meet OMI's needs at the Isis production facilities.

2. **Supply; Forecasting.**

(a) Isis and OMI will establish an [***] Calendar Quarter rolling forecast (the "Rolling Production Forecast") that sets forth a good faith estimate of the quantity of API for each Compound OMI expects to receive from Isis within the following [***] Calendar Quarter period. This Rolling Production Forecast will be updated on the first business day of each subsequent Calendar Quarter by OMI's project manager. The first [***] Calendar Quarters of the Rolling Production Forecast constitute a firm order ("Firm Order"). OMI will provide purchase orders for Firm Orders with each new Rolling Production Forecast. Quarters [***] through [***] are estimated quantities to be used for

planning purposes only. Not later than [***] after the Effective Date, OMI's project manager will provide Isis with the first Rolling Production Forecast, which will initially cover the [***] quarter period beginning October 1, 2007. The quantities set forth in a Firm Order will be binding on both parties, and OMI will be obligated to purchase from Isis, and Isis will be obligated to supply, the specified quantities of API.

Notwithstanding the foregoing, the Parties will use commercially reasonable efforts to deliver the API to support the planned clinical trials starting in [***] for ISIS 325568 and ISIS 377131. In addition, upon OMI's Designation of a Compound as a Clinical Candidate, Isis and OMI will mutually agree on an initial quantity and delivery date for API for such Compound to support the rapid and efficient start of IND-Enabling Studies and first human dose for such Compound (such quantity and delivery dates to be consistent with Isis' then existing manufacturing schedule).

(b) Notwithstanding the foregoing, each Firm Order is subject to the following conditions:

- Isis will not be required to supply during a Calendar Quarter more than an aggregate of [***] of API and further that the batch size is no larger than [***] unless agreed to in advance by Isis.
- Isis will not be required to supply [***] Compounds during any Calendar Quarter.
- For the first order for Compound ordered under this Supply Agreement, the minimum order is [***].
- For any subsequent orders of Compounds under this Supply Agreement, the minimum order is [***] unless agreed to in advance by Isis.
- Isis will not be required to supply more than [***] of the API forecasted for a Calendar Quarter when that Calendar Quarter was the [***] Calendar Quarter of a Rolling Production Forecast.

(c) Isis agrees to use commercially reasonable efforts to supply OMI, upon request, with quantities in excess of the quantity restrictions described in this Section 2(b) above.

3. **Delivery -** For each Calendar Quarter in a Firm Order, Isis will set the delivery date for the API ordered in such quarter and will promptly notify OMI of such delivery date (each, a "Delivery Date"). Isis will deliver the API ordered in each Firm Order by the applicable Delivery Date. The quantity of API specified in each Firm Order, invoiced and paid for will be [***] the API after lyophilization [***]. In addition, so long as Isis supplies the quantity of API specified in the applicable Firm Order for such Compound within [***], Isis will be deemed to have satisfied the amount specified in the Firm Order and the full purchase Price specified in the Firm Order will apply to such quantity of API delivered.

4. **Shortfall**

(a) In the event that at any time Isis anticipates that it will be unable to supply in whole or in part the quantities of API set forth in an agreed-upon Firm Order for any reason, including without limitation force majeure, Isis will notify OMI in writing within [***] of the prediction of such non-supply.

(b) If Isis cannot Manufacture as set forth in (a) above, or should OMI determine at any time after the Effective Date, at its sole discretion that it shall pursue a different manufacturing source at any time, upon written request by OMI, Isis will transfer to OMI all documentation and information, and permit OMI to reference and use any regulatory filings, and otherwise fully cooperate with OMI to enable OMI to make or have made API for use by OMI in accordance with the License Agreement. In the event that OMI has elected to pursue a different manufacturing source, the provisions of 4.5.3 of the License Agreement shall control.

5. **Specifications** — For each Firm Order of Compound OMI requests Isis to supply under this Supply Agreement, Isis and OMI will mutually agree on the specifications for such API and will attach and/or reference such specifications (as maintained in the Quality Agreement) in the applicable Firm Order (the "Specifications").

6. **API Pricing** - In [***] of each year, starting [***], Isis will provide OMI the purchase price (each, a "Purchase Price") applicable to the manufacture and supply of API scheduled for delivery in the following calendar year. Such Purchase Prices will be binding on both Parties; *provided, however*, that such price will (i) not exceed [***] of API and (ii) represent Isis' good faith estimate of its [***] to manufacture such API [***]. Upon reasonable request, OMI reserves the right to confirm such methodology annually, not to exceed one time per year. This price includes [***] All payments are in US Dollars. If Isis supplies active pharmaceutical ingredient for another ASO having similar length and chemistry as the API supplied hereunder to a Third Party at similar volumes on terms when taken as a whole are more favorable than the terms provided OMI under this Agreement, OMI will have the right to receive the clinical supply of API on the same terms offered by Isis to such Third Party.

7. **Terms of Payment** —

- A pre-payment representing [***] of the Purchase Price contained in a Firm Order from OMI is payable in cash by OMI to Isis by wire transfer or other customary means within [***] from the date of receipt by OMI of a corresponding invoice from Isis reflecting said component not prior to delivery of the applicable Firm Order.

- The remaining amount of the Purchase Price is due in cash by OMI to Isis by wire transfer or other customary means within [***] from the

date of receipt of invoice by OMI, following shipment by Isis to OMI or its designee of the API.

- In addition to the price stated in this Agreement, OMI will pay to Isis all taxes and duties (except income tax) imposed upon Isis, in connection with the API and will reimburse Isis for the insurance and freight expenses discussed in Section 9 below.

8. **Term** – This Supply Agreement will remain in effect as long as Isis and OMI mutually agree for Isis to supply Compounds as described in the License Agreement.

9. **Title & Transportation:** Isis will ship the API to OMI when released by OMI Quality Assurance Department as specified in the Clinical Trial Material Quality Agreement attached as Appendix 9 in the License Agreement. In the event that OMI has not concluded its review suitable to release such API within [***] of Isis' delivery of all required release documentation ("OMI Review Period"), Isis will be allowed to invoice for the remaining amounts due on such API at the expiration of the OMI Review Period. Title to API will transfer to OMI EXW (Incoterms 2000) Isis' facility. Isis will insure against the replacement cost of the API until title transfers. Risk of loss passes simultaneously with the title. Transportation and transit insurance arrangements will be made by Isis as specified by OMI. Isis will pay all freight and other charges for such transportation and transit insurance and add such costs to the invoice. For the purposes of this Section 9, Incoterms 2000 means the International Commercial Terms published by the International Chamber of Commerce, as amended from time to time, codifying the contractual rules for the interpretation of standardized commercial terms for transactions.

10. **Drug Product; Stability Testing**

Isis will manage the stability testing of any API manufactured under this Supply Agreement per Isis' current stability protocol, [***]

Isis will perform stability testing on ISIS 325568 finished drug product pursuant to the protocol [***].

Isis will complete the ongoing preparation of final drug product through its contract manufacturer for the ISIS 377131 drug product that is scheduled to be completed in the [***] Isis will notify its contract manufacturer of its relationship with OMI prior to the manufacturing in the [***] and request its contract manufacturer to continue its manufacturing relationship with OMI substantially the same as it currently exists with Isis. Isis will instruct its contract manufacturer that OMI shall have access to any and all information connected with the ISIS 377131 drug product manufacturing that is in the contract manufacturer's possession. Isis shall transfer or assign any relevant documents to OMI to support such transfer of the manufacturing relationship. Isis will perform stability testing on such drug product pursuant to a stability

protocol that is mutually developed and agreed to by OMI and Isis, [***]. Isis will instruct the contract manufacturer to retain suitable samples for retesting or other purposes from such production as directed by OMI.

The price for the stability testing of the API will be [***]

The price for the stability testing of drug product will be [***]. The price for the stability testing is payable within [***] of the end of the Calendar Quarter in which such testing was performed.

Except as otherwise specified in the R&D Plan or this Supply Agreement, the Parties acknowledge and agree that OMI will be solely responsible for the manufacturing, stability testing and supply of finished drug Product.

11. CMC Work – Except as specifically set forth in the R&D Plan, OMI will be responsible for all CMC work associated with the API and drug product. OMI may engage Isis to perform CMC work for the API and drug product, including without limitation support in preparing regulatory filings, in accordance with Section 5.1 of the License Agreement.

12. Intellectual Property; Technology Transfer — Isis will retain the rights to any inventions it develops while producing the API. Isis will license all of its Intellectual Property necessary for the manufacture of the Compounds and subsequent improvements to OMI as per the terms of the License Agreement.

Isis and OMI will perform a technology transfer related to manufacturing technology in accordance with Section 4.5.3 of the License Agreement. In addition, OMI shall have the right to observe the manufacturing process at any time upon giving Isis reasonable advance notice thereof.

13. Hazards; Risk Sharing

If after the raw materials for a batch of API [***], Isis encounters any unforeseen difficulties or hazards during the manufacturing of the API that prevent Isis from successfully manufacturing such batch of API in accordance with this Agreement (including but not limited to the failure of such API to conform to the warranty set forth in Section 14), Isis will use commercially reasonable efforts to [***], such that OMI receives such API as close to the originally-scheduled delivery date as possible.

For any such [***], the cost of the manufacture will be [***] by OMI and Isis as follows: Isis will be responsible for the [***] components for such batch of API; and, to the extent not [***], OMI will be responsible for the [***] component; *provided, however* that OMI will not be responsible if such failure results from Isis' gross negligence. For purposes of clarity and assuming none of the exceptions above apply, the total price payable upon delivery of such API will equal the price for such API originally quoted in the Firm Order *plus* the [***] attributable to the [***]. For purposes of clarity, any batch failures due to incorrect addition of raw materials or utility failures for any reason or other pre-solution losses of any kind will be solely for the account of

Isis. Further, Isis will be responsible for the cost of any equipment replacement, as necessary.

14. Limited Warranty; Certificate of Compliance: SUBJECT TO THE LIMITATIONS OF PARAGRAPHS 15, 16 AND 17, Isis warrants, with respect to all the API, that at the time of the applicable shipment of the API to OMI: (a) any API manufactured by Isis meets the applicable Specifications and was manufactured in accordance with cGMP and the obligations of the Quality Agreement, (b) that the API is free from BSE/TSE, and (c) the API is conveyed with good and marketable title, free from any and all security interests, liens or encumbrances. Furthermore, Isis will include with the API at the time of transfer a certificate of conformance (or its equivalent) in accordance with the Quality Agreement.

15. Disclaimer Of Warranties: THE LIMITED WARRANTIES CONTAINED IN PARAGRAPH 14 OF THIS DOCUMENT ARE THE SOLE WARRANTIES WITH RESPECT TO THE API AND ARE MADE EXPRESSLY IN LIEU OF AND EXCLUDE ANY IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE AND ALL OTHER EXPRESS OR IMPLIED REPRESENTATIONS AND WARRANTIES PROVIDED BY COMMON LAW OR STATUTE.

16. Limitation Of Remedies: OMI'S EXCLUSIVE REMEDY AND ISIS' TOTAL LIABILITY TO OMI FOR CLAIMS BASED UPON SUPPLY OF THE API (OR FAILURE TO SUPPLY) (INCLUDING, WITHOUT LIMITATION, THOSE ARISING OUT OF STRICT LIABILITY, BREACH OF WARRANTY AND NEGLIGENCE) IS EXPRESSLY LIMITED TO THE REMEDY SET FORTH IN SECTIONS 4 AND 13 ABOVE.

OMI WAIVES ALL OTHER CLAIMS BY OMI AGAINST ISIS UNDER THIS SUPPLY AGREEMENT WITH RESPECT TO SUPPLY OF THE API. NEITHER PARTY WILL BE UNDER ANY LIABILITY TO THE OTHER PARTY FOR ANY INCIDENTAL, CONSEQUENTIAL, SPECIAL, EXEMPLARY OR PUNITIVE DAMAGES. THE FOREGOING LIMITATION WILL NOT APPLY TO OR BE DEEMED TO LIMIT ANY CLAIMS FOR INDEMNIFICATION IN ACCORDANCE WITH THE TERMS AND CONDITIONS OF SECTION 20.

17. Inspection And Notice Of Claims: Promptly upon receipt of each shipment of API, OMI will inspect and test (or cause to be inspected and tested if API is shipped to a third party) such API for any damage, defect or shortage. ALL CLAIMS (INCLUDING, WITHOUT LIMITATION, THOSE ARISING OUT OF STRICT LIABILITY, BREACH OF WARRANTY AND NEGLIGENCE) BY OMI WILL BE DEEMED WAIVED UNLESS MADE BY OMI IN WRITING AND RECEIVED BY ISIS WITHIN [***] OF THE RECEIPT OF THE API, EXCEPT THAT IN THE CASE OF A LATENT FAILURE OF THE API TO MEET THE

SPECIFICATIONS SUCH TIME LIMIT WILL BE EXTENDED TO [***] OF THE RECEIPT OF THE API.

18. **Quality Systems.** If OMI requests changes to Isis' quality systems or standard operating procedures, Isis and OMI will mutually agree on the scope and form of such changes and payment will occur as outlined below. Isis will be responsible to implement and pay for any modifications that either a Regulatory Authority requires or the Parties mutually agree are necessary to remain compliant with GMP or applicable ICH guidelines to manufacture Compounds and OMI will pay for such modifications specific to the manufacturing of Compounds that are not required by GMP or applicable ICH guidelines. The costs of implementation will include out of pocket costs as well as for the FTEs to implement such changes at the then applicable Isis FTE Rate. The current billable FTE Rate for Isis employees is [***].

19. **Force Majeure:** Neither Party will be liable for failures or delays in performance of any obligation under this Supply Agreement, other than for payment for API already transferred, to the extent that such failure or delay is caused by force majeure, being any event, occurrence or circumstance beyond the control of that Party (a "Force Majeure Event"), including but not limited to the following: failure or delay caused by or resulting from acts of God, strikes, earthquakes, fires, floods, accidents, wars, riots, acts of terrorism, restrictions imposed by any governmental authority (including allocations, priorities, requisitions quotas and price controls). The Party whose performance is affected by a Force Majeure Event will give prompt notice to the other Party stating the details and expected duration of the event.

20. **Indemnity.** All Sections of Article 12 of the License Agreement will apply to this Supply Agreement and the matters covered by this Supply Agreement.

21. **Assignment:** This Supply Agreement is not assignable or transferable by either Party without the prior written consent of the other Party; *provided that* a Party may assign the Supply Agreement to its successor in interest pursuant to the acquisition, merger or sale of all or substantially all of the assets of such Party, so long as such successor assumes in writing all of the assigning Party's obligations under this Supply Agreement.

22. **Governing Law:** The interpretation, validity, and performance of this document will be governed by New York law, without regard to any conflict-of-law rules.

23. **Termination.** Either Party will have the right to terminate this Supply Agreement if the other Party materially breaches its obligations under this Supply Agreement in accordance with Section 10.3 of the License Agreement.

24. **Survival:** Sections 12 through 17, 19 through 26, and 28 through 35 will survive expiration or termination of the Agreement. Any expiration or early termination of this Agreement will be without prejudice to the rights of either Party against the other accrued or accruing under this Agreement prior to

termination. No expiration of this Agreement will relieve a Party of its obligation to pay fees.

25. **Notices:** Any notice required or permitted to be given under this Supply Agreement by any Party will be in writing and will be (a) delivered personally, (b) sent by registered mail, return receipt requested, postage prepaid, (c) sent by a nationally-recognized courier service guaranteeing next-day or second day delivery, charges prepaid, or (d) delivered by facsimile (with the original promptly sent by any of the foregoing manners), to the addresses or facsimile numbers of the other Parties set forth below, or at such other addresses as may from time to time be furnished by similar notice by any Party. The effective date of any notice under this Supply Agreement will be the date of receipt by the receiving Party.

26. **Defined Terms.** Unless otherwise specified in this Supply Agreement, the terms used in this Supply Agreement shall have the meaning given to such terms in the License Agreement.

27. **Representations and Warranties**.

a. Isis represents and warrants that the execution, delivery and performance of this Supply Agreement does not conflict with any agreement, instrument or understanding, oral or written, or Law by which it is bound and Isis covenants that it will not enter into any such conflicting agreements during the term of this Agreement.

b. Isis represents, warrants and covenants that neither it nor any of its employees performing hereunder, have ever been, or are currently the subject of a proceeding that could lead to it or such employees or agents becoming, as applicable, a Debarred Entity or Individual, an Excluded Entity or Individual or Convicted Entity or Individual. Isis further covenants, represents and warrants that if, during the term of this Supply Agreement, it, or any of its employees or agents performing hereunder, become or are the subject of a proceeding that could lead to Isis becoming, as applicable, a Debarred Entity or Individual, an Excluded Entity or Individual or a Convicted Entity or Individual, Isis shall immediately notify OMI and OMI shall have the right to immediately terminate this Supply Agreement. For purposes of this provision, the following definitions shall apply:

i. A "Debarred Individual" is an individual who has been debarred by the FDA pursuant to 21 U.S.C 335(a) or (b) from providing services in any capacity to a person that has an approved or pending drug product application.

ii. A "Debarred Entity" is a corporation, partnership or association that has been debarred by the FDA pursuant to 21 USC 335 (a) or (b) from submitting or assisting in the submission of any abbreviated drug application, or a subsidiary or affiliate of a Debarred Entity.

iii. An "Excluded Individual or entity" is (a) an individual or entity, as applicable who has been excluded, debarred, suspended or is otherwise ineligible to participate in federal health care programs such as Medicare or Medicaid by the Office of the Inspector General (OIG/HHS) of the US Department of Health and Human Services, or (b) is an individual or entity as applicable, who

has been excluded, debarred, suspended or is otherwise ineligible to participate in federal procurement and non-procurement programs, including those produced by the US Genearl Services Administration (GSA).

iv. A "Convicted Individual or Entity" is an individual or entity, as applicable, who has been convicted of a criminal offense that falls within the ambit of 21 USC 335(a) or 42 USC 1320a-7(a), but has not yet been excluded, debarred, suspended or otherwise declared ineligible.

Notices will be sent to the following addresses or facsimile numbers:
In the case of Isis,

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attention: VP, Manufacturing/Operations
Facsimile: 760-603-4655

With a copy to:

1. General Counsel (fax: 760.268.4922); and
2. Executive Vice President & CFO (fax: 760.603.4650)

In the Case of OMI:

Ortho McNeil, Inc.
1000 US Route 202
Raritan, New Jersey, 08869
Attention: President
Facsimile: 908-707-9757

With copy to:

Chief Patent Counsel
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, New Jersey 08933
Facsimile: (732) 524-5575

28. Waiver: No waiver of any term, provision or condition of this Supply Agreement whether by conduct or otherwise in any one or more instances will be deemed to be or construed as a further or continuing waiver of any such term, provision or condition or of any other term, provision or condition of this Supply Agreement.

29. Counterparts: This Supply Agreement and any amendment hereto may be executed in any number of counterparts, each of which will for all purposes be deemed an original and all of which will constitute the same instrument. This Supply Agreement will be effective upon full execution by facsimile or original, and a facsimile signature will be deemed to be and will be as effective as an original signature

30. Attachments: All attachments referred to herein form an integral part of this Supply Agreement and are incorporated into this Supply Agreement by such reference.

31. Inadvertent or Involuntary Omissions: The Parties acknowledge that they have expended substantial effort in preparing this Supply Agreement and attempting to describe in the Attachments, as thoroughly and precisely as possible, certain specifications and other information. However, despite these efforts, the Parties acknowledge the possibility of involuntary or inadvertent omissions from the Attachments. If the Parties agree in writing regarding any involuntary or inadvertent omission, the changes will be made to the Attachments to repair said inadvertent or involuntary omissions and any such written agreement executed by the Parties will serve as an amendment to this Supply Agreement.

32. Construction: Each Party to this Supply Agreement and its counsel have reviewed and revised this Supply Agreement. The rule of construction to the effect that any ambiguities are to be resolved against the drafting Party will not be employed in the interpretation of this Supply Agreement or any amendment or Attachment to this Supply Agreement.

33. Time: Time is of the essence in this Supply Agreement.

34. Preference: Unless otherwise specifically provided for in the Attachment or the Quality Agreement, the terms of this Supply Agreement will prevail in the event of a conflict between this Supply Agreement and any such Attachments or Quality Agreement.

35. Entire Agreement: This Supply Agreement, the related Quality Agreement and the related License Agreement constitute the full understanding of the Parties, and is the final, complete and exclusive statement of the terms and conditions of their agreement regarding the subject matter hereof. All representations, offers, and undertakings, of the Parties made prior to the signing of this Agreement are hereby superseded. All amendments or

modifications to this Supply Agreement must be in writing, identified as an Amendment to this Supply Agreement and signed by an authorized representative of each Party.

The Parties executing this Supply Agreement:

ISIS PHARMACEUTICALS, INC.	**ORTHO MCNEIL, INC.**
NAME: _____	NAME: _____
TITLE: _____	TITLE: _____
SIGNATURE: _____	SIGNATURE: _____

APPENDIX 9

CLINICAL QUALITY AGREEMENT
Isis Pharmaceuticals and Ortho McNeil, Inc.

The purpose of this Clinical Quality Agreement is to establish, clarify and communicate quality expectations primarily for the manufacture and testing of API performed by Isis Pharmaceuticals, Carlsbad, CA ("Isis") for Ortho McNeil Inc.'s ("OMI") use in clinical trials. For contractual responsibilities, refer to the Manufacturing and Supply Agreement dated _____, 2007.

WHEREAS, the Parties have signed a Collaboration and License Agreement contemporaneous with the present Clinical Quality Agreement;

WHEREAS, the Collaboration and License Agreement provides that Isis shall be responsible for the manufacture of Compound through [***];

WHEREAS, the Parties agree that the terms of this Clinical Quality Agreement will apply to all manufactured lots of active pharmaceutical ingredient (API) made and supplied under this Clinical Quality Agreement. All changes to this agreement must be documented as an addendum to the original agreement, reviewed and approved by both parties Quality Assurance representatives; and

NOW, THEREFORE in consideration of the premises and mutual covenants herein contained, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties hereto agree to this Agreement as follows:

1. Unless otherwise specified in this Agreement, the terms used in this Agreement shall have the meaning given to such terms in the Collaboration and License Agreement.

2. Isis will manufacture, produce and test the API in accordance with U.S. current Good Manufacturing Practices regulations (cGMP), ICH guidelines, and EMEA guidelines, and all such operations will be fully documented. OMI will notify Isis if it is conducting a clinical trial that will require API to be manufactured in accordance with international guidelines that are more stringent than or different from cGMP or ICH Guidelines and the Parties will mutually agree on how to manufacture such API in accordance with such more stringent or different standards.

3. Isis will maintain adequately trained staff and appropriate records of training and competence. Isis will monitor and maintain records respecting its compliance with cGMP, including the process of establishment and implementation of the operating procedures and the training of staff as necessary to assure such compliance.

4. Isis will retain, in accordance with cGMP, full records (such as manufacturing batch records, analytical testing methods, analytical test results and appropriate reports) related to the APIs being manufactured and supplied.

5. Isis will provide approval/audit of the API using routine Quality Assurance (QA) procedures and will keep all appropriate records of such approval/audit processes conducted.

6. Isis will provide OMI with a copy of batch records, and a certificate of analysis (COA) which will contain (i) analytical results from Isis and any associated contract laboratories and (ii) a statement of compliance with cGMP, and signed by Isis QA. OMI will be responsible for the final review, approval, and release of the API, and retains full responsibility for the disposition and release of the API for any purpose.

7. Isis will provide OMI with samples of the API including the appropriate documentation, if requested by OMI.

8. Original production and laboratory data and records will be retained and made available for review by OMI or its designees on-site at Isis.

9. Material changes to master batch records, specifications, test methods, and stability protocols (in each case as they apply to the API) will be agreed and approved by both parties.

10. Material changes to master batch records, specifications, test methods, and stability protocols (in each case as they apply to drug product provided by Isis) will be agreed and approved by both parties.

11. Any raw material and component, which Isis will use for the production of API, will be tested and released utilizing cGMP compliant and Isis approved specifications, sampling, testing and release procedures.

12. Isis will document and notify OMI of all significant changes to or deviations from the process or testing procedures and the investigations thereof. Documentation on process changes and deviations will be part of the batch record. A "Significant" change is understood as anything that deviates from the approved regulatory filing and/or anything reasonably likely to materially affect Safety, Identity, Strength, Purity or Quality (SISPQ). (This would not include changes such as use of a different but equivalent room, "like for like" equipment changes, etc.). In the event of an out of specification (OOS) result, Isis will promptly notify OMI on first confirmation of the OOS result.

13. Isis will ship or will arrange for third parties to ship all API once the lot(s) are released by both parties to OMI or other designated site(s) with appropriate documentation and in suitable, labeled containers. This will also include the use of temperature monitoring devices if deemed by OMI necessary to ensure the quality of the API.

14. Isis will make available to OMI at Isis' facility copies of all Isis Standard Operating Procedures used by Isis in connection with the manufacture of the API.

15. Isis will discuss with OMI in advance if Isis desires to use Subcontractors (Third Party) outside of Isis' approved list of subcontractors. Isis will be responsible for qualification and routine compliance auditing of suppliers and subcontractors, in accordance with Isis's current procedures.

16. Isis will inform OMI of a notice and result of any regulatory investigation by a Regulatory Authority (including any OMI documentation requested) relating to or impacting any API or service being provided to OMI. OMI will have the opportunity to review and give input to the response to such investigations.

17. If Regulatory Authorities audit OMI, make investigations at OMI or ask questions of OMI about the activities conducted at Isis or third parties retained by Isis, then Isis will fully

cooperate with OMI to provide adequate answers to and documentation for the Regulatory Authorities. Isis will have the opportunity to review and give input to the response to such investigations.

18. Once every [***], a maximum or [***] OMI representatives will be entitled to visit and inspect ("audit") the production, manufacturing, quality control and warehousing facilities Isis is using in connection with the API, including the corresponding documentation. Such audit may not exceed [***]. Isis agrees to provide OMI with the necessary assistance and information. OMI will provide Isis with at least [***] advanced notice of a requested inspection. Isis will provide corrective action plans to address identified non-compliance concerns. As necessary, the Parties will mutually agree in good faith to additional inspections.

19. Subject to applicable law, Isis will inform OMI within [***], and vice-versa, on any matter which, in Isis' reasonable judgment, may have a bearing on drug safety or pharmaceutical quality in relation to the APIs, and supply all necessary information and co-operation for the investigation of such events. In cases where patient/subject safety may be concerned, Isis must inform OMI by telephone and in writing as soon as practicable, and vice-versa.

20. Isis will retain samples ([***]) for all API and other OMI material produced to date including the API. Isis will retain the samples through a date specified in writing by OMI, and such date will not exceed [***] after the last lot produced by Isis of the drug product in which the API was used. Thereafter, OMI will make arrangements to assume responsibility for storage of such samples.

21. In event of an out of specification (OOS) result encountered in release or stability testing, Isis QA shall promptly (within [***] of confirmation) notify OMI QA.

22. All product complaints, as established by principle investigator entities, clinical monitoring bodies or international authorities (e.g., customs) will be handled principally by OMI and supported by Isis in conjunction with OMI. All complaint events will be shared between both parties within [***] of receipt.

23. All primary data (or authenticated copies thereof) and result reports will be maintained in the Isis archives through a date specified in writing by OMI, which such date will not exceed [***] after the final expiration date of the drug product in which the API was used. Thereafter, OMI will make arrangements for continued storage of such data at OMI's expense as is necessary.

24. The names of each responsible contact person(s) as of the Effective Date from Isis and OMI are listed in Appendix A.

The Parties Quality Assurance representatives executing this Agreement:

ISIS PHARMACEUTICALS, INC.	OMI
NAME: _____	NAME: _____
TITLE: _____	TITLE: _____
SIGNATURE: _____	SIGNATURE: _____
DATE: _____	DATE: _____

APPENDIX 10

JOHNSON & JOHNSON UNIVERSAL CALENDAR

2007 UNIVERSAL CALENDAR

	M	T	W	T	F	S	S
JAN	1	2	3	4	5	6	7
(4 Weeks)	8	9	10	11	12	13	14
	15	16	17	18	19	20	21
	22	23	24	25	26	27	28
FEB	29	30	31				
(4 Weeks)				1	2	3	4
	5	6	7	8	9	10	11
	12	13	14	15	16	17	18
	19	20	21	22	23	24	25
MAR	26	27	28				
(5 Weeks)				1	2	3	4
	5	6	7	8	9	10	11
	12	13	14	15	16	17	18
	19	20	21	22	23	24	25
	26	27	28	29	30	31	
							1
APR	2	3	4	5	6	7	8
(4 Weeks)	9	10	11	12	13	14	15
	16	17	18	19	20	21	22
	23	24	25	26	27	28	29
MAY	30						
(4 Weeks)		1	2	3	4	5	6
	7	8	9	10	11	12	13
	14	15	16	17	18	19	20
	21	22	23	24	25	26	27
JUN	28	29	30	31			
(5 Weeks)					1	2	3
	4	5	6	7	8	9	10
	11	12	13	14	15	16	17
	18	19	20	21	22	23	24
	25	26	27	28	29	30	
							1

	M	T	W	T	F	S	S
JUL	2	3	4	5	6	7	8
(4 Weeks)	9	10	11	12	13	14	15
	16	17	18	19	20	21	22
	23	24	25	26	27	28	29
AUG	30	31					
(4 Weeks)			1	2	3	4	5
	6	7	8	9	10	11	12
	13	14	15	16	17	18	19
	20	21	22	23	24	25	26
SEP	27	28	29	30	31		
(5 Weeks)						1	2
	3	4	5	6	7	8	9
	10	11	12	13	14	15	16
	17	18	19	20	21	22	23
	24	25	26	27	28	29	30
OCT	1	2	3	4	5	6	7
(4 Weeks)	8	9	10	11	12	13	14
	15	16	17	18	19	20	21
	22	23	24	25	26	27	28
NOV	29	30	31				
(4 Weeks)				1	2	3	4
	5	6	7	8	9	10	11
	12	13	14	15	16	17	18
	19	20	21	22	23	24	25
DEC	26	27	28	29	30		
(5 Weeks)						1	2
	3	4	5	6	7	8	9
	10	11	12	13	14	15	16
	17	18	19	20	21	22	23
	24	25	26	27	28	29	30

APPENDIX 11

DESCRIPTION FOR ISIS 325568 AND ISIS 377131

[***]

APPENDIX 12

TARGET POOL & SELECTED GENE TARGETS

[***]

APPENDIX 13

OMI MINIMUM COUNTRIES

[***]

APPENDIX 14

ISIS INSURANCE REQUIREMENTS

Insurance Requirements

Isis shall procure and maintain, at all times, and at its own expense, during the Collaboration Term the types of insurance(s) specified below. For product liability/completed operations and clinical trials, insurance coverage will remain in effect through at least [***] after the Term of the Agreement. Isis' insurance will cover Isis, its contractors, subcontractors and consultants performing work under the R&D Plan.

A. Commercial General Liability
Isis shall provide coverage on a Commercial General Liability Occurrence Form with the exception of product liability/completed operations and clinical trials which will be written on a Claims Made Form. The limits will not be less than $[***] each occurrence and $[***] annual aggregate. Such insurance shall include worldwide coverage including coverage for USA jurisdiction claims and occurrences.

B. Property Insurance
Isis shall provide Property Insurance in an amount not less than [***], as is comparable to the insurance reasonably and customarily carried by a company of similar size, location and business as Isis.

C. Miscellaneous
All insurance companies must be rated [***] or better with a financial rating of [***] or better in the most recent *A. M. Best's Rating Guide.*

Isis will promptly notify OMI in writing in the event of [***] of an insurance policy that is the subject of this Appendix.

Certificates of insurance for all required coverages shall be provided to OMI prior to commencement of any work on the project. Failure by OMI to request such copies or documents shall not waive OMI's rights to coverage under this agreement.

APPENDIX 15
PART 1
CONFIRMATION OF CLOSING
, 2007

WHEREAS, Isis Pharmaceuticals, Inc. ("Isis") and Symphony GenIsis Holdings LLC ("Holdings") are parties to the Purchase Option Agreement dated April 7, 2006 (the "Purchase Option Agreement");

WHEREAS, Isis has exercised the Purchase Option, pursuant to which Isis has purchased all of the outstanding Symphony GenIsis Equity Securities by paying the Purchase Price to Holdings; and

WHEREAS, in connection with the Purchase Option Closing, Isis and Holdings hereby acknowledge, confirm and agree as follows;

1. The Purchase Option Closing occurred on _____, 2007;

2. Holdings has received the full Purchase Price;

3. Title to all of the Symphony GenIsis Equity Securities has been transferred to Isis;

4. Holdings has removed all directors serving on the Symphony GenIsis Board, other than the Isis Director from Symphony GenIsis Board;

5. The Development Committee is disbanded and terminated;

6. Holdings consents to the termination of the Novated Technology License Agreement by Isis and Symphony GenIsis; and

7. Except for the rights and obligations that specifically survive termination, as set forth in Section 7.3 of the Novated Technology License Agreement, Holdings has no residual rights in the Licensed Intellectual Property, including but not limited to any residual royalty interest or information rights.

Capitalized terms used, but not otherwise defined herein will have the meaning ascribed to them in the Purchase Option Agreement.

[SIGNATURES FOLLOW ON NEXT PAGE]

IN WITNESS WHEREOF, the parties hereto have signed this Confirmation of Closing as of the day and year first above written.

ISIS PHARMACEUTICALS, INC.

By: _____
Name: B. Lynne Parshall, J.D.
Title: Executive Vice President, CFO and Secretary

SYMPHONY GENISIS HOLDINGS LLC

By: Symphony Capital Partners, L.P.,
its Manager

By: Symphony Capital GP, L.P.,
its general partner

By: Symphony GP, LLC,
its general partner

By: _____
Name: Mark Kessel
Title: Managing Member

APPENDIX 15
PART 2
CONFIRMATION OF TERMINATION
, 2007

WHEREAS, Isis Pharmaceuticals, Inc. ("Isis") and Symphony GenIsis, Inc. ("Symphony GenIsis") are parties to the Novated and Restated Technology License Agreement dated April 7, 2006 (the "Technology License Agreement");

WHEREAS, Isis has exercised the Purchase Option, pursuant to which Isis has purchased all of the outstanding Symphony GenIsis Equity Securities by paying the Purchase Price to Holdings; and

WHEREAS, Isis and Symphony GenIsis hereby acknowledge, confirm and agree that, notwithstanding Section 7.2, 7.3 or any other provision of the Technology License Agreement, the Technology License Agreement is terminated *in full* such that all of the rights, obligations and other terms of the technology License Agreement are no longer in force or effect with no survival.

Capitalized terms used, but not otherwise defined herein will have the meaning ascribed to them in the Technology License Agreement.

IN WITNESS WHEREOF, the parties hereto have signed this Confirmation of Termination as of the day and year first above written.

ISIS PHARMACEUTICALS, INC.

By: _____
Name: B. Lynne Parshall, J.D.
Title: Executive Vice President, CFO and Secretary

SYMPHONY GENISIS, INC.

By: _____
Name: Stanley T. Crooke, M.D., Ph.D.
Title: Sole Director

APPENDIX 16

[***]

APPENDIX 17

Assignment of Isis Product Specific Patents

Isis Pharmaceuticals, Inc. conveys, assigns and transfers its entire right, title and interest in and to Isis Product Specific Patents, Research results and data from the R&D Plan that relate to the Designated Compound or Product, pursuant to Section 9.2.3(b) of the Agreement. In consideration for this Assignment, Ortho-McNeil, Inc. agrees to pay Isis' royalties pursuant to the provisions of Table 3 of Article 6 of the Agreement. In this Assignment, all defined terms have the same definition as in the Agreement.

ISIS Pharmaceuticals, Inc.

Isis Pharmaceuticals, Inc. requests that the marked portions of the agreement be granted confidential treatment under Rule 24b-2 of the Securities Exchange Act of 1934.	Exhibit 10.2

LICENSE AND COLLABORATION AGREEMENT

This License and Collaboration Agreement (the "License Agreement" or the "Agreement") is entered into as of the 6th day of September 2007 (the "Effective Date") by and among Alnylam Pharmaceuticals, Inc., a Delaware corporation, with its principal place of business at 300 Third Street, Cambridge, Massachusetts 02142 ("Alnylam"), Isis Pharmaceuticals, Inc., a Delaware corporation, with its principal place of business at 1896 Rutherford Road, Carlsbad, California 92008 ("Isis", and each of Alnylam and Isis, a "Licensor" and together, the "Licensors"), and Regulus Therapeutics LLC, a Delaware limited liability company, with its principal place of business at 1896 Rutherford Road, Carlsbad, California 92008 ("Regulus").

INTRODUCTION

1. Isis and Alnylam each Controls certain intellectual property relating to miRNAs (each as defined below).

2. Isis and Alnylam are creating a new entity, Regulus, to exploit miRNA Compounds.

3. Regulus desires to obtain a license from Isis and Alnylam to such intellectual property for the purpose of developing and commercializing certain products, and Isis and Alnylam each desires to grant such a license to Regulus in accordance with the terms and conditions of this Agreement.

4. On the Effective Date, the Parties are entering into a Services Agreement pursuant to which the Licensors will provide certain services to Regulus.

In consideration of the mutual covenants contained herein, and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, Isis, Alnylam and Regulus each agrees as follows:

1. DEFINITIONS

Capitalized terms used herein and not defined elsewhere herein have the meanings set forth in Exhibit 1.

2. ASSIGNMENT; LICENSES

2.1 Assignments to Regulus.

(a) Isis hereby grants, sells, conveys, transfers, assigns, releases and delivers to Regulus all right, title and interest in and to the Patent Rights and contracts listed on **SCHEDULE 2.1(A)** attached hereto, to have and hold the same unto itself, its successors and assigns forever, and Regulus hereby accepts such grant, sale, conveyance, etc.

(b) Alnylam hereby grants, sells, conveys, transfers, assigns, releases and delivers to Regulus all right, title and interest in and to the Patent Rights and contracts listed on

---

SCHEDULE 2.1(B) attached hereto, to have and hold the same unto itself, its successors and assigns forever, and Regulus hereby accepts such grant, sale, conveyance, etc.

(c) Notwithstanding the foregoing, to the extent any contract for which assignment is provided for herein is not assignable pursuant to such contract without the written consent of another party or requires novation, if assigned, this Agreement will not constitute an assignment or an attempted assignment thereof if such assignment or attempted assignment would constitute a breach thereof. To the extent a contract is not assigned pursuant to this provision, the applicable Licensor will cooperate with the other Parties and will use its Commercially Reasonable Efforts to provide Regulus the economic and other benefits intended to be assigned to Regulus under the relevant contract.

2.2 Licenses Granted to Regulus.

(a) Grants. Subject to the terms and conditions of this Agreement (including but not limited to Section 2.4), each Licensor hereby grants to Regulus a worldwide, royalty-bearing, sublicenseable (in accordance with Section 2.5) license in the Field, under such Licensor's Licensed IP,

(i) to Develop miRNA Compounds and miRNA Therapeutics,

(ii) to Manufacture miRNA Compounds and miRNA Therapeutics, and

(iii) to Commercialize miRNA Therapeutics.

Subject to Section 2.4, the rights granted under clauses (i), (ii) and (iii) will be (y) exclusive with respect to miRNA Compounds which are miRNA Antagonists and miRNA Therapeutics containing such miRNA Compounds, and (z) non-exclusive with respect to miRNA Compounds which are Approved Precursor Antagonists and miRNA Therapeutics containing such miRNA Compounds.

(b) Request to License miRNA Mimics and Additional miRNA Precursor Antagonists. Regulus may request a worldwide, royalty-bearing, sublicenseable (in accordance with Section 2.5), non-exclusive license in the Field, under each Licensor's Licensed IP, to Develop, Manufacture and Commercialize a specific miRNA Mimic or a specific miRNA Precursor Antagonist that is not then an Approved Precursor Antagonist, and miRNA Therapeutics containing such miRNA Mimic or miRNA Precursor Antagonist, by providing written notice to Licensors thereof on a miRNA Mimic-by-miRNA Mimic or miRNA Precursor Antagonist-by-miRNA Precursor Antagonist basis. Such license is subject to (i) review and affirmative approval by the Licensors, which approval may be withheld by a Licensor in such Party's sole discretion, and (ii) compliance with relevant Third Party Rights ([***]). For the

avoidance of doubt, Regulus will have no rights to such miRNA Mimic or miRNA Precursor Antagonist hereunder unless and until the affirmative approval of the relevant Licensor(s) and any required consents or approvals from Third Parties have been obtained and Regulus agrees to comply with all Third Party Rights, even to the extent inconsistent with the terms of this Agreement, following which such miRNA Mimic or miRNA Precursor Antagonist will be deemed to be an Approved Mimic or Approved Precursor Antagonist, respectively.

(c) Retained Rights. The exclusive license granted to Regulus by Alnylam pursuant to Section 2.2(a) is subject to Alnylam's retained right to use and exploit its Licensed IP solely to support its own internal Research in the Alnylam Field. The exclusive license granted to Regulus by Isis pursuant to Section 2.2(a) is subject to Isis' retained right to use and exploit its Licensed IP solely to support its own internal Research in the Isis Field. All rights in and to each Licensor's Licensed IP not expressly licensed pursuant to Sections 2.2(a) and (b), and any other Patent Rights or Know-How of such Licensor, are hereby retained by such Licensor.

2.3 Licenses Granted to Licensors Under Regulus IP. Subject to the terms and conditions of this Agreement and to Third Party Rights:

(a) Regulus hereby grants to Alnylam a worldwide, exclusive, royalty-free, perpetual and irrevocable license, with the right to grant sublicenses, under the Regulus IP solely to the extent necessary or useful to research, discover, develop, make, have made, use, sell, offer to sell and/or otherwise commercialize double-stranded oligonucleotides (other than Approved Mimics) and any product containing double-stranded oligonucleotides (other than Approved Mimics) (the "Alnylam Field").

(b) Regulus hereby grants to Isis a worldwide, exclusive, royalty-free, perpetual and irrevocable license, with the right to grant sublicenses, under the Regulus IP solely to the extent necessary or useful to research, discover, develop, make, have made, use, sell, offer to sell and/or otherwise commercialize single-stranded oligonucleotides (other than miRNA Antagonists, Approved Precursor Antagonists, or Approved Mimics) and any product containing single-stranded oligonucleotides (other than miRNA Antagonists, Approved Precursor Antagonists or Approved Mimics) (the "Isis Field").

2.4 Third Party Rights; Additional Rights.

(a) *Existing Out-License Agreements.* The licenses granted under Section 2.2 and 2.3 are subject to and limited by the licenses granted, and other obligations owed, by each Licensor to a Third Party prior to the Effective Date under a Licensed Patent Right Controlled by such Licensor, pursuant to agreements described on (i) **PART 1 OF SCHEDULE 2.4(A)** in the case of Licensed Patent Rights Controlled by Isis, and (ii) **PART 2 OF SCHEDULE 2.4(A)** in the case of Licensed Patent Rights Controlled by Alnylam, and (iii) in an addendum transmittal instrument delivered by each Licensor within 30 days after the Effective Date. The schedules and instruments provided under this Section 2.4(a) will be collectively referred to as the "Out-License Summary", and the agreements described therein will be collectively referred to as the "Out-License Agreements").

(b) *Existing In-Licenses from Third Parties*.

(i) Certain of the Licensed Patent Rights as of the Effective Date that are licensed to Regulus under Section 2.2 are in-licensed or were acquired by the applicable Licensor under agreements with Third Party licensors or sellers that may contain restrictions on the scope of the licenses or trigger payment or other material obligations or restrictions (such license or purchase agreements in effect as of the Effective Date being the "In-License Agreements"). The licenses and other rights (including sublicense and disclosure rights) granted to a Party pursuant to this Agreement are subject to, and are limited to the extent of the terms of

any (i) In-License Agreements between Isis and any Third Party licensor, as specifically described on **PART 1 OF SCHEDULE 2.4(B)** and (ii) any In-License Agreement between Alnylam and any Third Party, as specifically described on **PART 2 OF SCHEDULE 2.4(B).** The schedules provided under this Section 2.4(b) will be collectively referred to as "In-License Summary." Each Part of the In-License Summary summarizes all material restrictions on the scope of the licenses, and all material payment obligations owed, under the In-License Agreements (other than the Previous Agreements) which the applicable Licensor reasonably believes apply to the licenses granted to Regulus hereunder as of the Effective Date. Except as provided in Section 5.6(d), Regulus will assume all financial and other obligations to the relevant Third Party, and be subject to all restrictions, set forth on the In-License Summary and arising from the grant to Regulus of the licenses pursuant to Section 2.2(a) as of the Effective Date.

(ii) In addition to the financial obligations and scope limitations set forth on the In-License Summary and the Out-License Summary, and to the extent access to such terms have been made available to such licensed Party in unredacted form (provided, however, that such licensed Party has not failed to request such access in accordance with Section 2.4(e)), a Party receiving a license or sublicense under Licensed IP hereunder will comply, and will cause its Affiliates and Sublicensees to comply, with all other terms of the In-License Agreements and Out-License Agreements, including without limitation diligence requirements, applicable to the licenses granted to such Party hereunder.

(c) *Optional In-Licenses*. Notwithstanding anything to the contrary herein, the licenses to Isis' Licensed IP hereunder initially shall not include licenses to Patent Rights or Know-How licensed by Isis under the agreements listed and described on **PART 1 OF SCHEDULE 2.4(C)** and the licenses to Alnylam's Licensed IP hereunder initially shall not include licenses to Patent Rights or Know-How licensed by Alnylam under the agreements listed and described on **PART 2 OF SCHEDULE 2.4(C)** (such agreements on Schedule 2.4(C) referred to as the "Optional In-Licenses"). Regulus is hereby granted the option of expanding its licenses under Section 2.2 to include Patent Rights and Know-How licensed to the relevant Licensor pursuant to [***] Optional In-Licenses, with respect to [***] miRNA Compounds and related miRNA Therapeutics, by notifying the Parties in writing of the relevant Optional In-License, and each miRNA Compound with respect thereto, for which such option is exercised. Upon such exercise and Regulus' written agreement to assume all financial and other obligations and restrictions imposed by the desired Optional In-License (including, to the extent access to such terms have been made available to Regulus in unredacted form (provided, however, that Regulus has not failed to request such access in accordance with Section 2.4(e)), all other terms of such Optional In-License applicable to the licenses granted to Regulus hereunder), the Patent Rights and Know-How licensed to the relevant Licensor pursuant to the specified Optional In-License shall be deemed included in such Licensor's Licensed IP solely with respect to the relevant miRNA Compounds and related miRNA Therapeutics.

(d) *Additional Rights after Effective Date*. If after the Effective Date, a Party (the "Controlling Party") invents or acquires rights or title to an invention claimed by a Patent Right that would be included in the Licensed Patent Rights or Regulus Patent Rights (the "Additional Rights"), then, on the anniversary of the Effective Date following such invention or acquisition of such Additional Right, or as otherwise reasonably requested by a Party, the Controlling Party must notify each other Party (each, a "Non-Controlling Party") of such acquisition or invention. If a Non-Controlling Party wishes to include such Additional Rights

under the licenses granted pursuant to Sections 2.2, 2.3 or 5.6 (as the case may be), such Non-Controlling Party will notify the Controlling Party of its desire to do so, the Controlling Party will provide the Non-Controlling Party a summary of all material restrictions on the scope of the licenses granted, and all material payment obligations owed, under any Third Party Agreement applicable to such Additional Rights and the Non-Controlling Party may, upon written notice to the Controlling Party, obtain a license under such Additional Rights and will assume all financial and other obligations to, and be subject to all restrictions imposed by, the Controlling Party's licensors or collaborators, if any, arising from the grant to such Non-Controlling Party of such license (including, to the extent access to such terms have been made available to such Non-Controlling Party in unredacted form (provided, however, that such Non-Controlling Party has not failed to request such access in accordance with Section 2.4(e)), all other terms of such Third Party Agreements applicable to the licenses granted to such Non-Controlling Party hereunder). Notwithstanding the foregoing, any Additional Rights that do not carry financial or other obligations or restrictions will be automatically included under the licenses granted pursuant to Section 2.2, 2.3 or 5.6. If the Controlling Party pays any upfront payments or similar acquisition costs to access Additional Rights, the Controlling Party and relevant Non-Controlling Party(ies) will negotiate in good faith regarding sharing such acquisition costs and payments. When acquiring or creating such Additional Rights pursuant to any agreement entered into after the Effective Date, each Party will endeavor in good faith to secure the right to sublicense such Additional Rights to the other Parties.

(e) *Applicable Agreements*. Each Party agrees to provide, upon the request of a Party, access to each Third Party Agreement that is the subject of any provision of this Section 2.4; provided, however, that the Parties agree and acknowledge that (i) the Third Party Agreements so provided may, to the extent necessary to protect confidential information of the relevant Third Party or financial information of the relevant Party, be redacted, and (ii) if so redacted, the Party assuming any obligations or accepting any limitations under a Third Party Agreement pursuant to this Section 2.4, will only be liable to the extent access to such terms have been made available to such licensed Party in unredacted form.

2.5 Sublicenses.

(a) Subject to Third Party Rights, Regulus will have the right to grant to its Affiliates and Third Parties sublicenses under the licenses granted in Sections 2.2(a) and (b).

(b) Subject to Third Party Rights, the Opt-In Party will have the right to grant to its Affiliates and Third Parties sublicenses under the rights granted to such Licensor in Section 5.6(a).

(c) Each such sublicense will be subject and subordinate to, and consistent with, the terms and conditions of this Agreement, and will provide that any such Affiliate and Sublicensee will not further sublicense except on terms consistent with this Section 2.5. Regulus or the Opt-In Party, as applicable, will provide the other Parties with a copy of any sublicense granted pursuant to this Section 2.5 within 30 days after the execution thereof. Such copy may be redacted to exclude confidential scientific information and other information required by a Sublicensee to be kept confidential; provided that all relevant financial terms and information will be retained. Regulus or the Opt-In Party, as applicable, will remain responsible for the performance of its Affiliates and Sublicensees, and will ensure that all such

Affiliates and Sublicensees comply with the relevant provisions of this Agreement. In the event of a material default by any of its Affiliates or Sublicensees under a sublicense agreement, Regulus or the Opt-In Party, as applicable, will inform the other Parties and will take such action, after consultation with such other Parties, which, in Regulus' or the Opt-in Party's (as applicable) reasonable business judgment, will address such default.

3. TECHNOLOGY TRANSFER

3.1 Technology Transfer to Regulus. At each meeting of the Collaboration Working Group the representatives will discuss new Know-How and Patent Rights of Isis and Alnylam that are included in such Licensor's Licensed Patents and Licensed Know-How hereunder at the level of detail necessary to enable Regulus to effectively practice such Patent Rights and Know-How.

3.2 Technology Transfer from Regulus; Identification and Improvements. At each Collaboration Working Group meeting Regulus will present a description of all Regulus IP developed by it or on its behalf, or over which Regulus otherwise acquired Control, since the last meeting. The description will be at a level of detail necessary to enable Isis, Alnylam or both, as appropriate, to effectively practice such Regulus IP in accordance with their respective licenses under Section 2.3.

4. DILIGENCE

4.1 General Diligence. Except to the extent a Licensor receives a license from Regulus pursuant to this Agreement to Develop, Manufacture and Commercialize miRNA Therapeutics, Regulus will use Commercially Reasonable Efforts to Develop, and Commercialize miRNA Compounds and miRNA Therapeutics in the Field.

4.2 Compliance with Laws. Each Party will, and will ensure that its Affiliates and Sublicensees will, comply with all relevant Laws in exercising their rights and fulfilling their obligations under this Agreement.

4.3 Reporting. By January 31st of each year, Regulus will prepare and furnish each Licensor with a written report summarizing Regulus' activities conducted during the prior calendar year to Develop, Manufacture and Commercialize miRNA Therapeutics in the Field and identifying the results obtained or benchmarks achieved since the last report to the Licensors.

4.4 Designation of Research Programs and Development Projects. Regulus' officers will be responsible for reviewing the results of Research and Development activities under the Operating Plan and designating (subject to the approval of the Managing Board) from time to time Research Programs and Development Projects. A "Research Program" will begin upon the commencement of discovery or characterization activities focused on one or more specific miRNA(s) after preliminary validation of the biological function of such miRNA(s) has been identified (i.e., compound discovery, not target validation) and will include all activities with respect to the Development, Manufacturing and Commercialization of miRNA Compounds and miRNA Therapeutics directed to such miRNA(s). A Research Program will become a "Development Project" (and thereafter will no longer be a Research Program) when Regulus' officers recommend, and the Managing Board agrees, that a sufficient portfolio of data exists to

support the initiation of a [***] on a miRNA Compound drug candidate targeting such miRNA(s). Regulus will maintain a written list of the then-current Research Programs and Development Projects (each, a "Program/Project List").

5. RIGHT TO OPT-IN

5.1 Notice of Development Project Status. Concurrently with the conversion of a Research Program into a Development Project, Regulus will notify each Licensor of such conversion and whether or not Regulus will continue to pursue the Development and Commercialization of such newly designated Development Project.

5.2 Continued Development by Regulus of Development Projects. If Regulus notifies Licensors pursuant to Section 5.1 that Regulus will continue to pursue the Development and Commercialization of such Development Project, then, without limiting the generality of Section 4.1, Regulus will use Commercially Reasonable Efforts to Develop and Commercialize the relevant Development Compounds and Development Therapeutics in the Field. Regulus will also (a) pay to each Licensor a royalty of [***]% of Net Sales of such Development Therapeutics which are Royalty-Bearing Products, during the relevant Royalty Term (provided, however, that, for the remainder of the relevant Royalty Term following the end of the relevant Exclusivity Period, the royalty rate will be [***]%) and (b) be responsible for all milestones, royalties and other payments payable to Third Parties in respect of the Development, Manufacture and Commercialization of such Development Therapeutics in the Field, by Regulus, its Affiliates and Sublicensees, including any amounts payable by either Licensor to Third Parties under the Third Party Rights. The Parties will use reasonable efforts to [***]. Regulus agrees that the royalty described in clause (a) of this Section 5.2 is payable to each Licensor, regardless of whether a particular Royalty-Bearing Product is covered by such Licensor's Licensed IP. Each Party agrees and acknowledges that such royalty structure (i) is freely entered into by such Party, (ii) is a fair reflection of the value received by Regulus from the licenses granted by the Licensors, and (iii) is a reasonable allocation of the value received by Regulus from each Licensor, due to the difficulty of determining the extent to which Licensor's Licensed IP covers or has enabled each Royalty-Bearing Product.

5.3 Opt-In Election. If Regulus notifies Licensors pursuant to Section 5.1 that it will not continue to pursue the Development and Commercialization of such Development Project, each Licensor will have the right, exercisable by providing written notice to Regulus and the other Licensor within [***] days following receipt of such notice ("Initial Opt-In Election Period"), to elect to continue to pursue the Development and Commercialization of such Development Project ("Opt-In Election").

(a) Opt-In by One Licensor. If only one, but not both, of the Licensors (the "Opt-In Party") makes an Opt-In Election with respect to such Development Project within the Initial Opt-In Election Period, the High Terms set forth in Section 5.4 and the terms of Section 5.6 will apply following the end of such Initial Opt-In Election Period and the Licensor who did not elect to opt-in will waive its right to opt-in with respect to such Development Project.

(b) No Opt-In; Second Opt-In Election. If, within the Initial Opt-In Election Period, neither Licensor makes an Opt-In Election (or both Licensors fail to submit any response), then Regulus will use diligent efforts to negotiate and finalize, within [***] months

following the end of the Initial Opt-In Election Period, a term sheet with a Third Party pursuant to which such Third Party will Develop and Commercialize, either by itself or with or on behalf of Regulus, such Development Project in the Field.

(i) If, despite diligent efforts, Regulus is unable to finalize such term sheet with a Third Party with respect to the Development Project within such [***] month period, or Regulus is able to finalize such term sheet with a Third Party with respect to the Development Project within such [***] month period, but Regulus is unable to execute a definitive agreement substantially in conformance with such term sheet within [***] months after finalizing such term sheet, Regulus will notify Licensors thereof and each Licensor will again have the right, exercisable by providing written notice to Regulus and the other Licensor, within [***] days following Regulus' notice ("Second Opt-In Election Period"), to elect to continue to pursue the Development and Commercialization of such Development Project on the Low Terms set forth in Section 5.5.

(ii) If only one, but not both, of the Licensors, makes an Opt-In Election within the Second Opt-In Election Period (the "Opt-In Party"), the Low Terms set forth in Section 5.5 and the terms of Section 5.6 will apply following the end of such Second Opt-In Election Period and the Licensor who did not make an Opt-In Election, within such Second Opt-In Election Period, will have waived its right to opt-in with respect to such Development Project.

(iii) If, within the Second Opt-In Election Period, neither Licensor makes an Opt-In Election (or both Licensors fail to submit any response), then Regulus will retain all rights to such Development Project.

(c) Opt-In by Both Licensors. If, within the Initial Opt-In Election Period or Second Opt-In Election Period, both Licensors submit an Opt-In Election with respect to such Development Project, then the Parties will, to the extent mutually agreed, work together to amend the Operating Plan to support Regulus in Developing and Commercializing the Development Project, including, as applicable, creating a funding and early development plan, and the designation of roles and responsibilities of each Party in the execution of such Operating Plan.

5.4 Opt-In on High Terms. In the event that an Opt-In Election is made by only one of the Licensors during the Initial Opt-In Election Period pursuant to Section 5.3(a), the following terms will apply ("High Terms"):

(a) Upfront Payment. The Opt-In Party will pay to Regulus, within 15 days following the end of the Initial Opt-In Election Period, a one-time payment of [***] Dollars ($[***]).

(b) Royalties. During the relevant Royalty Term, the Opt-In Party will pay to Regulus the following royalties on Net Sales (aggregated from all relevant countries) of each Royalty-Bearing Product in a calendar year:

On the portion of Net Sales during the calendar year:	Royalty Rate on Net Sales During Exclusivity Period	Royalty Rate on Net Sales After Exclusivity Period
Less than or equal to $[***]:	[***]%	[***]%
Greater than $[***]:	[***]%	[***]%

The Opt-In Party's obligation to pay royalties under this Section 5.4(b) is imposed only once with respect to the same unit of Royalty-Bearing Product.

(c) Milestone Payments. Subject to Section 5.6(f), the Opt-In Party will pay to Regulus the following payments upon the achievement of the events set forth below by a Royalty-Bearing Product for the relevant Development Project:

Milestone Event:	Payment [***]:
(i) Filing of IND for first Royalty-Bearing Product	$[***]
(ii) Upon Completion of the first Phase IIa Clinical Trial	$[***]
(iii) Initiation (i.e., dosing of first patient) of the first Phase III Clinical Trial	$[***]
(iv) Filing of NDA in U.S. for first Royalty-Bearing Product	$[***]
(v) Filing of NDA in the European Union for first Royalty-Bearing Product	$[***]
(vi) Regulatory Approval in U.S. for the first Royalty-Bearing Product	$[***]
(vii) Regulatory Approval in any Major Country in the European Union for the first Royalty-Bearing Product	$[***]

The Opt-In Party will notify the other Parties within 15 days following achievement or occurrence of a milestone event. Each milestone payment under this Section 5.4(c) will be payable only once with respect to the first Royalty-Bearing Product under the relevant Development Project to achieve the milestone event. If an event in clause (ii), (iii), (iv) or (v) occurs before an event in a preceding clause (i), (ii) or (iii), the milestone payment described in such clause (i), (ii) or (iii) will be paid when the milestone payment described in such clause (ii), (iii), (iv) or (v) is paid.

Milestone payments will continue to be due for milestone events occurring after any grant by the Opt-In Party or its Affiliates to a Third Party of a sublicense of the Regulus IP or Licensed IP licensed to the Opt-In Party under Section 5.6(a) with respect to the relevant Development Project.

(d) Sublicense Income. Subject to Section 5.6(f), the Opt-In Party will pay to Regulus a portion of the Sublicense Income received by the Opt-In Party or its Affiliates, in accordance with the following table:

Sublicense agreement initially entered into during this timeframe:	**Percentage of Sublicense Income**
Prior to Completion of first Phase IIa Clinical Trial	[***]%
After Completion of first Phase IIa Clinical Trial, but prior to completion of first Phase III Clinical Trial	[***]%
After Completion of first Phase III Clinical Trial	[***]%

5.5 Opt-In on Low Terms. In the event that an Opt-In Election is made by only one, but not both, of the Licensors during the Second Opt-In Election Period pursuant to Section 5.3(b)(ii), the following terms will apply ("Low Terms"):

(a) Upfront Payment. The Opt-In Party will pay to Regulus, within 15 days following the end of the Second Opt-In Election Period, a one-time payment of [***] Dollars ($[***]).

(b) Royalties. During the relevant Royalty Term, the Opt-In Party will pay to Regulus the following royalties on Net Sales (aggregated from all relevant countries) of each Royalty-Bearing Product in a calendar year:

On the portion of Net Sales during the calendar year:	Royalty Rate on Net Sales During Exclusivity Period	Royalty Rate on Net Sales After Exclusivity Period
Less than or equal to $[***]:	[***]%	[***]%
Greater than $[***]:	[***]%	[***]%

The Opt-In Party's obligation to pay royalties under this Section 5.5(b) is imposed only once with respect to the same unit of Royalty-Bearing Product.

(c) Milestone Payments. Subject to Section 5.6(f), the Opt-In Party will pay to Regulus the following payments upon the achievement of the events set forth below by a Royalty-Bearing Product for the relevant Development Project:

Milestone Event:	Payment for Royalty-Bearing Product [***]:
(i) Filing of IND for first Royalty-Bearing Product	$[***]
(ii) Upon Completion of the first Phase IIa Clinical Trial	$[***]
(iii) Initiation (i.e., dosing of first patient) of the first Phase III Clinical Trial	$[***]
(iv) Filing of NDA in U.S. for first Royalty-Bearing Product	$[***]
(v) Regulatory Approval in U.S. for the first Royalty-Bearing Product	$[***]

The Opt-In Party will notify the other Parties within 15 days following achievement or occurrence of a milestone event. Each milestone payment under this Section 5.4(c) will be payable only once with respect to the first Royalty-Bearing Product under the relevant Development Project to achieve the milestone event. If an event in clause (ii), (iii), (iv) or (v) occurs before an event in a preceding clause (i), (ii) or (iii), the milestone payment described in such clause (i), (ii) or (iii) will be paid when the milestone payment described in such clause (ii), (iii), (iv) or (v) is paid.

Milestone payments will continue to be due for milestone events occurring after any grant by the Opt-In Party or its Affiliates to a Third Party of a sublicense of the Regulus IP or Licensed IP licensed to the Opt-In Party under Section 5.6(a) with respect to the relevant Development Project.

(d) Sublicense Income. Subject to Section 5.6(f), the Opt-In Party will pay to Regulus a portion of the Sublicense Income received by the Opt-In Party or its Affiliates, in accordance with the following table:

Sublicense agreement initially entered into during this timeframe:	**Percentage of Sublicense Income**
Prior to Completion of first Phase IIa Clinical Trial	[***]%
After Completion of first Phase IIa Clinical Trial, but prior to completion of first Phase III Clinical Trial	[***]%
After Completion of first Phase III Clinical Trial	[***]%

5.6 Other Terms Applicable to Opt-In Party.

(a) License Grant.

(i) Regulus will, and hereby does, grant to the Opt-In Party, subject to and limited by the Third Party Rights, a worldwide, royalty-bearing, sublicenseable (in accordance with Section 2.5), (x) license under all Regulus IP, and (y) sublicense under all Licensed IP (within the scope of the license granted to Regulus under such Licensed IP pursuant to Sections 2.2(a) and 2.2(b)), solely for purposes of Developing, Manufacturing and Commercializing the relevant Development Project's Development Compounds and Development Therapeutics in the Field on the terms set forth in this Section 5.6. Regulus shall comply with the provisions of Section 2.4 with respect to the disclosure of information with respect to the relevant Third Party Rights.

(ii) Subject to Third Party Rights, the rights granted under Section 5.6(a)(i) to the Opt-In Party will be exclusive, to the fullest extent possible, under Regulus IP and under Licensed IP. For the sake of clarity, this means that Regulus IP will be exclusively licensed by Regulus to the Opt-In Party with respect to the relevant Development Project, and Regulus' rights under the Licensed IP will be exclusively sublicensed by Regulus to the Opt-In Party with respect to the relevant

Development Project, but any non-exclusive licenses grant by the relevant Licensor to Regulus with respect to Licensed IP shall not be deemed to have been expanded to exclusive licenses to Regulus.

(b) Diligence. The Opt-In Party will use Commercially Reasonable Efforts to Develop, Manufacture and Commercialize the relevant Development Compounds and Development Therapeutics, at such Opt-In Party's own expense, in the Field, either by itself or with or through its Affiliates or Sublicensees.

(c) Non-Compete. The non-Opt-In Party with respect to a Development Project will not, itself or through its Affiliates or with Third Parties, Develop, Manufacture or Commercialize Development Compounds or Development Therapeutics with respect to such Development Project during the period (i) [***] of a Royalty-Bearing Product with respect to such Development Project anywhere in the world as long as such Opt-In Party reasonably believes that a Development Therapeutic would be a Royalty-Bearing Product upon first commercial sale, and (ii) [***] of a Royalty-Bearing Product with respect to such Development Project anywhere in the world, until the expiration of [***] for such Development Project; provided, however that each Party will be entitled to grant Permitted Licenses.

(d) Third Party and Inter-Licensor Payments. In addition to the royalties and milestones payable under Section 5.4 or 5.5 above, the Opt-In Party will be responsible for all milestones, royalties and other payments payable to Third Party Licensors and assumed under Section 2.4. The Parties will use reasonable efforts to [***]. In addition, the Opt-In Party will

be responsible for any other payments to the Third Parties in respect of the Development, Manufacture and Commercialization of such Development Compounds and Development Therapeutics in the Field. In addition, the Licensors agree that any amounts otherwise owed by one Licensor to another pursuant to a Previous Agreement is hereby waived with respect to such Development Project.

(e) No Longer a Development Project. If one, but not both, Licensors make an Opt-In Election with respect to a Development Project, such Development Project will be permanently removed from the Program/Project List.

(f) Credit for Prepaid Amounts. The Parties agree that, with respect to any Development Project, the relevant Opt-In Party should pay the greater of the cumulative Guaranteed Payments and the cumulative Sublicense Income Payments as of the end of each calendar quarter, and, because the timing of the Guaranteed Payments and the Sublicense Income Payments with respect to any given Development Project may not align, the Parties agree that the relevant Opt-In Party will not, with respect to any calendar quarter, be required to pay more than the amount necessary to bring the cumulative payments made by such Opt-In Party with respect to such Development Project up to the greater of the cumulative Guaranteed Payments and the cumulative Sublicense Income Payments with respect to such calendar quarter. Therefore, with respect to any calendar quarter, the relevant Opt-In Party shall pay the difference (if positive) between (i) the Cumulative Amount Owed as of the end of such calendar quarter, minus (ii) the Cumulative Amount Owed (if any) as of the end of the immediately prior calendar quarter. Several examples are provided in Schedule 5.6(f).

(A) "Cumulative Amount Owed" means, with respect to a Development Project and a calendar quarter, the greater of (1) the cumulative Guaranteed Payments as of the end of such calendar quarter, and (2) the cumulative Sublicense Income Payments as of the end of such calendar quarter.

(B) "Guaranteed Payments" means, with respect to a Development Project and a calendar quarter, (1) if High Terms apply, the payments paid or payable pursuant to Sections 5.4(a) and 5.4(c) with respect to such calendar quarter, and (2) if Low Terms apply, the payments paid or payable pursuant to Section 5.5(a) and 5.5(c) with respect to such calendar quarter.

6. [Intentionally Deleted]

7. [Intentionally Deleted]

8. PAYMENT TERMS; REPORTS; RECORD-KEEPING AND AUDIT RIGHTS

8.1 Reports and Payments. The Party paying any royalties, milestones or Sublicense Income Payments hereunder (the "Paying Party") to another Party (each, a "Payee Party") will deliver to such Payee Party(ies), within 15 days after the end of each calendar quarter, a report with a reasonably detailed written accounting of Net Sales of Royalty-Bearing Products that are subject to royalty payments due to the Payee Party(ies) for such calendar quarter, milestones payable and Sublicense Income received or accrued during such period. Such quarterly reports

will indicate gross sales on a country-by-country and Royalty-Bearing Product-by-Royalty-Bearing Product basis, the deductions from gross sales used in calculating Net Sales and the resulting calculation of the royalties due to the Payee Party(ies). Royalties or other payments accrued for the period covered by each such quarterly report will be due and payable 45 days after the end of each relevant calendar quarter. All amounts in this Agreement are expressed in U.S. Dollars and all payments due to the Payee Party(ies) hereunder will be paid in U.S. Dollars. If any conversion of foreign currency to U.S. Dollars is required in connection with any such payments, such conversion will be made by using the conversion rate existing in the United States (as reported in *The Wall Street Journal*) on the last Business Day of the reporting period to which such payments relate, or such other publication as the Parties agree.

8.2 Tax Withholding. The Paying Party will use all reasonable and legal efforts to reduce tax withholding with respect to payments to be made to the Payee Party(ies). Notwithstanding such efforts, if the Paying Party concludes that tax withholdings are required with respect to payments to the Payee Party(ies), the Paying Party will withhold the required amount and pay it to the appropriate governmental authority. In any such case, the Paying Party will promptly provide the Payee Party(ies) with original receipts or other evidence reasonably sufficient to allow the Payee Party(ies) to document such tax withholdings for purposes of claiming foreign tax credits and similar benefits.

8.3 Late Payments. Any payments that are not made on or before the due date will bear interest at the lesser of (a) 1.5% per month or (b) the maximum permissible rate under applicable law, for the period from the date on which such payment was due through the date on which payment is actually

made.

8.4 Financial Records. Unless otherwise required by the LLC Agreement, the Paying Party will maintain, and will require its Affiliates and Sublicensees to maintain, for 3 years after the relevant reporting period all financial records relating to the transactions and activities contemplated by this Agreement in sufficient detail to verify compliance with the terms of this Agreement.

8.5 Audit Right. Once during each calendar year, each Payee Party may retain an independent certified public accountant reasonably acceptable to the Paying Party to audit the financial records described in Section 8.4, upon reasonable notice to the Paying Party, during regular business hours and under an obligation of confidentiality to the Paying Party. Such Payee Party will bear all of the costs of such audit, except as provided below. The results of such audit will be made available to all Parties; provided, that, such results will be deemed the Confidential Information of the Paying Party hereunder. If the audit demonstrates that the payments owed under this Agreement have been understated, the Paying Party will pay the balance to the Payee Party, together with interest in accordance with Section 8.3. Further, if the amount of the understatement is greater than 5% of the amount owed to such Payee Party with respect to the audited period, then the Paying Party will reimburse the Payee Party for the reasonable cost of the audit. If the audit demonstrates that the payments owed under this Agreement have been overstated, the Payee Party will refund to the Paying Party the amount of such overpayment. All payments owed by the Paying Party or Payee Party under this Section 8.5 will be made within 30 days after the results of the audit are delivered to the Parties unless the Paying Party is disputing in good faith the results of the audit in which case the payment will be made within 30 days after resolution of such dispute.

9. INTELLECTUAL PROPERTY

9.1 Ownership.

(a) As among the Parties, (i) all of Alnylam's Licensed IP will be owned solely by Alnylam, (ii) all of Isis' Licensed IP will be owned solely by Isis, and (iii) subject to the Buy-Out process, all Work Product, and the Intellectual Property therein, will be owned by Regulus, and each Licensor hereby assigns, and will cause its Affiliates to assign, to Regulus all Work Product and the Intellectual Property therein.

(b) If Regulus enters into an agreement (other than the Services Agreement) with one of its Affiliates, a Licensor, an Affiliate of a Licensor or a Third Party pursuant to which Regulus IP could be developed, Regulus will use Commercially Reasonable Efforts to require such Person to assign to Regulus all right, title and interest to Regulus IP developed by such Person, or otherwise ensure that Regulus Controls all such Regulus IP.

9.2 Prosecution and Maintenance of Patent Rights.

(a) Regulus IP. As among the Parties, Regulus will have the sole right to file, prosecute and maintain Patent Rights covering any Regulus IP, at Regulus' own expense.

(b) Licensor IP.

(i) As among the Parties, each Licensor will have the initial right to file, prosecute and maintain such Licensor's Licensed Patent Rights. Such activities will be at such Licensor's expense.

(ii) Subject to any Third Party Rights, in the event that a Licensor declines to file, prosecute or maintain such Licensor's Licensed Patent Rights, elects to allow any such Patent Rights to lapse, or elects to abandon any such Patent Rights before all appeals within the respective patent office have been exhausted, then:

(A) Such Licensor will provide Regulus with reasonable notice of its decision to decline to file, prosecute or maintain any such Patent Rights or its election to allow any such Patent Rights to lapse, or its election to abandon any such Patent Rights, so as to permit Regulus to decide whether to file, prosecute or maintain the same, and to take any necessary action.

(B) Regulus may assume control of the filing, prosecution and/or maintenance of such Patent Rights in the name of such Licensor, at Regulus' expense.

(C) Such Licensor will, at Regulus' expense and reasonable request, assist and cooperate in the filing, prosecution and maintenance of such Patent Rights.

(D) Regulus will provide such Licensor, sufficiently in advance for such Licensor to comment, with copies of all patent applications and other material submissions and correspondence with any patent counsel or patent authorities pertaining to such Patent Rights.

(E) Regulus will give due consideration to the comments of such Licensor, but will have the final say in determining whether or not to incorporate such comments.

(F) Regulus and such Licensor will promptly provide the other with copies of all material correspondence received from any patent counsel or patent authorities pertaining to such Patent Rights.

9.3 Enforcement.

(a) Competitive Infringement. Subject to any Third Party Rights, the terms of this Section 9.3(a) will apply with respect to any actual or suspected infringement of a Licensor's Licensed Patent Rights or Regulus Patent Rights by a Third Party making, using or selling a therapeutic product

that contains or consists of (y) a miRNA Compound as an active ingredient [***] or (z) if clause (y) does not apply, an oligonucleotide(s) that falls within the field of a Party's exclusive license under Section 2.3 of this Agreement. In the case of (z) above, the Party with the exclusive license in the field where the infringing product most reasonably falls will be considered the relevant Commercializing Party for purposes of this Section 9.3(a).

(i) Each Party will promptly report in writing to the other Parties any such infringement of which it becomes aware, including, without limitation, receipt of any certification received under the United States Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. Law 98-471), as amended (the "Hatch-Waxman Act"), claiming that any of the Licensed Patent Rights or Regulus Patent Rights is invalid, unenforceable or that no infringement will arise from the manufacture, use or sale of such product (a "Paragraph IV Certification").

(ii) The relevant Commercializing Party will have the initial right, at such Commercializing Party's expense, to initiate a legal action against such Third Party with respect to such infringement of the Regulus Patent Rights and, if such Commercializing Party is a Licensor, such Commercializing Party's Licensed Patent Rights. At the Commercializing Party's reasonable request and expense, the relevant Licensor(s) (if Regulus is the Commercializing Party) or the other Licensor (if a Licensor is the Commercializing Party) will use Commercially Reasonable Efforts to initiate a legal action against such Third Party with respect to an infringement described in clause (y) of this Section 9.3(a) of such other Licensor(s)' Licensed Patent Rights. Each other Party will join in any such

action(s) as a party at the Commercializing Party's request and at the Commercializing Party's expense in the event that an adverse party asserts, the court rules or other Laws then applicable provide, or the Commercializing Party determines in good faith, that a court would lack jurisdiction based on such other Party's absence as a party in such suit. Each other Party may also at any time join in the Commercializing Party's action and may be represented by counsel of its choice, at such Party's expense; but in any event control of such action will remain with the Commercializing Party. At the Commercializing Party's or enforcing Licensor's reasonable request and expense, the other Parties will provide reasonable assistance to the Commercializing Party or enforcing Licensor, as the case may be, in connection with any such action. Without the prior written consent of the relevant other Party(ies), the Commercializing Party or enforcing Licensor, as the case may be, will not enter into any settlement admitting the invalidity of, impacting the scope or interpretation of or otherwise impairing such other Party(ies)' rights, as the case may be, in any such Patent Rights.

(iii) Any recoveries resulting from an action brought under Section 9.3(a)(ii) in connection with an infringement described in clause (y) of Section 9.3(a) (whether undertaken by the Commercializing Party or the enforcing Licensor) will be applied as follows:

(A) First, to reimburse each Party for all litigation costs in connection with such proceeding paid by such Party (on a pro rata basis, based on each Party's respective litigation costs, to the extent the recovery was less than all such litigation costs); and

(B) The remainder of the recovery will be retained by the Commercializing Party and [***].

Any recoveries resulting from an action brought under Section 9.3(a)(ii) in connection with an infringement described in clause (z) of Section 9.3(a) will be retained by the Commercializing Party.

(iv) If the Commercializing Party does not, within 6 months of written notice from another Party or otherwise becoming aware of such infringement (or within 30 days of the Commercializing Party's receipt of a Paragraph IV Certification), commence and reasonably pursue a legal action to prevent such infringement with respect to the Regulus Patent Rights, Regulus will be entitled, at its expense, to commence the action in its name. Each Licensor will join in such action as a party at Regulus' request and expense in the event that an adverse party asserts, the court rules or other Laws then

applicable provide, or Regulus determines in good faith, that a court would lack jurisdiction based on such Licensor's absence as a party in such suit, but control of such action will remain with Regulus. Any recoveries resulting from such an action will be retained by Regulus.

(b) Non-Competitive Infringement.

(i) As among the Parties, except as provided in Sections 9.3(a), Regulus will have the sole right to protect Regulus Patent Rights from any actual or suspected infringement or misappropriation, at Regulus' own expense. Any recoveries resulting from such an action will be retained by Regulus [***].

(ii) As among the Parties, except as provided in Section 9.3(a), each Licensor will have the sole right to protect such Licensor's Licensed Patent Rights from any actual or suspected infringement or misappropriation. Such activities will be at such Licensor's expense. Any recoveries resulting from such an action will be retained by such Licensor.

9.4 Invalidity Claims. Subject to any Third Party Rights, if a Third Party at any time asserts a claim that a Licensor's Licensed IP or the Regulus IP is invalid or otherwise unenforceable (an "Invalidity Claim"), whether as a defense in an infringement action brought by a Party pursuant to Section 9.3 or in an action brought against a Party under Section 9.5, the general concepts of Section 9.3 will apply to such Invalidity Claim (i.e., each Party has the right to defend its own intellectual property, except that the Commercializing Party will have the initial right, to the extent provided in Section 9.3(a), to defend such Invalidity Claim, and Regulus will have a step-in right, to the extent provided in Section 9.3(a), to defend such Invalidity Claim).

9.5 Claimed Infringement.

(a) Regulus will promptly notify the Licensors of the receipt of any claim that the Development or Manufacture of miRNA Compounds or miRNA Therapeutics or Commercialization of miRNA Therapeutics infringes the Patent Rights or misappropriates Know-How of any Third Party or the commencement of any action, suit or proceeding with respect thereto, enclosing a copy of the claim and all papers served.

(b) If a Party becomes aware that the Development or Manufacture of miRNA Compounds or miRNA Therapeutics or the Commercialization of miRNA Therapeutics in the Field, by a Commercializing Party, its Affiliates or Sublicensees, infringes or misappropriates, or is likely to or is alleged to infringe or misappropriate, the Patent Rights or Know-How of any Third Party, such Party will promptly notify intellectual property counsel to the other Parties, and such Commercializing Party will have the sole right and responsibility to take any action it deems appropriate with respect thereto; provided, however, that, to the extent that any action would involve the enforcement of another Party's Licensed IP or the Regulus IP (if the Commercializing Party is a Licensor), or the defense of an Invalidity Claim with respect to such

other Party's Licensed IP or the Regulus IP, the general concepts of Section 9.3 will apply to the enforcement of such other Party's Licensed IP or the Regulus IP or the defense of such Invalidity Claim (i.e., each Party has the right to enforce its own intellectual property, except that the relevant Commercializing Party will have the initial right, to the extent provided in Section 9.3(a), to enforce such Licensed IP or Regulus IP or defend such Invalidity Claim, and Regulus will have a step-in right, to the extent provided in Section 9.3(a), to enforce such Patent Right or defend such Invalidity Claim).

9.6 Additional Right. Notwithstanding any provision of Section 9, Isis will actively participate in the planning and conduct of any enforcement of Regulus IP or Isis IP and will take the lead of such enforcement to the extent that the scope or validity of any Licensed Patent Right Controlled by Isis [***].

10. CONFIDENTIAL INFORMATION

10.1 Permitted Disclosures. Each Party may make Permitted Disclosures of another Party's Confidential Information.

10.2 Scientific Publications. No Party will publish, present or otherwise disclose to the public the results of any Research Program or Development Project ("Research Results"), except as specifically approved by the Collaboration Working Group or as provided in this Section 10.2 below or in Section 10.3. The Collaboration Working Group will agree upon the form and timing of any publication or presentation or other disclosure (such as an abstract, manuscript or presentation) to the public of the Research Results subject to the Collaboration Working Group's approval. For clarification, this Section 10.2 and Section 10.3 will not apply with respect to the use and disclosure of another Party's Confidential Information as specifically provided for in the LLC Agreement or Section 10.1 of this Agreement or for disclosure of any Party's own information to comply with Law.

10.3 Disclosures Regarding Royalty-Bearing Products. In addition, each Commercializing Party may, without the Collaboration Working Group's approval, make disclosures pertaining solely to its Royalty-Bearing Products; provided, however, that, (i) Regulus will immediately notify (and provide as much advance notice as possible to) the other Parties of any event materially related to its Royalty-Bearing Products (including any regulatory approval) so that the Parties may analyze the need to or desirability of publicly disclosing or reporting such event and (ii) any press release or other similar public communication by any Party related to efficacy or safety data and/or results of a Royalty-Bearing Product will be submitted to the other Parties for review at least [***] Business Days (to the extent permitted by Law) in advance of such proposed public disclosure, the other Parties shall have the right to expeditiously review and recommend changes to such communication and the Party whose communication has been reviewed shall in good faith consider any changes that are timely recommended by the reviewing Parties. Notwithstanding the foregoing, in each case such right of review and recommendation shall only apply for the first time that specific information is to be disclosed, and shall not apply to the subsequent disclosure of information that (A) is substantially similar to a previously reviewed disclosure and (B) in the context of the subsequent disclosure, does not carry a substantially different qualitative message than that carried by the previously reviewed disclosure.

11. INDEMNIFICATION

11.1 Indemnification by Regulus. Regulus agrees to defend each Licensor, the Affiliates of each Licensor, and their respective agents, directors, officers and employees (the "Licensor Indemnitees"), at Regulus' cost and expense, and will indemnify and hold harmless the Licensor Indemnitees from and against any and all losses, costs, damages, fees or expenses ("Losses") relating to or in connection with a Third Party claim arising out of (a) any actual or alleged death, personal bodily injury or damage to real or tangible personal property claimed to result, directly or indirectly, from the manufacture, storage, possession, use or consumption of, treatment with or sale, any miRNA Compound or miRNA Therapeutic (other than as set forth in Section 11.2(a) or in the LLC Agreement), regardless of the form in which any such claim is made or whether actual negligence is found, (b) any actual or alleged infringement or unauthorized use or misappropriation of any Patent Right or other intellectual property right of a Third Party with respect to the activities of Regulus, its Affiliates or Sublicensees under this Agreement or the Services Agreement, (c) breach by Regulus of its representations, warranties or covenants made under this Agreement or the Services Agreement, or (d) any negligent act or omission or willful misconduct of Regulus, its Affiliates or Sublicensees or any of their employees, contractors or agents, in performing its obligations or exercising its rights under this Agreement or the Services Agreement; provided, however, that, with respect to each Licensor and its related Licensor Indemnitees, the foregoing indemnity will not apply to the extent that any such Losses (i) are attributable to the gross negligence or willful misconduct of such Licensor or its related Licensor Indemnitees, or (ii) are otherwise subject to an obligation by such Licensor to indemnify the Superset Indemnitees under Section 11.2(a)-(d).

11.2 Indemnification by Licensor(s). Each Licensor agrees to defend Regulus and its Affiliates, and their respective agents, directors, officers and employees (the "Regulus Indemnitees") and the other Licensor, and its related Licensor Indemnitees (the Regulus Indemnitees, such other Licensor and its related Licensor Indemnitees, collectively, the "Superset Indemnitees"), at such Licensor's cost and expense, and will indemnify and hold harmless the Superset Indemnitees from and against any and all Losses, relating to or in connection with a Third Party claim arising out of (a) any actual or alleged death, personal bodily injury or damage to real or tangible personal property claimed to result, directly or indirectly, from the manufacture, storage, possession, use or consumption of, treatment with or sale, any miRNA Compound or miRNA Therapeutic Developed, Manufactured and/or Commercialized by such Licensor, its Affiliates or Sublicensees pursuant to Section 5, regardless of the form in which any such claim is made or whether actual negligence is found,

(b) any actual or alleged infringement or unauthorized use or misappropriation of any Patent Right or other intellectual property right of a Third Party with respect to the activities of such Licensor, its Affiliates or Sublicensees under this Agreement or the Services Agreement, (c) any breach by such Licensor of its representations, warranties or covenants under this Agreement or the Services Agreement given to the other Party seeking indemnification hereunder, or (d) any negligent act or omission or willful misconduct of such Licensor or its Affiliates, or any of their employees, contractors or agents, in performing its obligations or exercising its rights under this Agreement or the Services Agreement; provided, however, that with respect to Regulus or the indemnified Licensor, and the relevant Superset Indemnitees, the foregoing indemnity will not apply to the extent that any such Losses (i) are attributable to the gross negligence or willful misconduct of such Party or its Superset Indemnitees, or (ii) are otherwise subject to an obligation by such Party to indemnify the Licensor Indemnitees under Section 11.1(a)-(d).

11.3 Notification of Claims; Conditions to Indemnification Obligations. A Party entitled to indemnification under this Section 11 will (a) promptly notify the indemnifying Party as soon as it becomes aware of a claim or action for which indemnification may be sought pursuant hereto, (b) cooperate with the indemnifying Party in the defense of such claim or suit, and (c) permit the indemnifying Party to control the defense of such claim or suit, including without limitation the right to select defense counsel; provided that if the Party entitled to indemnification fails to promptly notify the indemnifying Party pursuant to the foregoing clause (a), the indemnifying Party will only be relieved of its indemnification obligation to the extent prejudiced by such failure. In no event, however, may the indemnifying Party compromise or settle any claim or suit in a manner which admits fault or negligence on the part of the indemnified Party, or which imposes obligations on the indemnified Party, other than financial obligations that are covered by the indemnifying Party's indemnification obligation, without the prior written consent of the indemnified Party. The indemnifying Party will have no liability under this Section 11 with respect to claims or suits settled or compromised without its prior written consent and the indemnified Party may not, without the prior written consent of the indemnifying Party, compromise or settle any claim or suit in a manner which admits fault or negligence on the part of the indemnifying Party, or which imposes obligations on the indemnified Party.

11.4 Allocation. In the event a claim is based partially on an indemnified claim under this Agreement or the LLC Agreement and partially on a non-indemnified claim or based partially on a claim indemnified by one Party under this Agreement or the LLC Agreement and partially on a claim indemnified by another Party(ies) under this Agreement or the LLC Agreement, any payments in connection with such claims are to be apportioned between the Parties in accordance with the degree of cause attributable to each Party.

12. INSURANCE

12.1 Without limiting a Party's undertaking to defend, indemnify, and hold the other Parties harmless as set forth in Section 11, to the extent available on commercially reasonable terms each Party will obtain and maintain a commercial general liability policy, including coverage for commercial general liability claims and coverage for products liability claims, taking into account the stage of development of the miRNA Compound or miRNA Therapeutic to which such Party has rights under this Agreement, in amounts reasonably sufficient to protect against liability under Section 11. The foregoing coverage will continue during the term of this Agreement and for a period of 3 years thereafter. The Parties have the right to ascertain from time to time that such coverage exists, such right to be exercised in a reasonable manner.

13. WARRANTIES

13.1 Mutual Warranties. Each Party warrants that as of the Effective Date: (a) it is a corporation (with respect to each Licensor) or a limited liability company (with respect to Regulus) duly organized and in good standing under the laws of the jurisdiction of its incorporation or organization, and it has full power and authority and the legal right to own and operate its property and assets and to carry on its business as it is now being conducted and as it is contemplated to be conducted under this Agreement and the Services Agreement; (b) it has the full right, power and authority to enter into this Agreement and the Services Agreement and to grant the rights and licenses granted by it under this Agreement and the Services Agreement; (c)

there are no existing or, to its knowledge, threatened actions, suits or claims pending with respect to the subject matter hereof or its right to enter into and perform its obligations under this Agreement and the Services Agreement; (d) it has taken all necessary action on its part to authorize the execution and delivery of this Agreement and the Services Agreement and the performance of its obligations under this Agreement and the Services Agreement; (e) this Agreement and the Services Agreement have been duly executed and delivered on behalf of it, and each constitutes a legal, valid, binding obligation, enforceable against it in accordance with the terms hereof, subject to the general principles of equity and to bankruptcy, insolvency, moratorium and other similar laws affecting the enforcement of creditors' rights generally; (f) all necessary consents, approvals and authorizations of all regulatory and governmental authorities and other persons required to be obtained by it in connection with the execution and delivery of this Agreement and the Services Agreement and the performance of its obligations under this Agreement and the Services Agreement have been obtained; and (g) the execution and delivery of this Agreement and the Services Agreement and the performance of its obligations under this Agreement and the Services Agreement do not conflict with, or constitute a default under, any of its existing contractual obligations.

13.2 Additional Licensor Warranties.

(a) Each Licensor warrants to Regulus that, as of the Effective Date, except as set forth on Schedule 2.4(A) or in accordance with Section 2.4: (i) such Licensor has the right to grant to Regulus the rights granted to Regulus under such Licensor's Licensed IP hereunder; and (ii) no written claim has been made against such Licensor alleging that such Licensor's Licensed Patent Rights are invalid or unenforceable.

(b) Each Licensor further warrants to each other Party that such Licensor has prepared, or will prepare, as applicable, its respective In-License Summary, Out-License Summary and descriptions of Optional In-Licenses, in good faith and having used reasonable and diligent efforts to disclose, in summary form, all material issues relating to the scope of the license granted to Regulus and all material pass-through payment obligations. The Parties agree and acknowledge that a Licensor shall be deemed to be in breach of the warranty in this Section 13.2(b) if such Licensor knowingly omitted from, or knowingly misrepresented in, its In-License Summary, Out-License Summary or Optional In-License description any material issues relating to the scope of the license granted to Regulus or any material pass-through payment obligations. For the sake of clarity, the Parties agree and acknowledge, by way of example and not limitation, that a Licensor shall not be deemed to be in breach of the warranty in this Section 13.2(b) if its In-License Summary, Out-License

Summary or Optional In-License description is incorrect or misleading in light of facts, issues or technology changes which occur or become known after the date such In-License Summary, Out-License Summary or Optional In-License description is provided to the other Licensor.

(c) Each Licensor further warrants to each other Party that such Licensor has set forth on Schedule 2.2(A), in good faith and having used reasonable and diligent efforts to identify, all Patent Rights Controlled by such Licensor on the Effective Date that (1) are reasonably necessary or useful to the research, development and commercialization of miRNA Compounds or miRNA Therapeutics as contemplated by the current Operating Plan and (2) claim (a) miRNA Compounds or miRNA Therapeutics in general, (b) specific miRNA Compounds or miRNA Therapeutics, (c) chemistry or delivery of miRNA Compounds or

miRNA Therapeutics, (d) mechanism(s) of action by which a miRNA Antagonist directly prevents the production of the specific miRNA, or (e) methods of treating an Indication by modulating one or more miRNAs; except, in each case for manufacturing technology (including but not limited to analytical methods). In the event a Licensor is in breach of this warranty, the Parties will work in good faith to amend Schedule 2.2(A) such that the Patent Right that is the subject of the breach is including as a Licensed Patent Right under this Agreement.

13.3 Disclaimer. EXCEPT AS OTHERWISE EXPRESSLY SET FORTH IN THIS SECTION 13, NEITHER PARTY MAKES ANY REPRESENTATIONS OR EXTENDS ANY WARRANTIES OF ANY KIND, EITHER EXPRESS OR IMPLIED, INCLUDING, BUT NOT LIMITED TO, WARRANTIES OF MERCHANTABILITY, QUALITY, FITNESS FOR A PARTICULAR PURPOSE, NONINFRINGEMENT, OR VALIDITY OF PATENT CLAIMS, WHETHER ISSUED OR PENDING.

14. LIMITATION OF LIABILITY

14.1 UNLESS RESULTING FROM A PARTY'S WILLFUL MISCONDUCT OR FROM A PARTY'S WILLFUL BREACH OF SECTION 10, NO PARTY HERETO WILL BE LIABLE TO ANY OTHER PARTY OR ITS AFFILIATES FOR SPECIAL, INCIDENTAL, CONSEQUENTIAL, EXEMPLARY, PUNITIVE, MULTIPLE OR OTHER INDIRECT DAMAGES ARISING OUT OF THIS AGREEMENT OR THE EXERCISE OF ITS RIGHTS HEREUNDER, OR FOR LOSS OF PROFITS, LOSS OF DATA, LOSS OF REVENUE, OR LOSS OF USE DAMAGES ARISING FROM OR RELATING TO ANY BREACH OF THIS AGREEMENT WHETHER BASED UPON WARRANTY, CONTRACT, TORT, NEGLIGENCE, STRICT LIABILITY OR OTHERWISE, REGARDLESS OF ANY NOTICE OF SUCH DAMAGES. NOTHING IN THIS SECTION 14 IS INTENDED TO LIMIT OR RESTRICT THE INDEMNIFICATION RIGHTS OR OBLIGATIONS OF ANY PARTY UNDER THIS AGREEMENT.

15. TERMINATION

15.1 Term. This Agreement will become effective as of the Effective Date, and will remain in effect until the earlier of (a) the termination of this Agreement in accordance with Section 15.2, (b) the cessation of all Development of potential Royalty-Bearing Products prior to the first commercial sale of a Royalty-Bearing Product anywhere in the world, or (c) following the first commercial sale of a Royalty-Bearing Product anywhere in the world, the expiration of the Royalty Terms for Royalty-Bearing Products on a country-by-country and a Royalty-Bearing Product-by-Royalty-Bearing Product basis.

15.2 Termination for Breach.

(a) If Regulus breaches any material provision of this Agreement (including any representation or warranty), and fails to remedy such breach within sixty (60) days after written notice from the Licensors, acting jointly, then the Licensors, acting jointly, shall have the right, but not the obligation, to initiate the Buy-Out. In such event, the Licensors will determine which Licensor will be considered the "Initiating Member" (as defined in the LLC Agreement) for purposes of the Buy-Out.

(b) If an Opt-In Party breaches any material provision of this Agreement with respect to the relevant Development Project, and fails to remedy such breach within 60 days after written notice from Regulus, then Regulus will have the right, but not the obligation, to terminate such Opt-In Party's rights and licenses with respect to such Development Project and the breaching Opt-In Party will promptly return to the aggrieved Party(ies) all related tangible Know-How and Confidential Information of such aggrieved Party(ies).

(c) Except as provided in Section 15.2(b), if a Licensor breaches any material provision of this Agreement (including any representation or warranty), and fails to remedy such breach within sixty (60) days after written notice from any other Party, then (i) if such other Party is a Licensor, such Licensor may initiate the Buy-Out, (ii) if such other Party is Regulus, Regulus may not terminate this Agreement, and (iii) whether such other Party is Regulus or a Licensor, such other Party has the right to seek other legal or equitable remedies with respect to such breach.

(d) Notwithstanding Section 15.2(b) or 15.2(c)(i), if a non-breaching Party gives the allegedly-breaching Party a notice pursuant to this Section 15.2 of a material breach by such alleged-breaching Party, and, as of the end of the cure period specified above, two or more Parties are engaged in an arbitration pursuant to Section 16.7 in which such allegedly-breaching Party is in good faith disputing the occurrence of the alleged material breach or the sufficiency of the cure with respect thereto, then the non-breaching Parties may not (i) initiate the Buy-Out in the case of Section 15.2(c)(i) or (ii) terminate the applicable license in the case of Section 15.2(b), as a result of such breach unless and until the arbitrator issues an award that such breach occurred (if that issue was in dispute) and/or that the cure was insufficient (if that issue was in dispute), following which the breaching Party shall have 60 days to cure such breach (or unless and until such allegedly-breaching Party is no longer disputing such issues in good faith, if earlier).

15.3 Effects of Termination.

(a) Any of Regulus' direct Sublicensees may, by providing written notice to the Licensors within the 60 day period immediately following termination of this Agreement with respect to Regulus, in whole or in part, obtain from each Licensor a direct license from such Licensor, on the same terms as the sublicense granted by Regulus to such Sublicensee with respect to such Licensor's Licensed IP, except to the extent that any such terms are inconsistent with the rights granted by such Licensor to Regulus under this Agreement, in which case any terms in this Agreement which are more protective of such Licensor's rights will instead apply. If a Sublicensee provides such notice, the Licensors will negotiate in good faith with such Sublicensee a written

agreement to reflect such terms; provided, that, (i) such Sublicensee is, at the time of termination of this Agreement, in compliance with its sublicense agreement with Regulus, and (ii) such Sublicensee cures any payment default of Regulus hereunder, with respect to any royalties or Sublicense Income Payments due to the Licensors with respect to the sublicense granted by Regulus to such Sublicensee hereunder.

15.4 Survival. Upon termination of this Agreement, the following sections of this Agreement will survive: Sections 2.1, 2.3, 8, 9.1(a), 9.3, 10, 11, 12, 14, 15.2, 15.3, 15.4 and 16, and, to the extent related to Section 9.3, Sections 9.4, 9.5 and 9.6. In addition, if this Agreement is terminated pursuant to a Buy-Out, then, with respect to each Development Project for which

an Opt-In Party has obtained a license under Section 5.6 before the initiation of the Buy-Out, the following sections of this Agreement will survive with respect to such Development Project: Sections 5.4 or 5.5 (as applicable), and Section 5.6, unless and until terminated pursuant to Section 15.2(b), subject to Section 15.2(d) (with Regulus' role in such termination sections being played by the other Member following the dissolution of Regulus). Upon any expiration of this Agreement with respect to a Royalty-Bearing Product under Section 15.1(c), the license granted under any Know-How that is part of the Licensed IP and/or Regulus IP to a Party with respect to such Royalty-Bearing Product will become a fully paid-up and perpetual license to Manufacture, import, use, sell or otherwise Commercialize such Royalty-Bearing Product.

16. MISCELLANEOUS

16.1 Assignment. Neither this Agreement nor any of the rights or obligations hereunder may be assigned by a Party without the prior written consent of the other Parties, except (a) Regulus shall assign both this Agreement and the Services Agreement to a Person that acquires, by merger, sale of assets or otherwise, all or substantially all of the business of Regulus to which the subject matter of this Agreement relates, (b) each Licensor shall assign both this Agreement and the Services Agreement along with the Transfer (as defined in the LLC Agreement) of such Licensor's Membership Interest (as defined in the LLC Agreement), and (c) each Party may assign or transfer its rights to receive royalties, milestones and Sublicense Income Payments under this Agreement (but no liabilities) to a Third Party in connection with [***]. Notwithstanding the foregoing, each Party will have the right to assign this Agreement, in whole or in part, to an Affiliate of such Party without the prior written consent of the other Parties; provided that such assignee assumes in writing all obligations of the assigning Party hereunder. Any assignment not in accordance with the foregoing will be void. This Agreement will be binding upon, and will inure to the benefit of, all permitted successors and assigns. Each Party agrees that, notwithstanding any provisions of this Agreement to the contrary, (y) in the event that this Agreement is assigned by a Party in connection with the sale or transfer of all or substantially all of the business of such Party to which the subject matter of this Agreement relates, such assignment will not provide the non-assigning Parties with rights or access to the Know-How or Patent Rights of the acquirer of such assigning Party, and (z) in the event of a Change of Control of a Party, the other Parties shall not acquire rights or access to the Know-How or Patent Rights of the acquirer of such acquired Party.

16.2 Force Majeure. No Party will be held liable or responsible to any other Party nor be deemed to have defaulted under or breached this Agreement for failure or reasonable delay in fulfilling or performing any term of this Agreement (except any obligation to pay upfront payments, milestones, royalties or Sublicense Income Payments) when such failure or delay is caused by or results from causes beyond the reasonable control of the affected Party, which may include, without limitation, embargoes, acts of war (whether war be declared or not), insurrections, riots, civil commotions, acts of terrorism, strikes, lockouts or other labor disturbances, or acts of God. The affected Party will notify the other Parties of such force majeure circumstances as soon as reasonably practical and will make every reasonable effort to mitigate the effects of such force majeure circumstances.

16.3 Section 365(n) of the Bankruptcy Code. All rights and licenses granted under or pursuant to any section of this Agreement are and will otherwise be deemed to be for purposes of Section 365(n) of the United States Bankruptcy Code (Title 11, U.S. Code), as amended (the

"Bankruptcy Code"), licenses of rights to "intellectual property" as defined in Section 101(35A) of the Bankruptcy Code. The Parties will retain and may fully exercise all of their respective rights and elections under the Bankruptcy Code. The Parties agree that each Party, as licensee of such rights under this Agreement, will retain and may fully exercise all of its rights and elections under the 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, will be promptly delivered to it upon the non subject Party's written request thereof. Any agreements supplemental hereto will be deemed to be "agreements supplementary to" this Agreement for purposes of Section 365(n) of the Bankruptcy Code.

16.4 Notices. Any notice required or provided for by the terms of this Agreement or the Services Agreement shall be delivered in accordance with Section 13.9 of the LLC Agreement.

16.5 Relationship of the Parties. It is expressly agreed that the Parties will be independent contractors hereunder and that the relationship among the Parties under this Agreement will not constitute a partnership, joint venture or agency. No Party will have the authority under this Agreement to make any statements, representations or commitments of any kind, or to take any action, which will be binding on any other Party, without the prior consent of such other Party. This Agreement will be understood to be a joint research agreement to discover miRNA Compounds and associated uses and to develop Royalty-Bearing Products in accordance with 35 U.S.C. § 103(c)(3).

16.6 Governing Law. This Agreement will be governed and interpreted in accordance with the substantive laws of the State of Delaware, excluding its conflicts of law rules; provided that matters of intellectual property law concerning the existence, validity, ownership, infringement or enforcement of intellectual property will be determined in accordance with the national intellectual property laws relevant to the intellectual property in question.

16.7 Dispute Resolution. Except (a) for matters of intellectual property law concerning the existence, validity, ownership, infringement or enforcement of intellectual property, which matters will not be subject to the terms of this Section 16.7, and (b) as other dispute resolution procedures are expressly provided herein, in the event of any dispute, controversy or claim arising out of or relating to this Agreement, the Parties will try to settle such

dispute, controversy or claim amicably between themselves, including referring such dispute, controversy or claim to the Executive Officers of the Parties. If the Parties are unable to so settle such dispute, controversy or claim within a period of 60 days from the date of such referral, then upon notice by any Party to the other Parties, any such dispute, controversy or claim arising out of or relating to any provision of this Agreement, or the interpretation, enforceability, performance, breach, termination or validity hereof, will be finally resolved under the Commercial Arbitration Rules of the American Arbitration Association by a single arbitrator appointed in accordance with such rules. The Parties will be entitled to the same discovery as permitted under the U.S. Federal Rules of Civil Procedure; provided that the arbitrator will be entitled in its discretion to grant a

request from a Party for expanded or more limited discovery. The place of arbitration will be New York, New York. The language of the arbitration will be English. At any time, a Party may seek or obtain preliminary, interim or conservatory measures from the arbitrators or from a court.

16.8 Severability. In the event any one or more of the provisions contained in this Agreement should be held invalid, illegal or unenforceable in any respect, the validity, legality and enforceability of the remaining provisions contained herein will not in any way be affected or impaired thereby, unless the absence of the invalidated provision(s) adversely affect the substantive rights of the Parties. The Parties will in such an instance use their best efforts to replace the invalid, illegal or unenforceable provision(s) with valid, legal and enforceable provision(s) which, insofar as practical, maintains the balance of the rights and obligations of the Parties under this Agreement.

16.9 Entire Agreement. This Agreement (including all schedules and exhibits hereto), the LLC Agreement and the Services Agreement constitute the entire agreement among the Parties with respect to the subject matter herein and supersedes all previous agreements (other than those listed in Schedule A (the "Previous Agreements")), whether written or oral, with respect to such subject matter. Unless otherwise expressly indicated, references herein to sections, subsections, paragraphs and the like are to such items within this Agreement. The Parties acknowledge that this Agreement is being executed and delivered simultaneously with the execution and delivery by the Parties and/or their Affiliates of the LLC Agreement and the Services Agreement. For purposes of clarity, nothing in this Agreement (other than Section 5.6(d)) will be deemed to modify or amend any provision of any of the Previous Agreements.

16.10 Amendment and Waiver. This Agreement may not be amended, nor any rights hereunder waived, except in a writing signed by the properly authorized representatives of each Party.

16.11 No Implied Waivers. The waiver by a Party of a breach or default of any provision of this Agreement by any other Party will not be construed as a waiver of any succeeding breach of the same or any other provision, nor will any delay or omission on the part of a Party to exercise or avail itself of any right, power or privilege that it has or may have hereunder operate as a waiver of any right, power or privilege by such Party.

16.12 Export Compliance. The Parties acknowledge that the exportation from the United States of materials, products and related technical data (and the re-export from elsewhere of United States origin items) may be subject to compliance with United States export Laws, including, without limitation, the United States Bureau of Export Administration's Export Administration Regulations, the Federal Food, Drug and Cosmetic Act and regulations of the FDA issued thereunder, and the United States Department of State's International Traffic and Arms Regulations which restrict export, re-export, and release of materials, products and their related technical data, and the direct products of such technical data. The Parties agree to comply with all exports Laws and to commit no act that, directly or indirectly, would violate any United States Law, or any other international treaty or agreement, relating to the export, re-export, or release of any materials, products or their related technical data to which the United States adheres or with which the United States complies.

16.13 Counterparts. This Agreement may be executed in any number of counterparts, each of which will be deemed an original, and all of which together will constitute one and the same instrument.

[Remainder of Page Intentionally Left Blank]

IN WITNESS WHEREOF, the Parties hereby execute this License Agreement as of the date first written above.

ALNYLAM PHARMACEUTICALS, INC.

By: /s/ Barry Greene
Name: Barry Greene
Title: Chief Operating Officer

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall
Name: B. Lynne Parshall
Title: EVP & CFO

REGULUS THERAPEUTICS LLC

By: /s/ Philip T. Chase
Name: Philip T. Chase
Title: Authorized Person

Exhibit 1

Defined Terms

1.1 "Additional Rights" will have the meaning set forth in Section 2.4(d).

1.2 "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. For purposes of this Agreement (a) Regulus will not be deemed to be an Affiliate of any Licensor and (b) a Licensor and its Affiliates will not be considered an Affiliate of Regulus.

1.3 "Agreement" will have the meaning set forth in the Preamble.

1.4 "Alnylam" will have the meaning set forth in the Preamble.

1.5 "Alnylam Field" will have the meaning set forth in Section 2.3(a).

1.6 "Approved Mimic" will have the meaning set forth in Section 1.61.

1.7 "Approved Precursor Antagonist" will have the meaning set forth in Section 1.61.

1.8 "Bankruptcy Code" will have the meaning set forth in Section 16.3.

1.9 "Business Day" means a day on which the banks in New York, New York are open for business.

1.10 "Buy-Out" will have the meaning set forth in the LLC Agreement.

1.11 "Change of Control" means, with respect to a Licensor, the earlier of (x) the public announcement of or (y) the closing of: (a) a merger, reorganization or consolidation involving such Licensor in which its shareholders immediately prior to such transaction would hold less than 50% of the securities or other ownership or voting interests representing the equity of the surviving entity immediately after such merger, reorganization or consolidation, or (b) a sale to a Third Party of all or substantially all of such Licensor's assets or business relating to this Agreement.

1.12 "Collaboration Working Group" means a group having equal representation from Isis, Alnylam and Regulus which will meet on a regular basis to share information about Know-How and Patent Rights relevant to the joint venture and to conduct the business necessary under this Agreement. Each Party will designate two Collaboration Working Group members within 30 days of the Effective Date. At its first meeting, which will be within 60 days of Effective Date, the Collaboration Working Group will create and adopt a Charter that will include meeting frequency and other relevant items.

1.13 "Combination Product" will have the meaning set forth in Section 1.67.

1.14 "Commercialization" or "Commercialize" means any and all activities directed to marketing, promoting, detailing, distributing, importing, having imported, exporting, having exported, selling or offering to sell a miRNA Therapeutic following receipt of Regulatory Approval for such miRNA Therapeutic.

1.15 "Commercializing Party" means the Party Manufacturing, Developing or Commercializing a miRNA Therapeutic under this Agreement pursuant to licenses granted under Sections 2.2 or 5.6.

1.16 "Commercially Reasonable Efforts" means, reasonable, diligent, good faith efforts to accomplish an objective as such Party would normally use to accomplish a similar objective, under similar circumstances exercising reasonable business judgment. With respect to the Development, Manufacturing or Commercialization of a miRNA Therapeutic, such efforts will be substantially equivalent to the efforts used by such Party with respect to other products at similar stages in their development or product life and of similar market potential, taking into account the profile of the miRNA Therapeutic, the competitive landscape and other relevant factors commonly considered in similar circumstances. For all Parties the level of effort will be at least that of a typical medium sized biopharmaceutical company.

1.17 "Completion" means, with respect to any clinical trial, the locking of the database pertaining to such clinical trial.

1.18 "Confidential Information" will have the meaning set forth in the LLC Agreement.

1.19 "Control" or "Controlled" means the possession of the right (whether by ownership, license or otherwise) to assign, or grant a license, sublicense or other right as provided for herein without violating the terms of any agreement or other arrangement with any Third Party; provided, however, that neither Licensor will be deemed to Control Regulus IP and no Party other than the relevant Licensor shall be deemed to Control such Licensor's Licensed IP.

1.20 "Controlling Party" will have the meaning set forth in Section 2.4(d).

1.21 "Cover", "Covered" or "Covering" means, (a) with respect to a patent, that, in the absence of a license granted to a Person under a Valid Claim included in such patent, the practice by such Person of an invention claimed in such patent would infringe such Valid Claim, or (b) with respect to a patent application, that, in the absence of a license granted to a Person under a Valid Claim included in such patent application, the practice by such Person of an invention claimed in such patent application would infringe such Valid Claim if it were to issue as a patent.

1.22 "Develop" or "Development" means, with respect to a miRNA Compound or miRNA Therapeutic, any discovery, characterization, preclinical or clinical activity with respect to such miRNA Compound or miRNA Therapeutic, including human clinical trials conducted after Regulatory Approval of such miRNA Therapeutic to seek Regulatory Approval for additional Indications for such miRNA Therapeutic.

1.23 "Development Compound" means, with respect to a Development Project, any miRNA Compound directed to the miRNA(s) which is the focus of such Development Project.

1.24 "Development Project" will have the meaning set forth in Section 4.4.

1.25 "Development Therapeutic" means, with respect to a Development Project, any miRNA Therapeutic containing an miRNA Compound(s) directed to the miRNA(s) which is the focus of such Development Project.

1.26 "Disclosing Party" will have the meaning set forth in the LLC Agreement.

1.27 "Effective Date" will have the meaning set forth in the Preamble.

1.28 "Exclusivity Period" means, with respect to a Royalty-Bearing Product in a country, that period of time beginning with the first commercial sale of such Royalty-Bearing Product in such country and ending on the later to expire of (a) the time during which the applicable Regulatory Authority in such country is not permitted to grant Regulatory Approval for a generic equivalent of such Royalty-Bearing Product and (b):

- with respect to a Royalty-Bearing Product being Commercialized by Regulus, the last Valid Claim of the Patent Rights licensed to Regulus pursuant to this Agreement or the Regulus Patent Rights Covering (i) the Manufacture of such Royalty-Bearing Product in such country or (ii) the use, sale or other Commercialization of such Royalty-Bearing Product in such country; or

- with respect to a Royalty-Bearing Product being Commercialized by a Licensor, the last Valid Claim of the Patent Rights licensed to such Licensor pursuant to this Agreement Covering (i) the Manufacture of such Royalty-Bearing Product in such country or (ii) the use, sale or other Commercialization of such Royalty-Bearing Product in such country.

1.29 "Executive Officer" means, with respect to a Party, the Chief Executive Officer of such Party (or the officer or employee of such Party then serving in a substantially equivalent capacity) or his/her designee of substantially equivalent rank.

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

1.31 "Field" means treatment and/or prophylaxis of any or all Indications.

1.32 "GAAP" means United States Generally Accepted Accounting Principles, consistently applied.

1.33 "GLP" means the then-current good laboratory practice standards promulgated or endorsed by the FDA as defined in 21 C.F.R. Part 58, and comparable foreign regulatory standards.

1.34 "[***]" means a [***].

1.35 "Hatch-Waxman Act" will have the meaning set forth in Section 9.3(a)(i)(A).

1.36 "High Terms" will have the meaning set forth in Section 5.4.

1.37 "In-License Agreement" will have the meaning set forth in Section 2.4(b).

1.38 "In-License Summary" will have the meaning set forth in Section 2.4(b).

1.39 "IND" means an Investigational New Drug Application or similar foreign application or submission for approval to conduct human clinical investigations.

1.40 "Indication" means any disease or condition, or sign or symptom of a disease or condition, or symptom associated with a disease or syndrome.

1.41 "Initial Opt-In Election Period" will have the meaning set forth in Section 5.3.

1.42 "Intellectual Property" will have the meaning set forth in the LLC Agreement.

1.43 "Invalidity Claim" will have the meaning set forth in Section 9.4.

1.44 "Isis" will have the meaning set forth in the Preamble.

1.45 "Isis Field" will have the meaning set forth in Section 2.3(b).

1.46 "Know-How" means any information, inventions, trade secrets or technology (excluding Patent Rights), whether or not proprietary or patentable and whether stored or transmitted in oral, documentary, electronic or other form. Know-How includes ideas, concepts, formulas, methods, procedures, designs, compositions, plans, documents, data, discoveries, developments, techniques, protocols, specifications, works of authorship, biological materials, and any information relating to research and development plans, experiments, results, compounds, therapeutic leads, candidates and products, clinical and preclinical data, clinical trial results, and Manufacturing information and plans.

1.47 "Law" means any law, statute, rule, regulation, ordinance or other pronouncement having the effect of law of any federal, national, multinational, state, provincial, county, city or other political subdivision, domestic or foreign.

1.48 "License Agreement" will have the meaning set forth in the Preamble.

1.49 "Licensed IP" means, with respect to a Licensor, such Licensor's Licensed Know-How and Licensed Patent Rights.

1.50 "Licensed Know-How" means, with respect to a Licensor, all Know-How Controlled by such Licensor on the Effective Date or during the term of this Agreement (except as otherwise expressly provided herein) that relates to (a) miRNA Compounds or miRNA Therapeutics in general, (b) specific miRNA Compounds or miRNA Therapeutics, (c) chemistry or delivery of miRNA Compounds or miRNA Therapeutics, (d) mechanism(s) of action by which a miRNA Antagonist directly prevents the production of a specific miRNA, or (e)

methods of treating an Indication by modulating one or more miRNAs; provided, however, that in each case, (i) for any such Know-How that include financial or other obligations to a Third Party, the provisions of Section 2.4 will govern whether such Know-How will be included as Licensed Know-How and (ii) Licensed Know How does not include manufacturing technology (including but not limited to analytical methods).

1.51 "Licensed Patent Rights" means, with respect to a Licensor, (A) all Patent Rights Controlled by such Licensor on the Effective Date and listed on **SCHEDULE 2.2(A)**, and (B) all Patent Rights Controlled by such Licensor during the term of this Agreement (except as otherwise expressly provided herein) that claim (a) miRNA Compounds or miRNA Therapeutics in general, (b) specific miRNA Compounds or miRNA Therapeutics, (c) chemistry or delivery of miRNA Compounds or miRNA Therapeutics, (d) mechanism(s) of action by which a miRNA Antagonist directly prevents the production of the specific miRNA, or (e) methods of treating an Indication by modulating one or more miRNAs; provided, however, that in each case, (i) for any such Patent Rights that include financial or other obligations to a Third Party, the provisions of Section 2.4 will govern whether such Patent Right will be included as a Licensed Patent Right and (ii) Licensed Patent Rights do not include manufacturing technology (including but not limited to analytical methods).

1.52 "Licensor" will have the meaning set forth in the Preamble.

1.53 "Licensor Indemnitees" will have the meaning set forth in Section 11.1.

1.54 "LLC Agreement" means the Limited Liability Company Agreement of Regulus among the Parties, dated as of the Effective Date, as the same may be amended from time to time after the Effective Date.

1.55 "Losses" will have the meaning set forth in Section 11.1.

1.56 "Low Terms" will have the meaning set forth in Section 5.5.

1.57 "Major Country" means France, Germany, Italy, Spain and the United Kingdom.

1.58 "Manufacture" or "Manufacturing" means any activity involved in or relating to the manufacturing, quality control testing (including in-process, release and stability testing), releasing or packaging, for pre-clinical, clinical or commercial purposes, of a miRNA Compound or a miRNA Therapeutic.

1.59 "miRNA" means a structurally defined functional RNA molecule usually between 21 and 25 nucleotides in length, which is derived from genetically-encoded non-coding RNA which is predicted to be processed into a hairpin RNA structure that is a substrate for the double-stranded RNA-specific ribonuclease Drosha and subsequently is predicted to serve as a substrate for the enzyme Dicer, a member of the RNase III enzyme family; including, without limitation, those miRNAs exemplified in miRBase (http://microrna.sanger.ac.uk/). To the extent that [***] for purposes of this Agreement; provided, however, that nothing contained herein shall require any Party hereto to [***].

1.60 "miRNA Antagonist" means a single-stranded oligonucleotide (or a single stranded analog thereof) that is designed to interfere with or inhibit a particular miRNA. For purposes of clarity, the definition of "miRNA Antagonist" is not intended to include oligonucleotides that function predominantly through the RNAi mechanism of action or the RNase H mechanism of action.

1.61 "miRNA Compound" means a compound consisting of (a) a miRNA Antagonist, (b) to the extent listed in Schedule 1.61 or otherwise agreed upon by Regulus and the relevant Licensor(s) pursuant to Section 2.2(b), a miRNA Precursor Antagonist (an "Approved Precursor Antagonist"), or (c) to the extent agreed upon by Regulus and the relevant Licensor(s) pursuant to Section 2.2(b), a miRNA Mimic (an "Approved Mimic").

1.62 "miRNA Mimic" means a double-stranded or single-stranded oligonucleotide or analog thereof with a substantially similar base composition as a particular miRNA and which is designed to mimic the activity of such miRNA.

1.63 "miRNA Precursor" means a transcript that originates from a genomic DNA and that contains, but not necessarily exclusively, a non-coding, structured RNA comprising one or more mature miRNA sequences, including, without limitation, (a) polycistronic transcripts comprising more than one miRNA sequence, (b) miRNA clusters comprising more than one miRNA sequence, (c) pri-miRNAs, and/or (d) pre-miRNAs.

1.64 "miRNA Precursor Antagonist" means a single-stranded oligonucleotide (or a single stranded analog thereof) that is designed to bind to a miRNA Precursor to prevent the production of one or more miRNAs. For purposes of clarity, the definition of "miRNA Precursor Antagonist" is not intended to include oligonucleotides that function predominantly through the RNAi mechanism of action or the RNase H mechanism of action.

1.65 "miRNA Therapeutic" means a therapeutic product having one or more miRNA Compounds as an active ingredient(s).

1.66 "NDA" means a New Drug Application or similar application or submission for approval to market and sell a new pharmaceutical product filed with or submitted to a Regulatory Authority.

1.67 "Net Sales" means, with respect to a Royalty-Bearing Product, the gross invoice price of all units of such Royalty-Bearing Products sold by the relevant Commercializing Party, its Affiliates and/or their direct Sublicensees to any Third Party, less the following items: (a) trade discounts, credits or allowances, (b) credits or allowances additionally granted upon returns, rejections or recalls, (c) freight, shipping and insurance charges, (d) taxes, duties or other governmental tariffs (other than income taxes), (e) government-mandated rebates, and (f) a reasonable reserve for bad debts. "Net Sales" under the following circumstances will mean the fair market value of such Royalty-Bearing Product: (i) Royalty-Bearing Products which are used by such Commercializing Party, its Affiliates or direct Sublicensees for any commercial purpose without charge or provision of invoice, (ii) Royalty-Bearing Products which are sold or disposed of in whole or in part for non cash consideration, or (iii) Royalty-Bearing Products which are provided to a Third Party by such Commercializing Party, its Affiliates or direct Sublicensees

without charge or provision of invoice and used by such Third Party except in the cases of Royalty-Bearing Products used to conduct clinical trials, reasonable amounts of Royalty-Bearing Products used as marketing samples and Royalty-Bearing Product provided without charge for compassionate or similar uses.

Net Sales will not include any transfer between or among a Party and any of its Affiliates or direct Sublicensees for resale.

In the event a Royalty-Bearing Product is sold as part of a Combination Product (as defined below), the Net Sales from the Combination Product, for the purposes of determining royalty payments, will be determined by multiplying the Net Sales (as determined without reference to this paragraph) of the Combination Product, by the fraction, A/A+B, where A is the average sale price of the Royalty-Bearing Product when sold separately in finished form and B is the average sale price of the other therapeutically active pharmaceutical compound(s) included in the Combination Product when sold separately in finished form, each during the applicable royalty period or, if sales of all compounds did not occur in such period, then in the most recent royalty reporting period in which sales of all occurred. In the event that such average sale price cannot be determined for both the Royalty-Bearing Product and all other therapeutically active pharmaceutical compounds included in the Combination Product, Net Sales for the purposes of determining royalty payments will be calculated as above, but the average sales price in the above equation will be replaced by a good faith estimate of the fair market value of the compound(s) for which no such price exists. As used above, the term "Combination Product" means any pharmaceutical product which consists of a Royalty-Bearing Product and other therapeutically active pharmaceutical compound(s).

1.68 "Non-Controlling Party" will have the meaning set forth in Section 2.4(d).

1.69 "[***]" means [***].

1.70 "[***]" means the [***].

1.71 "Operating Plan" has the meaning ascribed to it in the LLC Agreement.

1.72 "Opt-In Election" will have the meaning set forth in Section 5.3.

1.73 "Opt-In Party" will have the meaning set forth in Section 5.3(a) and 5.3(c).

1.74 "Opt-In Product" means any miRNA Therapeutic that is Developed, Manufactured or Commercialized pursuant to a Development Project for which one and only one Licensor has exercised an Opt-In Election and which the relevant Opt-In Party subsequently licensed.

1.75 "Optional In-License" will have the meaning set forth in Section 2.4(c).

1.76 "Out-License Agreement" will have the meaning set forth in Section 2.4(a).

1.77 "Out-License Summary" will have the meaning set forth in Section 2.4(a).

1.78 "Paragraph IV Certification" will have the meaning set forth in Section 9.3(a)(i)(A).

1.79 "Party" means Alnylam, Isis and/or Regulus; "Parties" means Alnylam, Isis and Regulus, or any combination thereof.

1.80 "Patent Rights" means (a) patent applications (including provisional applications and for certificates of invention); (b) any patents issuing from such patent applications (including certificates of invention); (c) all patents and patent applications based on, corresponding to, or claiming the priority

date(s) of any of the foregoing; and (d) any substitutions, extensions (including supplemental protection certificates), registrations, confirmations, reissues, divisionals, continuations, continuations-in-part, re-examinations, renewals and foreign counterparts thereof.

1.81 "Payee Party" will have the meaning set forth in Section 8.1.

1.82 "Paying Party" will have the meaning set forth in Section 8.1.

1.83 "Permitted Disclosures". The following are Permitted Disclosures:

(a) To the extent that a Recipient has been granted the right to sublicense under the terms of this Agreement, such Party will have the right to provide a Disclosing Party's Confidential Information to the employees, consultants and advisors of such Recipient's Affiliate and Third Party sublicensees and potential sublicensees who have a need to know the Confidential Information for purposes of exercising such sublicense and are bound by an obligation to maintain in confidence the Confidential Information of the Disclosing Party; provided, that such Persons are bound to maintain the confidentiality of such information to the same extent as if they were parties hereto.

(b) Each Recipient will have the right to provide a Disclosing Party's Confidential Information:

(i) to governmental or other regulatory agencies in order to seek or obtain patents, to seek or obtain approval to conduct clinical trials, or to gain Regulatory Approval, as contemplated by this Agreement; provided that such disclosure may be made only to the extent reasonably necessary to seek or obtain such patents or approvals; and

(ii) as necessary, if embodied in products, to develop and commercialize such products as contemplated by this Agreement.

1.84 "Permitted License" means a license granted by a Licensor to a Third Party to enable such Third Party to broadly manufacture or formulate oligonucleotides, where such Third Party is primarily engaged in [***]; provided, however, that any such license will not grant rights to research, manufacture or formulate miRNA Compounds or miRNA Therapeutics for which the other Licensor has obtained or later obtains a license pursuant to Section 5 or pursuant to the Buy-Out process in the LLC Agreement.

1.85 "Person" means any corporation, limited or general partnership, limited liability company, joint venture, trust, unincorporated association, governmental body, authority, bureau or agency, any other entity or body, or an individual.

1.86 "Phase IIa Clinical Trial" means, with respect to a Royalty-Bearing Product, any human clinical trial conducted in patients with a particular Indication for the purpose of studying the pharmacokinetic or pharmacodynamic properties and preliminary assessment of safety and efficacy of such Royalty-Bearing Product over a measured dose response, as described in 21 C.F.R. §312.21(b) or its foreign counterpart.

1.87 "Phase III Clinical Trial" means, with respect to a Royalty-Bearing Product, a controlled pivotal clinical study of such Royalty-Bearing Product that is prospectively designed to demonstrate statistically whether such Royalty-Bearing Product is safe and effective to treat a particular Indication in a manner sufficient to obtain Regulatory Approval to market such Royalty-Bearing Product, as described in 21 CFR 312.21(c) or its foreign counterpart.

1.88 "Previous Agreements" will have the meaning set forth in Section 16.9.

1.89 "Program/Project List" will have the meaning set forth in Section 4.4.

1.90 "Recipient" will have the meaning set forth in the LLC Agreement.

1.91 "Regulatory Approval" means the act of a Regulatory Authority necessary for the marketing and sale (including, if required for marketing and sales, pricing) of such product in a country or regulatory jurisdiction, including, without limitation, the approval of an NDA by the FDA.

1.92 "Regulatory Authority" means any applicable government regulatory authority involved in granting approvals for the marketing and/or pricing of a product in a country or regulatory jurisdiction including, without limitation, the FDA.

1.93 "Regulus" will have the meaning set forth in the Preamble.

1.94 "Regulus Indemnitees" will have the meaning set forth in Section 11.2.

1.95 "Regulus IP" means all Regulus Know-How and Regulus Patent Rights.

1.96 "Regulus Know-How" means all Know-How conceived and/or developed by or on behalf of Regulus (including by employees of a Licensor or its Affiliates in performance of the Services Agreement), or over which Regulus otherwise acquires Control, including but not limited to any Know-How assigned to Regulus by a Licensor under Section 9.1, but specifically excluding Licensed IP.

1.97 "Regulus Patent Rights" means any Patent Right claiming an invention conceived and/or developed by or on behalf of Regulus (including by employees of a Licensor or its Affiliates in performance of the Services Agreement), or over which Regulus otherwise acquires Control, including but not limited to any Patent Right assigned to Regulus by a Licensor under Sections 2.1 or 9.1, but specifically excluding Licensed IP.

1.98 "Research" means pre-clinical research including gene function, gene expression and target validation research, which may include small pilot toxicology studies but excludes the pharmacokinetic and toxicology studies required to meet the regulations for filing an IND, clinical development and commercialization.

1.99 "Research Program" will have the meaning set forth in Section 4.4.

1.100 "Royalty-Bearing Product" means

(a) a miRNA Therapeutic being Developed, Manufactured or Commercialized by Regulus that, on a country-by-country basis, is, or Regulus reasonably believes will be, at the time of first commercial sale of such miRNA Therapeutic, Covered in such country by a Valid Claim of a Patent Right or covered by Know-How of (i) a Licensed Patent Right licensed to it hereunder, or (ii) any Regulus IP (except any Regulus IP solely in-licensed or acquired by Regulus from a Third Party); or

(b) an Opt-In Product that, on a country-by-country basis, is, or the relevant Opt-In Party reasonably believes will be, at the time of first commercial sale of such Opt-In Product, Covered in such country by a Valid Claim of a Patent Right or covered by Know-How, which Patent Right or Know-How is licensed to the applicable Opt-In Party hereunder.

1.101 "Royalty Term" means, with respect to each Royalty-Bearing Product in a country, the period commencing upon first commercial sale of such Royalty-Bearing Product in such country and ending upon the later of (a) the expiration of the Exclusivity Period, or (b) 10 years following first commercial sale of such Royalty-Bearing Product.

1.102 "Second Opt-In Election Period" will have the meaning set forth in Section 5.3(c)(i).

1.103 "Services Agreement" means that certain Services Agreement by and between Regulus, Alnylam and Isis dated the Effective Date, as the same may be amended from time to time after the Effective Date.

1.104 "Sublicense Income" means all amounts received by the Opt-In Party or its Affiliates with respect to any sublicense granted to a Third Party by the Opt-In Party or its Affiliates of the Regulus IP or Licensed IP licensed to the Opt-In Party under Section 5.6(a), including, without limitation, upfront payments and milestones, but excluding:

(a) amounts received by the Opt-In Party or its Affiliates as payments for actual direct costs for performing future Development, Manufacturing or Commercialization activities undertaken by the Opt-In Party or its Affiliates for, or in collaboration with, such Sublicensee or its Affiliates with respect to the relevant Opt-In Products;

(b) amounts received by the Opt-In Party and/or its Affiliates from such Sublicensee or its Affiliates as the purchase price for the Opt-In Party's or any of its Affiliates'

debt or equity securities, *except* that amounts which exceed the fair market value of such debt or equity securities will be considered Sublicense Income;

(c) royalties paid by such Sublicensee or its Affiliates with respect to Net Sales of Royalty-Bearing Products; and

(d) amounts paid by such Sublicensee or its Affiliates to the Opt-In Party or its Affiliates to purchase Royalty-Bearing Products; *except* that any amount greater than the actual cost of goods (with no profit added) of such Royalty-Bearing Products, determined in accordance with GAAP, will be considered Sublicense Income.

1.105 "Sublicense Income Payments" means, with respect to a Development Project and a calendar quarter, the Sublicense Income received by the relevant Opt-In Party or its Affiliates in such calendar quarter with respect to such Development Project, multiplied by the relevant percentage determined pursuant to Section 5.4(d) or 5.5(d), as applicable.

1.106 "Sublicensee" means a Third Party to whom a Party, or its Affiliates or Sublicensees, has granted a sublicense in accordance with the terms of this Agreement.

1.107 "Superset Indemnitees" will have the meaning set forth in Section 11.2.

1.108 "Third Party" means any Person other than the Parties or any of their Affiliates.

1.109 "Third Party Agreement" means either (i) an out-license agreement described in the Out-License Summary, (ii) an In-License Agreement described on the In-License Summary, (iii) an Optional In-License or (iv) an agreement pursuant to which a Controlling Party obtained Control over an Additional Right.

1.110 "Third Party Rights" means, with respect to a Party, any rights of, and any limitations, restrictions or obligations imposed by, Third Parties pursuant to Third Party Agreements.

1.111 "Valid Claim" means a claim (a) of any issued, unexpired patent that has not been revoked or held unenforceable or invalid by a decision of a court or governmental agency of competent jurisdiction from which no appeal can be taken, or with respect to which an appeal is not taken within the time allowed for appeal, and that has not been disclaimed or admitted to be invalid or unenforceable through reissue, disclaimer or otherwise; or (b) of any patent application that has not been cancelled, withdrawn or abandoned, or been pending for more than [***] years.

1.112 "Work Product" means any data, documentation, inventions and other Know-How arising from or made in the performance of the Services (as defined in the Services Agreement) by a Licensor.

SCHEDULE A

Previous Agreements

Strategic Collaboration & License Agreement between Isis Pharmaceuticals, Inc. and Alnylam Pharmaceuticals, Inc., dated March 11, 2004, as supplemented or amended by letter agreements dated March 9, 2004 (as amended by letter agreement dated October 28, 2005), March 11, 2004, and June 10, 2005

License Agreement between Max Plank Innovation GmbH (formerly Garching Innovation GmbH), Isis Pharmaceuticals, Inc. and Alnylam Pharmaceuticals, Inc., dated October 18, 2004

Co-Exclusive License Agreement among The Board of Trustees of the Leland Stanford Junior University, Alnylam Pharmaceuticals, Inc. and Isis Pharmaceuticals, Inc., dated August 31, 2005

Schedule 1.61

Initial miRNA Precursor Antagonists

[***]

Schedule 2.1(A)
Patents and License Agreements Assigned to Regulus by Isis

Isis Patent Applications to be Assigned to Regulus

IsisDocket Number	Country	Serial Number	Filing Date	Priority Date	Title

[***]

Isis License Agreements to be Assigned to Regulus

[***]

Schedule 2.1(B)
Patents and License Agreements Assigned to Regulus by Alnylam

Alnylam Patent Applications to be Assigned to Regulus

CaseNumber	InvTitle	Country	CaseType	AppNumber	FilDate

[***]

Alnylam License Agreements to be Assigned to Regulus

License Agreement between The Rockefeller University and Alnylam Pharmaceuticals, Inc. effective August 15, 2005

[summary is attached as Exhibit 2]

Schedule 2.2(A)
Patents and Patent Applications Licensed to Regulus by Isis on the Effective Date

Isis Docket Number	Country	Serial Number	Filing Date	Priority Date	Title	Patent Number

[***]

Patents and Patent Applications Licensed to Regulus by Alnylam on the Effective Date

CaseNumber	InvTitle	Co.	AppNumber	FilDate	PubNumber	PubDate	PatNumber	IssDate

[***]

Schedule 2.4(A)
Part 1
Isis' Existing Out-License Agreements

This Appendix 2.4(A) contains a list and summary of certain agreements in effect as of the Effective Date between Isis and certain Third Parties that may, as applicable, place certain encumberances or limitations on the licenses or sublicenses granted to Regulus and the representations and warranties, where specified in the Agreement. Copies of the listed agreements will be provided at Regulus' request for a complete disclosure of the encumbrances and limitations in each agreement.

As set forth in the Agreement, the information and disclosures contained in this Appendix are intended only to qualify and limit the licenses granted by Isis to Regulus, the exclusivity covenants, and the representations and warranties given by Isis under the Agreement and do not expand in any way the scope or effect of any such licenses, representations or warranties.

Nothing herein constitutes an admission of any liability or obligation of Isis nor an admission against any interest of Isis. The inclusion of this Appendix or the information contained in this Appendix does not indicate that Isis has determined that this Appendix or the information contained in this Appendix when considered individually or in the aggregate, is necessarily material to Isis.

Regulus acknowledges that certain information contained in this Appendix may constitute material Confidential Information relating to Isis which may not be used for any other purpose other than that contemplated by the Agreement.

Capitalized terms used herein below, but not otherwise defined herein below, have the meanings given to such terms in the applicable agreement listed below, unless it is clear from the context that the term has the meaning set forth in the Agreement.

[***].

Schedule 2.4(A)
Part 2
Alnylam's Existing Out-License Agreements

License and Collaboration Agreement between Tekmira Pharmaceuticals Corporation (formerly INEX Pharmaceuticals Corporation) and Alnylam, dated January 8, 2007

License and Collaboration Agreement dated July 8, 2007, by and among Alnylam Pharmaceuticals, Inc., F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., effective on August 9, 2007

Research Collaboration and License Agreement between Novartis Institutes for BioMedical Research, Inc. and Alnylam Pharmaceuticals, Inc., effective October 12, 2005, as amended by the Addendum Re: Influenza Program effective as of December 13, 2005, Amendment No. 1 to such Addendum effective as of March 14, 2006, and Amendment No. 2 to such Addendum effective as of May 5, 2006

[summaries are attached as Exhibit 2]

Schedule 2.4(B)
Part 1
Isis' Existing In-License Agreements

This Appendix 2.4(B) contains a list and summary of certain agreements in effect as of the Effective Date between Isis and certain Third Parties that may, as applicable, place certain encumberances or limitations on the licenses or sublicenses granted to Regulus and the representations and warranties, where specified in the Agreement. Copies of the listed agreements will be provided at Regulus' request for a complete disclosure of the encumbrances and limitations in each agreement.

As set forth in the Agreement, the information and disclosures contained in this Appendix are intended only to qualify and limit the licenses granted by Isis to Regulus, the exclusivity covenants, and the representations and warranties given by Isis under the Agreement and do not expand in any way the scope or effect of any such licenses, representations or warranties.

Nothing herein constitutes an admission of any liability or obligation of Isis nor an admission against any interest of Isis. The inclusion of this Appendix or the information contained in this Appendix does not indicate that Isis has determined that this Appendix or the information contained in this Appendix when

considered individually or in the aggregate, is necessarily material to Isis.

Regulus acknowledges that certain information contained in this Appendix may constitute material Confidential Information relating to Isis which may not be used for any other purpose other than that contemplated by the Agreement.

Capitalized terms used herein below, but not otherwise defined herein below, have the meanings given to such terms in the applicable agreement listed below, unless it is clear from the context that the term has the meaning set forth in the Agreement.

[***].

Schedule 2.4(B)
Part 2
Alnylam's Existing In-License Agreements

License Agreement between The Rockefeller University and Alnylam Pharmaceuticals, Inc. effective May 8, 2006 (the "Tuschl Agreement")

Co-Exclusive License Agreement among The Board of Trustees of the Leland Stanford Junior University, Alnylam Pharmaceuticals, Inc. and Isis Pharmaceuticals, Inc. effective August 31, 2005

License Agreement among Garching Innovation GmbH, Alnylam Pharmaceuticals, Inc. and Isis Pharmaceuticals, Inc. effective October 18, 2004

[summaries are attached as Exhibit 2]

Schedule 2.4(C)
Part 1
Isis' Optional In-Licenses

This Appendix 2.4(C) contains a list and summary of certain agreements in effect as of the Effective Date between Isis and certain Third Parties that may, as applicable, place certain encumberances or limitations on the licenses or sublicenses granted to Regulus and the representations and warranties, where specified in the Agreement. Copies of the listed agreements will be provided at Regulus' request for a complete disclosure of the encumbrances and limitations in each agreement.

As set forth in the Agreement, the information and disclosures contained in this Appendix are intended only to qualify and limit the licenses granted by Isis to Regulus, the exclusivity covenants, and the representations and warranties given by Isis under the Agreement and do not expand in any way the scope or effect of any such licenses, representations or warranties.

Nothing herein constitutes an admission of any liability or obligation of Isis nor an admission against any interest of Isis. The inclusion of this Appendix or the information contained in this Appendix does not indicate that Isis has determined that this Appendix or the information contained in this Appendix when considered individually or in the aggregate, is necessarily material to Isis.

Regulus acknowledges that certain information contained in this Appendix may constitute material Confidential Information relating to Isis which may not be used for any other purpose other than that contemplated by the Agreement.

Capitalized terms used herein below, but not otherwise defined herein below, have the meanings given to such terms in the applicable agreement listed below, unless it is clear from the context that the term has the meaning set forth in the Agreement.

[***]
.

Schedule 2.4(C)
Part 2
Alnylam's Optional In-Licenses

Amended and Restated Exclusive Patent License Agreement between Massachusetts Institute of Technology ("MIT") and Alnylam, dated May 9, 2007

License and Collaboration Agreement between Tekmira Pharmaceuticals Corporation (formerly INEX Pharmaceuticals Corporation) ("Tekmira") and Alnylam, dated January 8, 2007

The Sublicense Agreement between Tekmira and Alnylam, dated January 8, 2007

[summaries are attached as Exhibit 2]

Schedule 5.6(f)

Examples regarding Payments Due

Example 1: [***]
Party opts-in at [***]
Party responsible for High Terms
Party sublicenses product mid Phase IIb at terms below

Milestones	"Guaranteed Payments" Due Under High Terms	Paid Before Sublicense	*Cumulative "Guaranteed Payments" Payable*	Sublicense Milestones	"Sublicense Income"	"Sublicense Income Payments" Due ([***]%)	*Cumulative "Sublicense Income Payments" Due*	"Cumulative Amount Owed"	Payments Payable By Opt-in Party
Upfront	[***]	[***]	[***]				[***]	[***]	[***]
IND filing	[***]	[***]	[***]				[***]	[***]	[***]
Completion of Phase IIa	[***]	[***]	[***]			[***]	[***]	[***]	[***]
			[***]	[***]	[***]	[***]	[***]	[***]	[***]
Phase III start	[***]		[***]	[***]	[***]	[***]	[***]	[***]	[***]
			[***]	[***]	[***]	[***]	[***]	[***]	[***]
FDA filing	[***]		[***]	[***]	[***]	[***]	[***]	[***]	[***]
EU filing	[***]		[***]	[***]	[***]	[***]	[***]	[***]	[***]
FDA approval	[***]		[***]	[***]	[***]	[***]	[***]	[***]	[***]
EU approval	[***]		[***]	[***]	[***]	[***]	[***]	[***]	[***]
			[***]	[***]	[***]	[***]	[***]	[***]	[***]
Total	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**

Example 2: [***]
Party opts-in at [***]
Party responsible for Low Terms
Party sublicenses product after IND at terms below

Milestones	"Guaranteed Payments" Due Under Low Terms	Paid Before Sublicense	*Cumulative "Guaranteed Payments" Payable*	Sublicense Milestones	"Sublicense Income"	"Sublicense Income Payments" Due ([***]%)	*Cumulative "Sublicense Income Payments" Due*	"Cumulative Amount Owed"	Payments Payable By Opt-in Party
Upfront	[***]	[***]	[***]				[***]	[***]	[***]
IND filing	[***]	[***]	[***]				[***]	[***]	[***]
Upfront sublicense	[***]		[***]	[***]	[***]	[***]	[***]	[***]	[***]
Completion of Phase IIa	[***]		[***]	[***]	[***]	[***]	[***]	[***]	[***]
Phase III start	[***]		[***]	[***]	[***]	[***]	[***]	[***]	[***]
P3 end	[***]		[***]	[***]	[***]	[***]	[***]	[***]	[***]
FDA filing	[***]		[***]	[***]	[***]	[***]	[***]	[***]	[***]
EU filing	[***]		[***]	[***]	[***]	[***]	[***]	[***]	[***]
FDA approval	[***]		[***]	[***]	[***]	[***]	[***]	[***]	[***]
EU approval	[***]		[***]	[***]	[***]	[***]	[***]	[***]	[***]
Japan approval	[***]		[***]	[***]	[***]	[***]	[***]	[***]	[***]
Total	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**

Example 3: [***]
Party opts-in at [***]
Party responsible for High Terms
Party sublicenses product mid Phase III at terms below

Milestones	"Guaranteed Payments" Due Under High Terms	Paid Before Sublicense	*Cumulative "Guaranteed Payments" Payable*	Sublicense Milestones	"Sublicense Income"	"Sublicense Income Payments" Due ([***]%)	*Cumulative "Sublicense Income Payments" Due*	"Cumulative Amount Owed"	Payments Payable By Opt-in Party
Upfront	[***]	[***]	[***]				[***]	[***]	[***]
IND filing	[***]	[***]	[***]				[***]	[***]	[***]
Completion of Phase IIa	[***]	[***]	[***]			[***]	[***]	[***]	[***]
Phase III start	[***]	[***]	[***]			[***]	[***]	[***]	[***]
			[***]	[***]	[***]	[***]	[***]	[***]	[***]
			[***]	[***]	[***]	[***]	[***]	[***]	[***]
FDA filing	[***]		[***]	[***]	[***]	[***]	[***]	[***]	[***]
EU filing	[***]		[***]	[***]	[***]	[***]	[***]	[***]	[***]
FDA approval	[***]		[***]	[***]	[***]	[***]	[***]	[***]	[***]
EU approval	[***]		[***]	[***]	[***]	[***]	[***]	[***]	[***]
			[***]	[***]	[***]	[***]	[***]	[***]	[***]
Total	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**

Attachments to Schedules 2.1(B), 2.4(A) Part 2, 2.4(B) Part 2 and 2.4(C) Part 2

Copies of the following agreements, some in redacted form, have been, or shall be, made available to Licensee as of the Effective Date:

Schedule 2.1(B): Patents and License Agreements Assigned to Regulus by Alnylam

- License Agreement between The Rockefeller University and Alnylam Pharmaceuticals, Inc. effective August 15, 2005

Schedule 2.4(A) Part 2: Alnylam's Existing Out-License Agreements

- License and Collaboration Agreement between Tekmira Pharmaceuticals Corporation (formerly INEX Pharmaceuticals Corporation) and Alnylam Pharmaceuticals, Inc., dated January 8, 2007.

- License and Collaboration Agreement dated July 8, 2007, by and among Alnylam Pharmaceuticals, Inc., F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., effective on August 9, 2007

- Research Collaboration and License Agreement between Novartis Institutes for BioMedical Research, Inc. and Alnylam Pharmaceuticals, Inc., effective October 12, 2005, as amended by the Addendum Re: Influenza Program effective as of December 13, 2005, Amendment No. 1 to such Addendum effective as of March 14, 2006, and Amendment No. 2 to such Addendum effective as of May 5, 2006

Schedule 2.4(B) Part 2: Alnylam's Existing In-License Agreements

- License Agreement between The Rockefeller University and Alnylam Pharmaceuticals, Inc. effective May 8, 2006

- Co-Exclusive License Agreement among The Board of Trustees of the Leland Stanford Junior University, Alnylam Pharmaceuticals, Inc. and Isis Pharmaceuticals, Inc. effective August 31, 2005

- License Agreement among Garching Innovation GmbH, Alnylam Pharmaceuticals, Inc. and Isis Pharmaceuticals, Inc. effective October 18, 2004

Schedule 2.4(C) Part 2: Alnylam's Optional In-Licenses

- Amended and Restated Exclusive Patent License Agreement between Alnylam Pharmaceuticals, Inc. and Massachusetts Institute of Technology, dated May 9, 2007.

- The Sublicense Agreement between Tekmira Pharmaceuticals Corporation (formerly INEX Pharmaceuticals Corporation) and Alnylam Pharmaceuticals, Inc., dated January 8, 2007.

This In-License Summary, Out-License Summary and summary of assigned contracts and Optional In-Licenses highlights certain obligations of, or restrictions on, Alnylam and/or its

---

assignees or sublicensees of Licensed IP under In-License Agreements, Out-License Agreements, assigned contracts and Optional In-Licenses, including without limitation In-License Agreement payment obligations, which are applicable to Regulus under the Agreement, in each case subject to the terms and conditions of such In-License Agreements. The summaries set forth in these summaries are not intended to be comprehensive or inclusive of all obligations or restrictions which may be applicable to assignees of such assigned contracts or sublicensees of Licensed IP under such In-License Agreements, Out-License Agreements or Optional In-Licenses.

Unless otherwise expressly stated, capitalized terms not otherwise defined in these summaries shall have the meanings ascribed to them in the applicable In-License Agreement, Out-License Agreement, assigned contract or Optional In-License and references to sections, articles, schedules or exhibits made in these summaries shall be to sections, articles, schedules or exhibits, as the case may be, in or to such applicable In-License Agreement, Out-License Agreement, assigned contract or Optional In-License.

ROCKEFELLER (Stoffel)

License Agreement between The Rockefeller University and Alnylam Pharmaceuticals, Inc. effective August 15, 2005 ("Stoffel Agreement")

Brief Summary of Technology Covered by License:

- Alnylam and The Rockefeller University jointly own intellectual property relating to chemically modified oligonucleotides as therapeutic agents for reduction or elimination of microRNA expression. These oligonucleotides or "antagomirs" target a miRNA by complimentary base pairing to a miRNA or pre-miRNA nucleotide sequence. Antagomirs may be chemically modified to resist nucleolytic degradation, or to enhance delivery into cells (e.g. by conjugation to cholesterol).

Scope of License (Section 1.1)

- Alnylam's worldwide, exclusive, sublicensable license is limited to a license to make, have made, use, have used, import, have imported, sell, offer for sale and have sold Licensed Products for all uses.

- Rockefeller reserves the right to use, and to permit other non-commercial entities to use the Rockefeller Patent Rights for educational and non-commercial research purposes.

- Rockefeller Patent Rights were developed with funding from the U.S. National Institutes of Health. The United States government retains rights in such intellectual property, including, but not limited to, requirements that products, which result from such intellectual property and are sold in the United States, must be substantially manufactured in the United States.

Certain Sublicense Terms (Section 1.5)

- Alnylam will prohibit the sublicensee from further sublicensing and require the sublicensee to comply with the terms and conditions of the Stoffel Agreement.

- Within thirty (30) days after Alnylam enters into a sublicense agreement, Alnylam will deliver to Rockefeller a copy of the sublicense agreement which may be redacted with respect to content that is not relevant to Alnylam's obligations under the Stoffel Agreement.

- Alnylam is primarily liable to Rockefeller for any act or omission of a sublicensee that would be a breach of the Stoffel Agreement if performed or omitted by Alnylam, and Alnylam will be deemed to be in breach of the Stoffel Agreement as a result of such act or omission.

Diligence (Section 2)

- By end of the year 2007, Alnylam (or sublicensees) will select the method of delivery.

- By the end of the year 2008, Alnylam (or sublicensees) will optimize the lead compound.

- By the end of the year 2010, Alnylam (or sublicensees) will conclude preclinical development

Payment Obligations (Sections 3 and 4)

- The following milestones are payable:

• First issuance in the U.S. of a patent under the Rockefeller Patent Rights covering a Licensed Product	• $[***]
• First dosing of a subject in a Phase II clinical trial for the first Licensed Product	• $[***]
• Approval by the U.S. FDA of a New Drug Application for the first Licensed Product	• $[***]

- A [***]% royalty is payable to Rockefeller on Net Sales of Licensed Products by Alnylam, its Affiliates and its sublicensees (no offsets).

- If Alnylam grants a sublicense under the Stoffel Agreement and receives payment in connection with such grant in the form of upfront fees, maintenance fees and milestone payments (net of any sums due to Rockefeller under this Agreement for the same milestone event), Alnylam will pay Rockefeller [***]% of such payments, excluding payments for costs incurred by Alnylam, Payments to Alnylam in the form of royalties paid by a sublicensee, equity investments in Alnylam by a sublicensee, loan proceeds paid to Alnylam by a sublicensee in an arms length transaction, full recourse debt financing and research and development funding paid to Alnylam in a bona fide transaction are also excluded from the sublicense income calculation.

- Payments are due to Rockefeller within 60 days after the end of the quarter in which the royalties or fees accrue.

Books and Records (Sections 4.3 and 4.4)

- Sub-licensees are required to keep complete and accurate books and records to verify Net Sales, and all of the royalties, fees, and other payments payable under the Stoffel Agreement. The records for each quarter will be maintained for at least three (3) years after submission of the applicable report required under the Stoffel Agreement.

- Upon reasonable prior written notice to Alnylam, sublicensees will provide an independent, reputable CPA appointed by Rockefeller and reasonably acceptable to Alnylam with access to all of the books and records required by the Stoffel Agreement to conduct a review or audit of Net Sales, and all of the royalties, fees, and other payments payable under the Stoffel Agreement. If the audit determines that Alnylam has underpaid any royalty payment by 5% or more, Alnylam will also promptly pay the costs of the review or audit.

Non-Use of Name (Section 5.4)

- Sublicensees may not use the name, logo, seal, trademark, or service mark (including any adaptation of them) of Rockefeller or any Rockefeller school, organization, employee, student or representative, without the prior written consent of Rockefeller, except for purposes of compliance with securities regulations.

Termination (Section 6.2)

- Alnylam may terminate for convenience

- Sublicenses will survive for 90 days following termination and Rockefeller agrees to enter into license agreement(s) directly with sublicensees upon the same terms as the terms of the Stoffel Agreement

- Alnylam must promptly inventory all finished product and works-in-product of Licensed Products of its sublicensees. Inventory may be sold off unless Rockefeller terminates for a breach by Alnylam or its sublicensees or Alnylam's bankruptcy.

Prosecution and Enforcement (Section 7)

- Alnylam will prepare the Rockefeller Patent Rights, but Rockefeller will prosecute and maintain the Rockefeller Patent Rights with Alnylam's input. Alnylam has a right to manage the prosecution and enforcement. Alnylam will reimburse Rockefeller's prosecution and maintenance costs.

- Alnylam must inform Rockefeller promptly, but no later than 30 days, after learning of infringement of the Rockefeller Patent Rights. Alnylam and Rockefeller will consult each other concerning response to infringement. Alnylam may enforce the Rockefeller Patent Rights; recoveries, after the parties' expenses are reimbursed, are treated as Net Sales subject to royalties. Rockefeller has step-in enforcement rights.

Definitions

"Licensed Products" means products that are made, made for, used, used for, imported, imported for, sold, sold for or offered for sale by Alnylam or its Affiliates or sublicensees and that either (i) in the absence of this Agreement, would infringe at least one Valid Claim of the Rockefeller Patent Rights, or (ii) use a process or machine covered by a Valid Claim of Rockefeller Patent Rights.

"Net Sales" means with respect to each Licensed Product the gross amount invoiced by Alnylam or its Affiliates or sublicensees on sales or other dispositions of such product to third parties less Qualifying Costs directly attributable to a sale and actually taken and/or identified on the invoice and borne by Company, or its Affiliates or sublicensees. "Qualifying Costs" means: (a) customary discounts in the trade for quantity purchased, prompt payment or wholesalers and distributors; (b) credits, allowances or refunds for claims or returns or retroactive price reductions (including government healthcare programs and similar types of rebates) that do not exceed the original invoice amount; (c) prepaid outbound transportation expenses and transportation insurance premiums; and (d) sales, transfer, excise and use taxes and other fees imposed by a governmental agency. Sales for clinical study purposes or compassionate, named patient or similar use shall not constitute Net Sales

"Rockefeller Patent Rights" means Rockefeller's interests in a specified patent application ([***]) and related patent family relating to reduction or elimination of miRNA expression.

TEKMIRA

License and Collaboration Agreement between Tekmira Pharmaceuticals Corporation (formerly INEX Pharmaceuticals Corporation) ("Tekmira") and Alnylam, dated January 8, 2007 ("Effective Date") ("Tekmira Agreement")

Brief Summary of Technology Covered by License:

- Tekmira (f.k.a. Inex Pharmaceuticals Corp.) granted Alnylam a license relating to liposomal delivery of siRNA and miRNA products. Alnylam granted Tekmira (i) an option to obtain exclusive, royalty-bearing, worldwide licenses under its fundamental siRNA intellectual property for 3 genetic targets and (ii) an exclusive, royalty bearing license to certain intellectual property relating to immunostimulatory RNA oligonucleotide compositions ("IOC Technology"). Alnylam retained certain rights to participate with Tekmira in commercialization of IOC Technology. In addition, Alnylam provided funding for a 2-year formulation development collaboration with Tekmira, a multi-year loan for capital expenditure purposes, and Tekmira will provide exclusive manufacturing services for Alnylam's development programs up until completion of Phase 2 clinical studies.

Limitations on Scope of License (Sections 6.1 and 6.4)

- The license granted to Alnylam is limited to an exclusive, royalty-bearing, worldwide license under Inex Technology, Inex Collaboration IP and Tekmira's interest in Joint Collaboration IP to Develop, Manufacture and Commercialize Alnylam Royalty Products in the Alnylam Field, subject to (a) Tekmira's non-exclusive license under Alnylam's rights in Inex Technology and Collaboration IP for purposes of performing Tekmira's obligations under the Collaboration with respect to Alnylam Royalty Products, and the Manufacturing Activities, and (b) Tekmira's exclusive, worldwide license under Alnylam's rights in Inex Technology and Collaboration IP to Develop, Manufacture and Commercialize Inex Development Products (as defined below) in the Alnylam Field.

- Any license granted by Alnylam to a Third Party under Alnylam RNAi Technology and Alnylam Collaboration IP would be subject to a non-exclusive, worldwide license granted to Tekmira for purposes of performing Tekmira's obligations under the Collaboration with respect to Alnylam Royalty Products, and the Manufacturing Activities.

- Any license granted by Alnylam to a Third Party under Alnylam Core Patent Rights, Alnylam Lipidoid Patent Rights, Alnylam Collaboration IP and Alnylam's interest in Joint Collaboration IP would be subject to an exclusive, worldwide license granted to Tekmira to Develop, Manufacture and Commercialize RNAi Products directed to up to three (3) Targets (each such Target, an "Inex Development Target," and such RNAi Products, the "Inex Development Products") which Tekmira may select (as described below) in the Alnylam Field. During the Selection Term, Tekmira has the right to nominate a Target, subject to (a) Alnylam's contractual obligation to a Third Party that would be breached by the inclusion of such Target as an Inex Development Target under the Tekmira Agreement, and (b) Alnylam's determination after good faith review of its ongoing or planned scientific and/or business activities that such Target is a Target of interest to Alnylam. If neither of these criteria apply, the Target is deemed to have been successfully nominated as an "Inex Development Target" and Alnylam is obligated to use Commercially Reasonable Efforts consistent with the terms of the Novartis Agreement to obtain Novartis' consent to such selection. If an Inex Development Target is not available for

license, then Tekmira may nominate an additional Target, until an aggregate of 3 Inex Development Targets have been identified and approved for selection. If all 3 Inex Development Targets have not been approved for selection by the expiration of the Selection Term, the Selection Term will be extended until the earlier of (i) the date on which an aggregate of 3 such Inex Development Targets have been identified and approved for selection, and (ii) January 8, 2014.

- Any license granted by Alnylam to a Third Party under Alnylam IOC Technology, Alnylam Collaboration IP and Alnylam's interest in Joint Collaboration IP would be subject to an exclusive license granted to Develop, Manufacture and Commercialize IOC Products in the Inex IOC Field in and for the United States.

Restrictions on Sublicensing by Alnylam (Sections 6.2 and 6.4)

- Alnylam may grant sublicenses to Third Parties to Develop, Manufacture and Commercialize Alnylam Royalty Products; provided, that (i) with respect to any sublicense of Alnylam's rights under Section 6.1.1(a) (i.e., the exclusive license under Inex Technology to develop and commercialize Alnylam Royalty Products in the Alnylam Field) of the Tekmira Agreement in respect of any Alnylam Royalty Product for which Tekmira has not initiated

Manufacturing of batches of finished dosage form for GLP toxicology studies, Alnylam is required to use Commercially Reasonable Efforts to facilitate a business discussion between Tekmira and Alnylam's Sublicensee (other than Tekmira or its Affiliates) with respect to the provision of manufacturing services by Tekmira to such Sublicensee; and (ii) with respect to any sublicense of Alnylam's rights under Section 6.1.1(a) of the Tekmira Agreement in respect of any Alnylam Royalty Product for which Tekmira has initiated Manufacturing of batches of finished dosage form for GLP toxicology studies, Alnylam's Sublicensee (other than Tekmira or its Affiliates) will be required to obtain its requirements of the bulk finished dosage form of such Alnylam Royalty Product from Tekmira on the terms set forth in Article 5 of the Tekmira Agreement. However, Tekmira agrees to negotiate in good faith with Alnylam and/or Alnylam's Sublicensee either an alternate or modified supply arrangement or the release of such Sublicensee from such exclusive supply obligation in return for reasonable compensation to Tekmira.

- Each license and/or sublicense granted by Alnylam under the Tekmira Agreement to develop, manufacture and commercialize Alnylam Royalty Products must be subject and subordinate to the terms and conditions of the Tekmira Agreement and must contain terms and conditions consistent with those in the Tekmira Agreement, including, without limitation, the requirements of Section 6.4 of the Tekmira Agreement (see below). Commercializing Sublicensees are also required to: (i) submit applicable sales or other reports consistent with those required under the Tekmira Agreement; (ii) comply with an audit requirement similar to the requirement set forth in Section 7.6 of the Tekmira Agreement; and (iii) comply with the confidentiality and non-use provisions of Article 8 of the Tekmira Agreement with respect to both Parties' Confidential Information. If Alnylam becomes aware of a material breach of any sublicense by a Third Party Sublicensee, Alnylam is required to promptly notify Tekmira of the particulars of same and take all Commercially Reasonable Efforts to enforce the terms of such sublicense.

- Section 6.4 of the Tekmira Agreement states that all licenses and other rights granted to Alnylam with respect to Inex Technology under Article 6 of the Tekmira Agreement are subject to (i) the rights granted to Tekmira, and to Tekmira's ability to grant rights to Alnylam under the Inex In-Licenses, and (ii) the provisions of the UBC Sublicense Documents governing or relating to the rights sublicensed to Alnylam.

Diligence and Annual Reports (Section 6.7)

- Alnylam is required to use Commercially Reasonable Efforts to Develop and Commercialize an Alnylam Royalty Product.

- Alnylam is required to deliver to Tekmira an annual report, due no later than December 31 of each Contract Year during the Agreement Term, which summarizes the major activities undertaken by Alnylam during the preceding 12 months to Develop and Commercialize its Royalty Products in the applicable field. The report will include an outline of the status of any such Royalty Products in clinical trials and the existence of any sublicenses with respect to such Royalty Products which have not been previously disclosed.

Financial Obligations (Sections 7.2-7.4 and 6.1.3)

Milestone Payments:

- (a) Alnylam will make milestone payments to Tekmira as set forth below on a Target-by-Target basis, no later than 30 calendar days after the earliest date on which the corresponding milestone event has been achieved with respect to the first Alnylam Royalty Product directed to a Target (other than a Biodefense Target) to achieve such milestone event:

Milestone Event	Payment
Initiation of first Phase I Study	$ [***]
Initiation of first Phase II Study	$[***]
Acceptance by a Regulatory Authority in a Major Market of the first NDA for filing	$[***]
First NDA Regulatory Approval in a Major Market	$[***]
Aggregate worldwide cumulative Net Sales equals or exceeds $[***]	$[***]

- (b) If, however, the Target is a Biodefense Target, in lieu of the milestone payments set forth above, the following milestone payments will be payable, on a Target-by-Target basis, no later than 30 calendar days after the later of (i) the earliest date on which the corresponding milestone event has been achieved with respect to the first Alnylam Royalty Product directed to a Biodefense Target to achieve such milestone event and (ii) receipt by Alnylam of all funding from a Funding Authority that Alnylam is eligible to receive for the achievement of such milestone event:

Milestone Event	Payment
Approval of the first IND filed by Alnylam	$ [***]
Positive safety data from the first Phase I Study to be completed	$ [***]
First Commercial Sale	$[***]

- Notwithstanding the foregoing: (i) if the first Alnylam Royalty Product directed to a Target to achieve a milestone event as set forth in clause (a) or (b) above is comprised of a formulation Covered by or employing any Third Party Liposome Patent Rights, then only [***]% of the corresponding milestone payment will be payable to Tekmira; and (ii) notwithstanding that a Target is a Biodefense Target, if Alnylam or its Related Parties Commercialize or sell an Alnylam Royalty Product directed to such Target other than to a Funding Authority, the milestone payment amounts set forth in clause (a) will then apply in lieu of the amounts set forth in clause (b).

- Each milestone payment by Alnylam to Tekmira hereunder will be payable only once for each Target, regardless of the number of times the milestone is achieved with respect to one or more Alnylam Royalty Products directed to such Target.

- On and after [***], Alnylam will be entitled to reduce each milestone payment payable by Alnylam under the Tekmira Agreement (after application of appropriate deductions by [***]% of such milestone payment, until such time as the aggregate amount of all such reductions hereunder equals $[***]. For clarity, Alnylam may offset (i) its obligation to pay the resulting milestone payment against (ii) certain obligations of Tekmira owed to Alnylam pursuant to the Loan Agreement, as provided in the Loan Agreement.

Royalty Payments:

- Royalties are payable to Tekmira on Net Sales of Alnylam Royalty Products worldwide as follows:

Aggregate Calendar Year Net Sales of the Alnylam Royalty Product	Royalty (as a percentage of Net Sales)
on the first $[***] - $[***]	[***]%
On the subsequent $[***] - $[***]	[***]%
Greater than $[***]	[***]%

- Notwithstanding the foregoing, if an Alnylam Royalty Product is comprised of a formulation Covered by or employing any Third Party Liposome Patent Rights then royalties on Net Sales of Alnylam Royalty Products will be calculated as follows:

Aggregate Calendar Year Net Sales of the Alnylam Royalty Product	Royalty (as a percentage of Net Sales)
on the first $[***] - $[***]	[***]%
On the subsequent $[***] - $[***]	[***]%
Greater than $[***]	[***]%

- If the Development, Manufacture or Commercialization of an Alnylam Royalty Product in accordance with the Tekmira Agreement infringes Necessary Third Party IP, the applicable royalties in each country payable to Tekmira will be reduced by [***]% of the amount paid by Alnylam of any royalties under all licenses of such Necessary Third Party IP that are reasonably allocable to the Development, Manufacture and Commercialization of the Alnylam Royalty Product in or for such country in the Alnylam Field; provided, however, that, on a country-by-country basis, in no event will the royalties payable to Tekmira with respect to Net Sales in a country for any Calendar Quarter be reduced below the greater of: (i) [***]% of the royalties otherwise payable to Tekmira for such Calendar Quarter, and (ii) the amount of any royalties payable under the In-licenses of Alnylam that are reasonably allocable to the Commercialization or Manufacture of the Alnylam Royalty Product in or for such country in the Field (where the royalties are calculated by adding one percentage point to the applicable royalty rate(s) in the applicable In-License(s)).

- If Alnylam is required to make any payments to UBC in respect of the Inex Technology or Inex Collaboration IP licensed to Alnylam pursuant to the UBC Sublicense Agreement, then Alnylam will be entitled to offset any amounts payable by Alnylam to Tekmira under the Tekmira Agreement by the amount of Alnylam's payments to UBC until such amounts have been credited in full.

Royalty Reports; Payment and Audit Rights (Sections 7.3.4 and 7.6)

- Commencing upon the First Commercial Sale of an Alnylam Royalty Product, Alnylam is required to provide to Tekmira a quarterly written report showing the quantity of Alnylam Royalty Products sold in each country (as measured in saleable units of product), the gross sales of such Alnylam Royalty Product in each country, total deductions for such Alnylam Royalty Product for each country included in the calculation of Net Sales, the Net Sales in each country of such Alnylam Royalty Product subject to royalty payments and the royalties payable with respect to such Alnylam Royalty Product. Quarterly reports are due no later than the 25th day following the close of each Calendar Quarter. Royalties shown to have accrued by each royalty report are due and payable on the date such royalty report is due.

- Complete and accurate records must be kept in sufficient detail to enable the royalties and other payments payable under the Tekmira Agreement to be determined.

- Upon the written request of Tekmira and not more than once in each Calendar Year, a Sublicensee must permit an independent certified public accounting firm of nationally recognized standing selected by Tekmira and reasonably acceptable to such Sublicensee to have access during normal business hours to such of the records of Sublicensee as may be reasonably necessary to verify the accuracy of the royalty and other financial reports required to be delivered under the Tekmira Agreement for any Calendar Year ending not more than [***] months prior to the date of such request, for the sole purpose of verifying the basis and accuracy of payments made under Article 7 of the Tekmira Agreement.

Prosecution and Enforcement (Sections 10.2, 10.3 and 10.4)

- Alnylam is solely responsible, at Alnylam's discretion, for filing, prosecuting, conducting *ex parte* and *inter partes* proceedings (including the defense of any interference or opposition

proceedings) and maintaining all Patent Rights comprising Alnylam RNAi Technology, Alnylam IOC Technology or Alnylam Collaboration IP, in Alnylam's name.

- Tekmira, at Tekmira's discretion, for filing, prosecuting, conducting *ex parte* and *inter partes* proceedings, (including the defense of any interference or opposition proceedings), and maintaining all Patent Rights comprising Inex Technology or Inex IOC Technology, in Tekmira's name, or Inex Collaboration IP, in UBC's name.

- Subject to Tekmira's continuing right to the prior review of, comment on, revision to and approval of material documents, which will not be unreasonably delayed or withheld, Alnylam is solely responsible, at Alnylam's discretion, for filing, conducting *ex parte* and *inter partes* prosecution, and maintaining (including the defense of any interference or opposition proceedings) all Patent Rights comprising Joint Collaboration IP, in the names of both Tekmira and Alnylam.

- If Alnylam elects not to seek or continue to seek or maintain patent protection on any Alnylam IOC Technology or Alnylam Collaboration IP which is subject to Tekmira's licensed rights under the Tekmira Agreement, or Joint Collaboration IP, then Tekmira will have step-in rights. If Alnylam declines to file, prosecute and/or maintain Valid Claims at Tekmira's request in Joint Collaboration IP, then Tekmira will have step-in rights.

- If Tekmira elects not to seek or continue to seek or maintain patent protection on any Inex Technology or Inex Collaboration IP, which is subject to Alnylam's licensed rights under the Tekmira Agreement, then subject to the provisions of the UBC Sublicense Documents, Alnylam will have rights (but not the obligation), at its expense, to prosecute and maintain in any country patent protection on such Inex Technology in the name of Tekmira or Inex Collaboration IP in the name of UBC.

- Each Party agrees: (a) to make its employees, agents and consultants reasonably available to the other Party (or to the other Party's authorized attorneys, agents or representatives), to the extent reasonably necessary to enable such Party to undertake patent prosecution; (b) to provide the other Party with copies of all material correspondence pertaining to prosecution with the patent offices; (c) to cooperate, if necessary and appropriate, with the other Party in gaining patent term extensions wherever applicable to Patent Rights; and (d) to endeavor in good faith to coordinate its efforts with the other Party to minimize or avoid interference with the prosecution and maintenance of the other Party's patent applications.

- The patent filing, prosecution and maintenance expenses incurred after the Effective Date with respect to Patent Rights comprised of Alnylam Core Patent Rights, Alnylam IOC Technology, Alnylam Lipidoid Patent Rights, Inex Technology, Inex IOC Technology and Collaboration IP will be borne by each Party having the right to file, prosecute and maintain such Patent Rights under the Tekmira Agreement.

- Subject to the provisions of any Inex In-License and the provisions of the UBC Sublicense Documents, in respect of the Alnylam Royalty Products in the Alnylam Field, Alnylam will have the sole and exclusive right to initiate an infringement or other appropriate suit anywhere in the world against any Third Party who at any time has infringed, or is suspected

of infringing, any Patent Rights, or of using without proper authorization, any Know-How, comprising any Inex Technology or Collaboration IP that is licensed to Alnylam under the Tekmira Agreement.

- Alnylam will have the sole and exclusive right to initiate an infringement or other appropriate suit anywhere in the world against any Third Party who at any time has infringed, or is suspected of infringing, any Patent Rights, or of using without proper authorization any Know-How, comprising Alnylam RNAi Technology, Alnylam IOC Technology or Alnylam Collaboration IP; provided, that if Alnylam fails to initiate a suit or take other appropriate action with respect to Alnylam IOC Technology in the United States with respect to an IOC Product that it has the initial right to initiate or take pursuant thereto within 90 days after becoming aware of the basis for such suit or action, then Tekmira may, in its discretion, provide Alnylam with written notice of Tekmira's intent to initiate a suit or take other appropriate action with respect to such IOC Product. If Alnylam fails to initiate a suit or take such other appropriate action within 30 days after receipt of such notice from Tekmira, then Tekmira will have the right to initiate a suit or take other appropriate action that it believes is reasonably required to protect its licensed interests under the Alnylam IOC Technology and Alnylam Collaboration IP with respect to such IOC Product.

- Alnylam may defend any Infringement Claim brought against either Party or its Affiliates or Sublicensees arising out of the Development, Manufacture or Commercialization of any Alnylam Royalty Product in the Alnylam Field. Tekmira may defend any Infringement Claim brought against either Party or its Affiliates or Sublicensees arising out of the Development, Manufacture or Commercialization of any Inex Royalty Product and in (a) the Alnylam Field, in the case of Inex Development Products or (b) the Inex IOC Field, in the case of Inex IOC Products.

- As the responsible party, Alnylam must keep Tekmira informed, and from time to time consult with Tekmira regarding the status of any such claims and provide Tekmira with copies of all documents filed in, and all written communications relating to, any suit brought in connection with such claims. Tekmira also has the right to participate and to be presented in any such claim or related suit. If Alnylam fails to exercise its right to assume such defense within 30 days following written notice of such Infringement Claim, Tekmira has the sole and exclusive right to control the defense of such Infringement Claim.

Termination for Patent Challenge (Section 11.5)

- If any Sublicensee asserts in any court or other governmental agency of competent jurisdiction that an Inex Patent Right or a Patent Right Controlled by Tekmira by virtue of the Inex-UBC License Agreement and sublicensed to Alnylam pursuant to the UBC Sublicense (in either case, an "Inex Patent") is invalid, unenforceable, or that no issued Valid Claim embodied in such Inex Patent excludes a Third Party from making, having made, using, selling, offering for sale, importing or having imported an Alnylam Royalty Product in such jurisdiction, then Tekmira may, upon written notice to Alnylam, terminate all licenses granted to Alnylam for such Alnylam Royalty Product(s) covered by such Inex Patent that is under challenge in the applicable jurisdiction; provided, however, that Tekmira will not terminate such license if within 30 days of Alnylam's receipt of Tekmira's notification under the Tekmira Agreement (a) it is confirmed by written notice to Tekmira that Sublicensee no longer intends to challenge the validity or

enforceability of such Inex Patent; or (b) documentation is provided to Tekmira to confirm Sublicensee's withdrawal of its filing, submission, or other process commenced in any court or other governmental agency of competent jurisdiction to challenge the validity or enforceability of any such Inex Patent.

Definitions

"Alnylam Collaboration IP" means, generally (a) any improvement, invention, or Know-How first discovered or developed by employees of Alnylam or its Affiliates or other persons not employed by Tekmira acting on behalf of Alnylam, in the performance of the Collaboration, the Manufacturing Activities, and/or Alnylam's obligations under the Original Agreements, and (b) any Patent Rights which claim, cover or relate to such Know-How. Alnylam Collaboration IP excludes Alnylam's interest in Joint Collaboration IP.

"Alnylam Core Patent Rights" means those Patent Rights set forth in Schedule 1.3 of the Tekmira Agreement, including various Tuschl I and Tuschl II patents and patent applications, as such Schedule is supplemented from time to time pursuant to Section 6.5.1 of the Tekmira Agreement.

"Alnylam Field" means the treatment, prophylaxis and diagnosis of diseases in humans using an RNAi Product or miRNA Product.

"Alnylam IOC Technology" mean, generally (a) Know-How Controlled by Alnylam as of the Effective Date that is useful or necessary to Develop, Commercialize and/or Manufacture an IOC Product in the Inex IOC Field (excluding any Alnylam Collaboration IP and Alnylam's interest in Joint Collaboration IP), and (b) those Patent Rights set forth in Schedule 1.5 of the Tekmira Agreement, including USSN [***].

"Alnylam Lipidoid Patent Rights" means those Patent Rights Controlled by Alnylam under a license from the Massachusetts Institute of Technology pursuant to the MIT License Agreement and that are set forth in Schedule 1.6 of the Tekmira Agreement, including USSN [***].

"Alnylam RNAi Know-How" means, generally, Know-How Controlled by Alnylam that Alnylam determines in its reasonable judgment to be useful or necessary to Develop, Commercialize and/or Manufacture an Alnylam Royalty Product in the Alnylam Field (excluding any Alnylam Collaboration IP and Alnylam's interest in Joint Collaboration IP).

"Alnylam RNAi Patent Rights" means, generally, Patent Rights Controlled by Alnylam that claim (a) Alnylam RNAi Know-How, or (b) the identification, characterization, optimization, construction, expression, formulation, use or production of an Alnylam Royalty Product, as the case may be, and which Alnylam determines in its reasonable judgment to be useful or necessary to Develop, Commercialize and/or Manufacture an Alnylam Royalty Product in the Alnylam Field (including, without limitation, the Alnylam Core Patent Rights and the Alnylam Lipidoid Patent Rights, but specifically excluding Alnylam IOC Technology and any Patent Rights included in Alnylam Collaboration IP or Alnylam's interest in Joint Collaboration IP).

"Alnylam RNAi Technology" means, collectively, Alnylam RNAi Know-How and Alnylam RNAi Patent Rights.

"Alnylam Royalty Product" means any RNAi Product or a miRNA Product that, but for the licenses granted hereunder, would be Covered by one or more Valid Claims of the Inex Patent Rights.

"Biodefense Target" means (a) a Target within the genome of one or more Category A, B and C pathogens, as defined by the National Institute of Allergy and Infectious Diseases, including without limitation, pathogens listed on Schedule 1.12 of the Tekmira Agreement, but specifically excluding influenza virus, or (b) an endogenous cellular Target against which Alnylam Develops

and/or Commercializes an Alnylam Royalty Product for commercial supply to one or more Funding Authorities.

"Collaboration IP" means, collectively, Alnylam Collaboration IP, Inex Collaboration IP and Joint Collaboration IP.

"Existing Inex In-Licenses" means the Third Party agreements listed on Schedule 1.30 to the Tekmira Agreement.

"IOC" or "Immunostimulatory Oligonucleotide Composition" means a single-stranded or double-stranded ribonucleic acid ("RNA") composition, or derivative thereof, that has activity solely through an immunostimulatory mechanism and has no RNAi activity against a human gene transcript or viral genomic sequence.

"IOC Product**"** means a product containing, comprised of or based on IOCs or IOC derivatives.

"Inex Collaboration IP" means, generally (a) any improvement, invention or Know-How first discovered or developed by employees of Tekmira or its Affiliates or other persons not employed by Alnylam acting on behalf of Tekmira, in the performance of the Collaboration, the Manufacturing Activities, and/or Tekmira's obligations under the Original Agreements, and (b) any Patent Rights which claim, cover or relate to such Know-How. Inex Collaboration IP excludes Tekmira's interest in Joint Collaboration IP.

"Inex In-License" means an agreement between Tekmira or its Affiliates, and a Third Party, pursuant to which Tekmira or any of its Affiliates Control(s) Inex Technology relating to the Alnylam Field under a license or sublicense from such Third Party, including without limitation, the Existing Inex In-Licenses.

"Inex IOC Field" means the treatment, prophylaxis and diagnosis of diseases in humans using an IOC Product.

"Inex IOC Technology" means, generally (a) Know-How Controlled by Tekmira or its Affiliates with respect to IOC Products and/or IOCs, and (b) Patent Rights Controlled by Tekmira and its Affiliates that claim such Know-How or the identification, characterization, optimization, construction, expression, formulation, delivery, use or production of an IOC Product and/or IOC, and are useful or necessary to Develop, Commercialize and/or Manufacture IOC Products in the Field.

"Inex Know-How" means, generally, Know-How Controlled by Tekmira or its Affiliates with respect to an RNAi Product or miRNA Product (excluding any Inex Collaboration IP, Tekmira's interest in Joint Collaboration IP and any such Know-How sublicensed to Alnylam pursuant to the UBC Sublicense).

"Inex Patent Rights" means, generally, Patent Rights Controlled by Tekmira or its Affiliates that claim (a) Inex Know-How or (b) the identification, characterization, optimization, construction, expression, formulation, delivery, use or production of an RNAi Product or miRNA Product, and are useful or necessary to Develop, Commercialize and/or Manufacture RNAi Products or miRNA Products in the Alnylam Field (excluding any Patent Rights included in Inex Collaboration IP, Tekmira's interest in Joint Collaboration IP and any such Patent Rights licensed to Alnylam pursuant to the UBC Sublicense).

"Inex Royalty Product" means any (a) Inex Development Product that, but for the licenses granted hereunder, would be Covered by one or more Valid Claims under the Alnylam Core Patent Rights or the Alnylam Lipidoid Patent Rights, or (b) IOC Product that but for the licenses granted hereunder, would be Covered by one or more Valid Claims under the Alnylam IOC Technology.

"Inex Technology" means, collectively, Inex Know-How and Inex Patent Rights.

"Inex-UBC License Agreement" means that certain license agreement between Tekmira and the University of British Columbia ("UBC") dated effective July 1, 1998, as amended by Amendment Agreement between Tekmira and UBC dated effective July 11, 2006, and Second Amendment Agreement dated effective the Effective Date.

"Joint Collaboration IP" means, generally (a) any improvement, discovery or Know-How first discovered or developed jointly by the Parties or their Affiliates or others acting on behalf of Tekmira and Alnylam in the performance of the Collaboration, the Manufacturing Activities and/or the obligations of the Parties under the Original Agreements, and (b) any Patent Rights which claim, cover or relate to such Know-How.

"Manufacturing Activities" means those activities performed by a party relating to the manufacture and supply of Alnylam Royalty Products.

"miRNA Product" means a product containing, comprised of or based on native or chemically modified RNA oligomers designed to either modulate an miRNA and/or provide the function of an miRNA.

"Necessary Third Party IP" means, on a country-by-country basis, Know-How or Patent Rights in such country owned or controlled by a Third Party that cover a Royalty Product.
"Pre-Existing Alliance Agreements" are listed on Schedule 1.79 to the Tekmira Agreement.
"RNAi Product" means a product containing, comprised of or based on siRNAs or siRNA derivatives or other moieties effective in gene function modulation and designed to modulate the function of particular genes or gene products by causing degradation of a Target mRNA to which such siRNAs or siRNA derivatives are complementary ("RNAi Interference Mechanism"), and that is not an miRNA Product.
"Royalty Product" means, either (a) an Alnylam Royalty Product, or (b) an Inex Royalty Product.
"Selection Term" means the period commencing on the Effective Date and continuing for five (5) Contract Years thereafter, unless such period is extended pursuant to Section 2.2 of the Tekmira Agreement.
"Small Interfering RNA" or "siRNA" means a double-stranded ribonucleic acid (RNA) composition designed to act primarily through an RNA Interference Mechanism that consists of either (a) two separate oligomers of native or chemically modified RNA that are hybridized to one another along a substantial portion of their lengths, or (b) a single oligomer of native or chemically modified RNA that is hybridized to itself by self-complementary base-pairing along a substantial portion of its length to form a hairpin.
"Target" means: (a) a polypeptide or entity comprising a combination of at least one polypeptide and other macromolecules, that is a site or potential site of therapeutic intervention by a therapeutic agent; or a nucleic acid which is required for expression of such polypeptide; (b) variants of a polypeptide, cellular entity or nucleic acid described in clause (a); (c) a defined non-peptide entity, including a microorganism, virus, bacterium or single cell parasite; provided that the entire genome of a virus will be regarded as a single Target; or (d) a naturally occurring interfering RNA or miRNA or precursor thereof.
"Third Party Liposome Patent Rights" means, with respect to an Alnylam Royalty Product, (a) the Alnylam Lipidoid Patent Rights and/or (b) other technology comprising a lipid component or liposomal formulation useful or necessary for the Development, Manufacture or Commercialization of such Alnylam Royalty Product and Controlled by Alnylam under a license from a Third Party, and in each case with respect to which Intellectual Property Rights Alnylam has granted to Tekmira a non-exclusive, royalty- and milestone fee-bearing (on a pass-through

basis) license to Develop, Manufacture and Commercialize Inex Royalty Products in the Alnylam Field in the case of Inex Development Product, and in the Inex IOC Field in the case of IOC Products.
"UBC Sublicense Documents" means the collective reference to (a) the Sublicense Agreement dated as of the Effective Date between the Parties (the "UBC Sublicense"), (b) the Consent and Agreement dated as of the Effective Date among the Parties and UBC, and (c) the Assignment dated the Effective Date between Tekmira and UBC.

ROCHE

License and Collaboration Agreement dated July 8, 2007, by and among Alnylam Pharmaceuticals, Inc., F. Hoffmann-La Roche Ltd ("Roche Basel") and Hoffmann-La Roche Inc. (together with Roche Basel, "Roche") ("Roche Agreement"), effective on August 9, 2007 ("Effective Date")

Brief Description of Technology Covered by License

- Alnylam granted Roche and its Affiliates a non-exclusive, worldwide license under Alnylam's rights to Architecture and Chemistry IP and Delivery IP as it existed at the effective time of the Agreement, to develop and commercialize RNAi Products for treatment/prophylaxis of indications in at least the fields of cancer, certain liver diseases, metabolic disease and pulmonary disease. Roche has the option to enter additional therapeutic fields and, prior to granting exclusive licenses in the other Fields, Alnylam must give Roche a right of first negotiation.

Limitations on Scope of License

Any license granted by Alnylam to a Third Party under Architecture and Chemistry IP or Delivery IP would be subject to the following limitations:

- *License Grant to Roche*. Roche and its Affiliates have a non-exclusive, worldwide license to develop and commercialize RNAi Products for the treatment/prophylaxis of indications in at least the primary fields of cancer, certain liver diseases, metabolic disease and pulmonary disease) and any additional fields (which are listed in a schedule to the Roche Agreement) to which Roche acquires non-exclusive rights (collectively, "Field").

- *Designated Targets*. If Roche selects a Target which is not a Blocked Target and such Target is cleared through the Novartis ROFO mechanism, Roche has non-exclusive rights within the scope of its basic license grant to develop and commercialize RNAi Products directed to such "Designated Target" in the Field.

- *Alnylam/Roche Discovery Collaboration*. Roche and Alnylam have agreed to collaborate on a specified number of targets during the term of the agreement.

- *ROFN*. If Alnylam intends to grant to any Third Party an exclusive license to any particular additional field which has not yet been acquired by Roche, Alnylam must first offer Roche the right to extend its non-exclusive licenses into such additional field upon payment of a specified field option fee.

- *Extension into Additional Fields*. Roche may extend its development and commercialization activities directed to a Target into any additional field, provided that Roche notify Alnylam of such extension and pay certain milestone payments.

Prosecution and Enforcement

- Alnylam is obligated to take reasonable measures to protect and, to the extent Alnylam has such a right, to enforce the IP being licensed to Roche under the Roche Agreement.

- Alnylam is also obligated to assume control of the defense of any aspects of any third party infringement claim that involves the validity, scope and/or enforceability of such licensed IP. Roche has the right to control the defense of any other third party infringement claim or

aspect thereof related to the licensed IP. Alnylam must keep Roche advised of status and consider Roche's recommendations.

Definitions

- "Architecture and Chemistry Intellectual Property" refers, generally, to Know-How and Patent Rights listed on Schedule C to the Roche Agreement, in each case Controlled by Alnylam as of the Effective Date, and covering (a) the general structure, architecture, or design of double-stranded oligonucleotide molecules which engage RNAi mechanisms in a cell; (b) chemical modifications of double-stranded oligonucleotides (including any modification to the base, sugar or internucleoside linkage, nucleotide mimetics, and any end modifications) which do not abolish the RNAi activity of the double-stranded oligonucleotides in (a); (c) manufacturing techniques for the double-stranded oligonucleotide molecules or chemical modifications of (a) and (b); or (d) all uses or applications of double-stranded oligonucleotide molecules or chemical modifications in (a) or (b); but excluding (i) IP to the extent specifically related to Blocked Targets, and (ii) Delivery IP. Includes future Patent Rights that claim priority to or common priority with any of the aforementioned Patent Rights.

- "Blocked Target" means any Target that is subject to a contractual obligation of a Pre-Existing Alliance Agreement that would be breached by the inclusion of such Target as a Designated Target under this Agreement

- "Delivery Intellectual Property" refers, generally, to Know-How and Patent Rights listed on Schedule C to the Roche Agreement, in each case Controlled by Alnylam as of the Effective Date, and covering (a) delivery technologies necessary or useful for delivery of double-stranded oligonucleotide molecules; or (b) manufacturing techniques for such delivery technologies of (a); but excluding Patent Rights which relate specifically to Blocked Targets. Includes future Patent Rights that claim priority to or common priority with any of the aforementioned Patent Rights.

- "RNAi Compound" means any compound that, in vitro or otherwise, functions through the mechanism of RNAi and consists of or encodes double-stranded oligonucleotides, and which double-stranded oligonucelotides optionally may be chemically modified to contain modified nucleotide bases or non-RNA nucleotides, and optionally may be administered in conjunction with a delivery vehicle or vector.

- "RNAi Product" means any product that contains one or more RNAi Compounds as an active ingredient.

- "Target" means (a) a polypeptide or entity comprising a combination of at least one polypeptide and other macromolecules, that is a site or potential site of therapeutic intervention by a therapeutic agent; or a nucleic acid which is required for expression of such polypeptide; (b) variants of a polypeptide (including any splice variant thereof), cellular entity or nucleic acid described in clause (a); or (c) a defined non-peptide entity, including a microorganism, virus, bacterium or single cell parasite; provided that the entire genome of a virus shall be regarded as a single Target.

NOVARTIS

Research Collaboration and License Agreement between Novartis Institutes for BioMedical Research, Inc. and Alnylam Pharmaceuticals, Inc., effective October 12, 2005, as amended by the Addendum Re: Influenza Program effective as of December 13, 2005, Amendment No. 1 to such Addendum effective as of March 14, 2006, and Amendment No. 2 to such Addendum effective as of May 5, 2006 ("Novartis Agreement")

Brief Description of Technology Covered by License

- Alnylam granted Novartis a right to exclusively develop a certain number of Targets using intellectual property controlled by Alnylam during the term of the Agreement. Some of the Targets would be developed through collaborative work between Novartis and Alnylam. In addition, Novartis has the right to convert their license from an exclusive license with respect to certain Targets to a broad, non-exclusive license.

Scope of Rights

- Novartis may select a specified number of Targets ("Selected Targets"). Alnylam and Novartis entered into a Research Collaboration to identify and optimize RNAi Compounds directed against Selected Targets and develop improved RNAi technology to enable and enhance the utility of such RNAi Compounds. (Section 2)

- Alnylam granted Novartis and its Affiliates worldwide licenses under Alnylam Intellectual Property to (i) perform Novartis's obligations under the Research Collaboration, (ii) Discover RNAi Compounds, (iii) Discover RNAi Compounds directed at the Selected Targets, and (iv) Discover, Develop, Commercialize or Manufacture Discovered RNAi Compounds and Collaboration Products. The rights under clauses (i) and (ii) are non-exclusive and non-sublicenseable, under clause (iii) are exclusive and non-sublicenseable, and under clause (iv) are exclusive and sublicenseable. (Sections 3.1(a) and (b))

- For a period of time, Novartis has an option, exercisable upon notice and payment of a fee, to obtain for itself and its Affiliates a non-exclusive, non-sublicenseable (except to third party contractors), worldwide, perpetual license under Broad RNAi Intellectual Property for any human, veterinary or agricultural applications (the "Adoption License"). Alnylam may not grant any exclusive rights or licenses under any Broad RNAi Intellectual Property except with respect to an opportunity Novartis does not acquire under the ROFO or in accordance with agreements existing before the effective date of the Novartis Agreement. (Section 3.1(c) and (e))

- Exclusivity: Alnylam and its Affiliates may not, either alone or directly or indirectly in conjunction with a Third Party, conduct Discovery of any RNAi Compound or RNAi Products directed to a Selected Target, or Discovery, Development, Commercialization or Manufacture of Discovered RNAi Compounds, Collaboration Products, or RNAi Compounds or RNAi Products directed to Selected Targets. Alnylam and its Affiliates may not grant to any Third Party any rights under Alnylam Intellectual Property to engage in any of the foregoing activities. (Section 2.6(a))

- ROFO: If Alnylam or any of its Affiliates seek, directly or indirectly in conjunction with a Third Party (with limited exceptions), or to license a Third Party (with limited exceptions) the right, to Discover, Develop, Commercialize or Manufacture any RNAi Compounds or RNAi Products directed at a Target(s), Alnylam must first provide written notice to Novartis. Novartis

has a period of time to accept or reject the opportunity. If Novartis rejects an opportunity for a program for which no IND has been filed in the US or Major Market Countries, or Novartis and Alnylam are unable to come to terms on a post-IND program, Alnylam may, within a specified period of time, enter an agreement with a Third Party, which can be no more favorable overall to such Third Party than those offered to Novartis under Section 2.6(c)(i). (Sections 2.6(b) and (c))

- In-Licensing IP: To the extent applicable, Alnylam must comply with Sections 2.6(b) and (c) when acquiring or licensing rights from Third Parties. In the course of acquiring or licensing additional Broad RNAi Intellectual Property or any other Alnylam Intellectual Property covering a Collaboration Product, Alnylam must use its best efforts to ensure that such rights include the right to sublicense to Novartis such Broad RNAi Intellectual Property or other Alnylam Intellectual Property. (Sections 2.6(d), 3.1(f))

- Technology Transfer: Alnylam will periodically deliver to Novartis all Alnylam Intellectual Property specifically relating to the Discovered RNAi Compounds, relating to the Research Collaboration, or otherwise necessary or useful to the Discovery, Development, Commercialization or Manufacture of Discovered RNAi Compounds or Collaboration Products. Once Novartis acquires the Adoption License, Alnylam will periodically deliver to Novartis all Broad RNAi Intellectual Property. The deliveries will include un-redacted copies of agreements that directly or indirectly grant or restrict rights in Alnylam Intellectual Property, which may be redacted to comply with confidentiality obligations and to exclude terms that do not relate to Novartis's rights or obligations; provided, that Alnylam will use commercially reasonable efforts to ensure that Novartis is granted access to un-redacted copies of such agreements.

- Alnylam may not assign, license or otherwise grant any rights or dispose of any Broad RNAi Intellectual Property or other Alnylam Intellectual Property covering a Collaboration Product without making such disposition expressly subject to Novartis's rights. (Section 3.1(g))

IP Ownership, Prosecution and Enforcement (Section 6)

- Novartis owns all IP jointly created by the parties in the Research Collaboration. Novartis grants Alnylam a worldwide, non-exclusive, sublicenseable (solely to Controlled Contractors) license under such jointly-created IP that is Broad RNAi Intellectual Property, to engage in any and all research activities directed to human, veterinary or agricultural applications.

- Novartis has a step-in right to prosecute Alnylam Patent Rights that pertain to a Discovered RNAi Compound or a Licensed Product.

- Alnylam will promptly report in writing to Novartis any known or suspected infringement or misappropriation of Alnylam Intellectual Property and will provide Novartis with all available evidence supporting such infringement or misappropriation.

- Alnylam has the right to protect the Alnylam Intellectual Property, and Alnylam will consult with Novartis regarding the status of any such action and will provide Novartis with copies of all material documents relating to such action. Notwithstanding the foregoing, Novartis has the sole and exclusive right to initiate a suit under Alnylam Intellectual Property to protect a Discovered RNAi Compound, a Licensed Product or IP created solely by Novartis or

jointly by Novartis and Alnylam in the Research Collaboration; Alnylam must provide reasonable assistance at Novartis' request. Recoveries will be shared in a specified manner.

- Novartis and Alnylam will cooperate in responding to a claim challenging the validity of any Alnylam Patent Right covering a Discovered RNAi Compound or a Licensed Product.

Definitions

"Adopted Product" means a product containing RNAi Compound(s) that are Discovered, Developed, Commercialized or Manufactured pursuant to the Adoption License.

"Alnylam Intellectual Property" means Know-How and Patent Rights now or in the future owned or licensed by Alnylam or its Affiliates, including Broad RNAi Intellectual Property.

"Broad RNAi Intellectual Property" means all Know-How and Patent Rights now or in the future owned or licensed by Alnylam or its Affiliates that relate to RNAi technology, products or processes, including (a) the general structure, architecture, or design of nucleic acid based molecules which engage RNAi mechanisms in a cell; (b) chemical modifications of nucleic acids (including any modification to the base, sugar or internucleoside linkage, nucleotide mimetics, and any end modifications) which do not abolish the RNAi activity of the nucleic acid molecules in (a); (c) manufacturing techniques for the nucleic acid based molecules or chemical modifications of (a) and (b); and (d) all uses or applications of nucleic acid based molecules or chemical modifications in (a) or (b); but excluding Patents which relates solely to (i) a specific Target or small group of Targets; or (ii) delivery technologies which may be broadly employed for delivery of nucleic acid based molecules.

"Collaboration Product" means any product that contains one or more Discovered RNAi Compound(s) as active ingredient(s).

"Discovered RNAi Compound" means an RNAi Compound directed to a Selected Target that is Discovered during the course of a program under the Novartis Agreement, together with all derivatives of such RNAi Compound, where "derivative" means a compound that may contain modified nucleotides or may have been modified by chemical or molecular genetic means but which still, at least in vitro, functions through an RNAi mechanism against the same Target.

"Licensed Products" means the Collaboration Products and the Adopted Products.

"RNAi Compound" means any compound that in vitro or otherwise functions through the mechanism of RNAi and consists of or encodes double-stranded RNA, and which double-stranded RNA is optionally chemically modified to contain modified nucleotide bases or non-RNA nucleotides, and optionally may be administered in conjunction with a delivery vehicle or vector.

"RNAi Product" means any product that contains one or more RNAi Compounds as an active ingredient.

"Target" means: (a) a polypeptide or entity comprising a combination of at least one polypeptide and other macromolecules, that is a site or potential site of therapeutic intervention by a therapeutic agent; or a nucleic acid which is required for expression of such polypeptide; (b) variants of a polypeptide, cellular entity or nucleic acid described in clause (a); (c) a defined non-peptide entity, including a microorganism, virus, bacterium or single cell parasite; provided that the entire genome of a virus shall be regarded as a single Target; or (d) a naturally occurring interfering RNA or microRNA or precursor thereof.

ROCKEFELLER (Tuschl)

License Agreement between The Rockefeller University and Alnylam Pharmaceuticals, Inc. effective May 8, 2006 ("Tuschl Agreement")
Brief Summary of Technology Covered by License:
The Rockefeller University granted Alnylam a license to intellectual property developed by Dr. Thomas Tuschl relating to sequence-specific inhibition of microRNAs (RU 681) (also known as "Tuschl IV").

Scope of License (Section 1.1)

- Alnylam's non-exclusive, world-wide, sublicensable license is limited to a license to research, develop, make, have made, use, have used, import, have imported, sell, offer for sale and have sold Licensed Products for human and animal therapeutics.

- Rockefeller Patent Rights were developed with funding from the U.S. National Institutes of Health. The United States government retains rights in such intellectual property, including, but not limited to, requirements that products, which result from such intellectual property and are sold in the United States, must be substantially manufactured in the United States.

Certain Sublicense Terms (Section 1.5)

- Alnylam will only have the right to grant sublicenses if such sublicense (a) is granted in conjunction with a license or sublicense of Alnylam's rights under proprietary intellectual property that is in addition to the Rockefeller Patent Rights, and (b) is granted in connection with a bona fide collaboration with one or more third parties established by written agreement that is for purposes of research and/or development of products under a jointly prepared research plan.

- Alnylam will prohibit the sublicensee from further sublicensing and require the sublicensee to comply with the terms and conditions of the Tuschl Agreement (other than Alnylam's payment and reporting obligations).

- Within thirty (30) days after Alnylam enters into a sublicense agreement, Alnylam will deliver to Rockefeller a copy of the sublicense agreement which may be redacted except with respect to terms, including financial terms that re not relevant to Alnylam's obligations under the Tuschl Agreement.

- Upon an Alnylam bankruptcy event, payments due to Alnylam from its Affiliates or sublicensees under the sublicense agreement in the form of milestone payments and royalties on Licensed Products will, upon notice from Rockefeller to such Affiliate or sublicensee, become payable directly to Rockefeller for the account of Alnylam. Upon receipt of such funds, Rockefeller will remit to Alnylam the amount by which such payments exceed the amounts owed by Alnylam to Rockefeller.

- Alnylam is primarily liable to Rockefeller for any act or omission of a sublicensee that would be a breach of the Stoffel Agreement if performed or omitted by Alnylam, and Alnylam will be deemed to be in breach of the Stoffel Agreement as a result of such act or omission.

Diligence (Section 2)

- Alnylam must provide Rockefeller within 30 days of the third and each subsequent anniversary of the Effective Date with written progress reports discussing the development, evaluation, testing and commercialization of all Licensed Products.

Payment Obligations (Sections 3 and 4)

- The following milestones are payable for each Licensed Product against an individual Gene Target:

Receipt of IND approval.	$[***]
Dosing of first patient in Phase II Clinical Trials.	$[***]
Dosing of first patient in Phase III Clinical Trials.	$[***]
Receipt of NDA approval.	$[***]

- A [***]% royalty is payable to Rockefeller on Net Sales of Licensed Products by Alnylam, its Affiliates and its sublicensees (no offsets).

- If Rockefeller grants a license under the Rockefeller Patent Rights to any third party, which will permit such third party to manufacture or sell for any use within the scope of the license at a lower royalty rate than that provided in the Tuschl Agreement, Rockefeller will promptly notify Alnylam of such license, including all material terms and conditions of such license, and offer to Alnylam the lower royalty rates and all of the material terms and conditions of such license. If Alnylam accepts such terms in writing, the royalty rate and all material terms and conditions of such notice shall thereafter apply to Alnylam and the parties will promptly execute an amendment to the Tuschl Agreement reflecting such terms and conditions.

- Alnylam must pay Rockefeller a one-time fee of $[***] within 30 days after granting a sublicense to a permitted sublicensee.

- Payments are due to Rockefeller within 60 days after the end of the quarter in which the royalties or fees accrue.

Books and Records (Sections 4.3 and 4.4)

- Sub-licensees are required to keep complete and accurate books and records to verify Sales, Net Sales, and all of the royalties, fees, and other payments payable under the Tuschl Agreement. The records for each quarter will be maintained for at least 3 years after submission of the applicable report required under the Tuschl Agreement.

- Upon reasonable prior written notice to Alnylam, sublicensees will provide an independent, reputable CPA appointed by Rockefeller and reasonably acceptable to Alnylam with access to all of the books and records required by the Tuschl Agreement to conduct a review or audit of Sales, Net Sales, and all of the royalties, fees, and other payments payable under the Tuschl Agreement. If the audit determines that Alnylam has underpaid any royalty payment by 5% or more, Alnylam will also promptly pay the costs of the review or audit.

Non-Use of Name (Section 5.4)

- Sublicensees may not use the name, logo, seal, trademark, or service mark (including any adaptation of them) of Rockefeller or any Rockefeller school, organization, employee, student or representative, without the prior written consent of Rockefeller.

Termination (Section 6.2)

- Alnylam may terminate for convenience

- Alnylam must promptly inventory all finished product and works-in-product of Licensed Products of its sublicensees. Inventory may be sold off unless Rockefeller terminates for a breach by Alnylam or its sublicensees or Alnylam's bankruptcy.

Prosecution and Enforcement (Section 7)

- Rockefeller controls the preparation, prosecution and maintenance of the Rockefeller Patent Rights and the selection of patent counsel, with input from Alnylam. Alnylam will be copied on, and allowed to comment upon, all substantive issues in the patent prosecution.

- Alnylam shall pay a pro rata share, not to exceed [***]%, for all reasonable out of pocket attorney charges and official fees incident to the preparation, prosecution, and maintenance of such patent applications and patents, not exceeding $[***]/year. If Rockefeller chooses not to prosecute or maintain the patent rights, Alnylam may do so and receive a credit against its royalty obligations in an amount equal to its expenses.

- Alnylam must inform Rockefeller promptly after learning of infringement of the Rockefeller Patent Rights. Alnylam and Rockefeller will consult each other concerning response to infringement. Rockefeller may enforce any infringement of the Rockefeller Patent Rights at Rockefeller's expense and retain the recoveries. If Rockefeller requests Alnylam to join such enforcement litigation and Alnylam elects to do so, the recoveries will be shared between Company and Rockefeller in proportion with their respective shares of the aggregate litigation expenditures. Alnylam has step-in enforcement rights. Alnylam must not settle or compromise any such litigation in a manner that imposes any obligations or restrictions on Rockefeller or grants any rights to the Rockefeller Patent Rights without Rockefeller's prior written permission. Step-in recoveries, after Alnylam's expenses are reimbursed, are treated as Net Sales subject to royalties.

Definitions

"Gene Target" means a genomic microRNA locus, any portion thereof, any RNA transcribed from within or overlapping such locus or portion, and all transcript and allelic variants thereof.

"Licensed Products" means products that are researched, developed, made, made for, used, used for, imported, imported for, sold, sold for or offered for sale by Alnylam or its Affiliates or sublicensees and that either (i) in the absence of this Agreement, would infringe at least one Valid Claim of the Rockefeller Patent Rights, or (ii) use a process or machine covered by a Valid Claim of Rockefeller Patent Rights.

"Net Sales" means with respect to each Licensed Product the gross amount invoiced by Alnylam or its Affiliates or sublicensees on sales or other dispositions of such product to third parties less Qualifying Costs directly attributable to a sale and actually taken and/or identified on the invoice and borne by Company, or its Affiliates or sublicensees. "Qualifying Costs" means: (a) customary discounts in the trade for quantity purchased, prompt payment or wholesalers and distributors; (b) credits, allowances or refunds for claims or returns or retroactive price reductions (including government healthcare programs and similar types of rebates) that do not exceed the original invoice amount; (c) prepaid outbound transportation expenses and transportation insurance premiums; and (d) sales, transfer, excise and use taxes and other fees imposed by a governmental agency. Sales for clinical study purposes or compassionate, named patient or similar use shall not constitute Net Sales

"Rockefeller Patent Rights" means a patent application entitled "Anti Micro-RNA Oligonucleotide Molecules" and related patent family, relating to sequence-specific inhibition of microRNAs (RU 681).

STANFORD (Sarnow/miR-122)

Co-Exclusive License Agreement among The Board of Trustees of the Leland Stanford Junior University, Alnylam Pharmaceuticals, Inc. and Isis Pharmaceuticals, Inc. effective August 31, 2005 (each of Alnylam and Isis, a "Licensee") ("Sarnow/miR-122")

Brief Summary of Technology Covered by License:

- Co-exclusive license to use of mir-122 to reduce HCV replication (Stanford Docket S04-097); research done in Sarnow lab supported by NIAID.

Scope of License (Section 3):

- Stanford grants to each of the Licensees a co-exclusive, worldwide right and license under the Licensed Patents in the Exclusive Licensed Field of Use to develop, make, have made, use, have used, import, offer to sell, and sell Licensed Products in the Licensed Territory.

- Stanford grants to each of Licensees a non-exclusive, worldwide right and license under the Licensed Patent in the Non-Exclusive Licensed Field of Use to develop, make, have made, use, have used, import, offer to sell and sell Licensed Products in the Licensed Territory.

- Stanford retains the right, on behalf of itself and all other non-profit academic research institutions, to practice the Licensed Patents for any non-profit purpose, including sponsored research and collaborations. Licensee agrees that, notwithstanding any other provision of this Agreement, it has no right to enforce the Licensed Patents against any such institution. Stanford and any such other institution have the right to publish any information included in the Licensed Patents. If Stanford alters its requirements for license agreements with respect to the subjects addressed in this Section, or enters into a license agreement with terms more favorable to a licensee than those set forth in this Section, Stanford agrees to negotiate in good faith with the Licensees to amend the terms of this Section based upon the reasonable written request of either Licensee.

- The Bayh-Dole Act, including U.S. manufacturing obligations, applies.

Sublicensing Rights (Section 4):

- Each Licensee may grant sublicenses in connection with (Section 4.1):

- a bona fide collaboration with one or more third parties established by written agreement (i) for purposes of research and/or development of products under a jointly prepared research plan; and (ii) which includes a license or sublicense of such Licensee's rights under related intellectual property covering proprietary know-how or patent rights in addition to a sublicense to the Licensed Patents; and/or

- provision of services to such Licensee, including without limitation contract manufacturing, and other services relating to development and commercialization of Licensed Products.

- If both of Licensees or their sublicensees are unable or unwilling to serve or develop a potential market or market territory for which there is a company willing to be a sublicensee, Stanford may request the Licensees to negotiate in good faith a sublicense under the Licensed Patents.

- Any sublicense:

- will prohibit any grant of a further sublicense by a sublicensee;

- will expressly include the provisions of Articles 8 (Royalty Reports, Payments, and Accounting), 9 (Exclusions and Negations of Warranties) and 10 (Indemnity) for the benefit of Stanford;

- will require the assumption of all obligations, including the payment of royalties specified in the sublicense, to Stanford or its designee, if this Agreement is terminated; and

- is subject to this Agreement.

- Each Licensee will submit to Stanford a copy of each sublicense after it becomes effective, which copy may be redacted except as to matters directly pertinent to such Licensee's obligations under this Agreement.

- If either Licensee grants a sublicense pursuant to Section 4.1(A), and receives an upfront payment in connection therewith, the following amounts, if applicable, will be due to Stanford from such Licensee within 60 days of the full execution of the agreement establishing such collaboration:

- (A) if such agreement includes an upfront payment equal to or less than $[***], a payment will be due to Stanford in the amount of $[***];

- (B) if such agreement includes an upfront payment greater than $[***] and equal to or less than $[***], a payment will be due to Stanford in the amount of $[***];

- (C) if such agreement includes an upfront payment greater than $[***], a payment will be due to Stanford in the amount of $[***].

- If Licensees jointly enter into a bona fide collaboration with a third party, the relevant upfront payment shall be due only once for such collaboration. Any amounts representing the reimbursement of costs previously incurred by a Licensee, including fully burdened personnel costs and patent expenses, will not be included in determining the amount of any up front payment.

- If Licensee pays all royalties due Stanford from a sublicensee's Net Sales, Licensee may grant that sublicensee a royalty-free or non-cash sublicense or cross-license.

Diligence:

- Each Licensee will use commercially reasonable efforts to (a) develop, manufacture, and sell Licensed Products and develop markets for Licensed Products; and (b) meet the milestones shown in its respective Appendix (see below). If a Licensee does not meet a milestone in its Appendix by its corresponding date, it will have 30 days to submit to Stanford a specific written plan designed to meet its obligations under this Section as promptly as

possible using commercially reasonable efforts. Each plan shall be subject to Stanford's written approval, which will not be unreasonably withheld. Such Licensee will have 3 months to demonstrate to Stanford's reasonable satisfaction its compliance with such plan.

- (Appendices) Each Licensee will be solely responsible for meeting the following diligence milestones in its development programs:

- By the end of the year 2006, such Licensee will commence optimization of miRNA inhibitors.

- By the end of the year 2007, such Licensee will select the method of delivery for such miRNA inhibitors.

- By the end of the year 2008, such Licensee (i) optimize a lead miRNA inhibitor and (ii) propose additional clinical milestones to Stanford.

- By the end of the year 2010, such Licensee will complete preclinical development

- If Alnylam and Isis are jointly developing a given Licensed Product, both will be deemed in compliance with their respective diligence obligations if either of Alnylam and Isis is fulfilling such obligations.

- By March 1 of each year, each Licensee will submit a written annual report to Stanford covering the preceding calendar year.

Payment Obligations (Section 7):

- The following annual maintenance fees are due under this Agreement:

- (A) $[***] on the first 4 anniversaries of the Effective Date;

- (B) $[***] on the 5th through 8th anniversaries of the Effective Date; and

- (C) $[***] on the 9th anniversary of the Effective Date and each anniversary thereafter.

Unless instructed otherwise by Licensees, Stanford will send invoices for one half of the above amounts to each Licensee.

- (Section 7.3)The following milestones are payable for each Licensee for the first Licensed Product in the Exclusive Field of Use:

IND acceptance in U.S. or first dosing of a subject outside the U.S.	$[***]
Dosing of first subject in first Phase III Clinical Trial	$[***]
NDA approval in U.S. or a foreign equivalent	$[***]

-

-

- Milestones payable with respect to the first Licensed Product of each Licensee in the Non-Exclusive Field of Use are [***]%) of those above..

- Milestones payable with respect to the second Licensed Product (i.e. a new molecular entity) of each Licensee in the Non-Exclusive Field of Use are [***]%) of those in the first chart above.

- For clarity, if Alnylam achieves any of the above milestone events, it does not relieve Isis of the obligation to pay similar milestones when Isis, or its sublicensee achieves the same milestone events; provided, however, that if Alnylam and Isis are jointly developing a given Licensed Product, payments are due only once in respect of the achievement of a milestone event for such Licensed Product.

- (Section 7.4) Each Licensee will pay Stanford earned royalties on Net Sales of [***]% of Net Sales of such Licensee's Licensed Product. If a Licensee becomes obligated to pay royalties to any third parties in connection with the sale of a Licensed Product, the royalties due to Stanford from such Licensee under this Section for such Licensed Product will be reduced in connection with amounts paid to such third parties as follows: for every [***]% of Net Sales which is paid to such third parties (in the aggregate) in a given calendar year, the royalty rate due to Stanford will be reduced by [***]%. In no event, however, will the royalty payable to Stanford by such Licensee be reduced below a floor of [***]%. If the Licensees are jointly developing and/or commercializing a Licensed Product, the royalty set forth above shall be due only once with respect to such Licensed Product.

- Royalty payments due to Stanford under Section 7.4 above in a particular year will be reduced by the license maintenance fee paid by such Licensee and applicable to such year.

Non-Use of Names (Section 12.2):

- The Licensees will not identify Stanford in any promotional statement, or otherwise use the name of any Stanford faculty member, employee, or student, or any trademark, service mark, trade name, or symbol of Stanford or its affiliated hospitals and clinics, including the Stanford name, unless Stanford has given its prior written consent or as required by law, rule or regulation. Permission may be withheld at Stanford's sole discretion.

Prosecution and Enforcement (Section 13):

- Subject to Stanford's approval, Isis will coordinate and be responsible for preparing, filing, prosecuting and maintaining the Licensed Patents in Stanford's name. The parties shall

work together to develop a prosecution strategy and decide in which countries the Licensed Patents will be filed.

- Isis will

- (i) keep Stanford and Alnylam informed as to the filing, prosecution, maintenance and abandonment, as applicable, of the Licensed Patents;

- (ii) furnish Stanford and Alnylam copies of documents relevant to any such filing, prosecution maintenance and abandonment, as applicable;

- (iii) allow Stanford and Alnylam reasonable opportunity to timely comment on documents to be filed with any patent office which would affect the Licensed Patents;

- (iv) give good faith consideration to the comments and advice of Stanford and Alnylam; provided however that Stanford will have the opportunity to provide Isis with final approval on how to proceed in any response or taking any such action; and

- (v) provide copies of any official written communications relating to the Licensed Patents to Stanford and Alnylam within 10 days of Isis receiving such communication and Stanford and Alnylam will provide any applicable comments to Isis no later than 5 days prior to the first deadline (without extensions) to file a response or take any action relating to such communication.

- Isis may use counsel of its choice, which must be acceptable to Stanford and Alnylam, for the filing, prosecution and maintenance of the Licensed Patents and the Licensees shall be billed directly by such counsel.

- A Licensee or the Licensees will reimburse Stanford the following costs:

- all Stanford's reasonable and actual out-of-pocket patenting expenses incurred after the Effective Date related to the Licensed Patents.

- If one and only one Licensee decides to abandon ongoing prosecution and/or maintenance of any of the Licensed Patents, on a country-by-country and Licensed Patent-by-Licensed Patent basis, the continuing Licensee will pay 100% of the ongoing expenses for such Licensed Patent. Stanford shall have the right to continue payment for such Licensed Patent in its own discretion and at its own expense if both Licensees decide to abandon ongoing prosecution and/or maintenance of the Licensed Patents. If Stanford decides to maintain such Licensed Patent, the license with respect to such Licensed Patent in such country under this Agreement shall terminate with respect to the ceasing Licensee(s). Cessation of payment by one Licensee as to a Licensed Patent will not affect the rights of the other Licensee with respect to such Licensed Patent. If Isis is the Licensee wishing to cease payment of a Licensed Patent, the responsibility for the prosecution of such Licensed Patent will transfer to Stanford.

- Each Licensee may assign its rights and obligations under Sections 13.1 and 13.2 to a sublicensee, subject to prior notification to and approval from Stanford.

- Stanford has the first right to institute action against a third party infringer which will be executed (if at all) within 90 days after Stanford first becomes aware of the infringing activity, and may name one or both Licensees as a party for standing purposes. Each Licensee may elect to jointly prosecute the action (with Stanford) by providing written notice within 30 days after the date of the notice from Stanford. If both Licensees elect not to jointly prosecute, Stanford may pursue the suit, at its sole cost (including costs of litigation) and in such event will be entitled to retain the entire amount of any recovery or settlement that is in excess of the parties' costs; if one or both Licensees elect to jointly prosecute, Stanford and the jointly prosecuting Licensees will proceed in accordance with the Joint Suit provisions. If a Licensee elects not to join a suit, that Licensee will discuss in good faith with Stanford the assignment of rights, causes of action, and damages necessary for Stanford to prosecute the alleged infringement.

- Joint Suit. If Stanford and either or both Licensees are jointly prosecuting an action against a third party infringer, they will share the out-of-pocket costs and any recovery or settlement equally; and agree how they will exercise control over the action.

- (Sections 13.6 and 13.7) If Stanford elects not to participate in a suit, either or both Licensee(s) may institute and prosecute a suit so long as it conforms with the requirements of this Section. The Licensee(s) will reach agreement on the institution and prosecution of such suit and the sharing of such costs among themselves and will diligently pursue the suit and the Licensee(s) instituting the suit will bear the entire cost (including necessary expenses incurred by Stanford) of the litigation. The Licensee(s) will keep Stanford reasonably apprised of all developments in the suit, and will seek Stanford's input and approval on any substantive submissions or positions taken in the litigation regarding the scope, validity and enforceability of the Licensed Patents. The Licensee(s) will not prosecute, settle or otherwise compromise any such suit in a manner that adversely affects Stanford's interests without Stanford's prior written consent. If either or both Licensees sue under Section 13.6, then any recovery in excess of any unrecovered litigation costs and fees will be shared with Stanford as follows:

- Any recovery for past sales by the infringer of products, which, if sold by a Licensee, would be Licensed Products will be deemed Net Sales for purposes of this Agreement, and such Licensees will pay Stanford royalties;

- Licensee and Stanford will negotiate in good faith appropriate compensation to Stanford for any non-cash settlement, non-cash cross-license or payment for the right to make future sales.

Term and Termination (Section 14, 18.1):

- Any termination shall only terminate this Agreement between Stanford and the affected Licensee, and it shall remain in full force and effect between Stanford and the non-affected Licensee.

- Each Licensee may terminate its rights and obligations under this Agreement by giving Stanford at least 30 days written notice.

- A breach by one Licensee of its obligations to Stanford under this Agreement may not be used as a basis for termination of this Agreement by the non-breaching Licensee, nor may a breach of any obligation arising between the Licensees under this Agreement be used as a basis for termination by one Licensee.

Assignment (Section 15):

- Each Licensee may assign this Agreement as part of a sale, regardless of whether such a sale occurs through an asset sale, stock sale, merger or other combination, or any other transfer of such Licensee's entire business, or that part of the Licensee's business to which this Agreement relates.

Definitions:

"Exclusive Licensed Field of Use" means the research, development, commercialization and monitoring of therapeutics for the treatment and prevention of Hepatitis C and directly related conditions and diseases (including without limitation chronic hepatitis, cirrhosis and primary liver cancer). The Exclusive Field of Use specifically excludes:

(A) diagnostics; and

(B) commercialization of reagents.

"Licensed Patents" means Stanford's U.S. Provisional Patent Application, Serial Number [***], and the related patent family. "Licensed Patent" excludes any continuation-in-part (CIP) patent application or patent unless the subject matter of such CIP patent application is specifically described or claimed in another Licensed Patent and is filed within three (3) years of the Effective Date. Licensed Patents exclude any claims relating to new matter that is invented by Stanford after the Effective Date.

"Licensed Product" means a product in either the Exclusive Licensed Field of Use or the Non-Exclusive Licensed Field of Use the making, using, importing or selling of which, absent this license, infringes a Valid Claim of a Licensed Patent.

"Non-Exclusive Licensed Field of Use" means the research, development, commercialization and monitoring of therapeutics for the treatment and prevention of all conditions or diseases other than Hepatitis C and directly related conditions or diseases.

GARCHING (Co-Exclusive)

License Agreement among Garching Innovation GmbH ("GI"), Alnylam Pharmaceuticals, Inc. and Isis Pharmaceuticals, Inc. effective October 18, 2004

Brief Summary of Technology Covered by License:

- The Max Planck Society granted co-exclusive rights Alnylam and Isis to patent applications (known as "Tuschl III") based on the microRNA work of Dr. Thomas Tuschl. These microRNAs have the potential to be new drug targets or therapeutic products and are the subjects of the licensed patent applications.

Scope of License (Section 2.1):

- GI hereby grants to each Alnylam and ISIS and their Affiliates a royalty-bearing co-exclusive worldwide license, with the right to grant sublicenses, under the Patent Rights to develop, make, have made, use, sell and import Licensed Products in the Field.

- MPG retains the right to practice under the Patent Rights for non-commercial scientific research, teaching, education, non-commercial collaboration (including industry-sponsored scientific collaborations) and publication purposes.

- Alnylam and ISIS acknowledge that the German government retains a royalty-free, non-exclusive, non-transferable license to practice any government-funded invention claimed in any Patent Rights for government purposes.

Sublicensing (Section 2.2):

- Alnylam and ISIS may each grant sublicenses to the rights granted to them under Section 2.1 to Third Parties, however only (i) as Naked Sublicenses, (ii) in connection with a Drug Discovery Collaboration or Development Collaboration, or (iii) to a Sales Partner.

- Each Naked Sublicense shall be subject to the prior written approval of GI, which shall not unreasonably be withheld. Alnylam or ISIS, as applicable, shall inform GI in writing at least 30 days prior to the intended signature of any such sublicense agreement in sufficient detail (in particular regarding financial terms and other relevant information) to permit GI to decide whether or not to approve. Any requested approval is deemed to be granted if GI does not refuse the approval in writing within 30 days after receiving the necessary information; in particular, GI may withhold its approval if GI deems the received information not sufficient.

- Each sublicense granted under this Agreement shall be subject and subordinate to, and consistent with, the terms and conditions of this Agreement. Alnylam or ISIS, as applicable, shall be liable that any subsequent sublicenses granted by the Sublicensees are subject and subordinate to, and consistent with, the terms and conditions of this Agreement. In the event of a material default by any sublicensee under an Isis or Alnylam sublicense, the applicable party will inform GI and take commercially reasonable efforts to cause the sublicensee to cure the default or will terminate the sublicense. (Section 4.6)

- Within 30 days after the signature of each sublicense granted under this Agreement, Alnylam or ISIS, as applicable, shall provide GI with a reasonably redacted copy of the signed sublicense agreement.

Diligence (Section 4):

- Alnylam and ISIS shall each use commercially reasonable efforts, and shall oblige their Affiliates and Sublicensees to use commercially reasonable efforts, to develop and commercialize their respective Licensed Products.

- Semi-annual progress reports. ALNYLAM and ISIS shall each furnish, and require their Affiliates to furnish to ALNYLAM and ISIS, to GI in writing, semi-annually, within 60 days after the end of each calendar half year, with a report, stating in reasonable detail the activities and the progress of their efforts (including the efforts of their Sublicensees) during the immediately preceding half year to develop and commercialize their respective Licensed Products, on a product-by-product and country-by-country basis. The report shall also contain a discussion of intended development and commercialisation efforts for the calendar half year in which the report is submitted.

Financial Obligations (Section 5):

- Alnylam and ISIS shall each pay to GI the following milestone payments for each of their respective Licensed Products (including Licensed Products of their Affiliates and Sublicensees) within 30 days:

Milestone Event	**Milestone Payment**
First Initiation of Phase I Clinical Study	$[***]
First Initiation of Phase II Clinical Study	$[***]
First Initiation of Phase III Clinical Study	$[***]
Regulatory Approval in USA, Japan or Europe	$[***]

Each of the above milestone payment is due from the Party that is engaged in the development and commercialization of such Licensed Product. For each Licensed Product, milestone payments will only be due the first time such Licensed Product achieves such milestone. A Licensed Product will be considered the same Licensed Product as long as it has not been modified in such a way (unless as the result of stabilizing, formulation or delivery technology) that would require the filing of a different IND for such Licensed Product.

- Royalties (Section 5.3):

- Alnylam and ISIS shall each pay to GI for each of their respective Licensed Products (including Licensed Products of their Affiliates and Sublicensees) covered by Valid Claims the following running royalties on the incremental portion of annual Net Sales:

- Less than or equal to $[***] US Dollars [***]%

- Between $[***] US Dollars and $[***] US Dollars [***]%

- Between $[***] US Dollars and $[***] US Dollars [***]%

- Greater than $[***] US Dollars [***]%

- Alnylam and ISIS shall each pay to GI for each of their respective Licensed Products (including Licensed Products of their Affiliates and Sublicensees) covered by Pending Claims [***]% of running royalties above

- If Alnylam or ISIS, or any of their Affiliates or Sublicensees, licenses any patents or patent applications Controlled by a Third Party in order to make, use, or sell a Licensed Product (explicitly excluding, without limitation, any Third Party patents and patent applications covering any formulation, stabilization, or delivery technology, or any target for a Licensed Product) the running royalties set forth in Sec. 5.3 will be reduced, on a country-by-country and product-by-product basis, from the date running royalties have to be actually paid to such Third Party, by [***]% of any running royalty owed to a Third Party for the manufacture, use or sale of a Licensed Product, provided however that the running royalties due to GI will not be reduced to less than [***]%.

- The running royalties stated in Section 5.3 shall in no event be reduced by the application of this Section 5.4 to less than a minimum royalty rate of (i) [***]% for Licensed Products covered by Valid Claims, and (ii) [***]% for Licensed Products covered by Pending Claims.

- In no event shall the total cumulative running royalty burden of Alnylam or Isis for a Licensed Product arising out of this Agreement and any Existing GI Licenses, calculated on a product-by-product and country-by-country basis, exceed [***]% for such a Licensed Product.

- Sublicense Revenues (Section 5.5):

- Subject to Section 5.5(d), in the event that Alnylam or ISIS grant a Naked Sublicense to a Third Party pursuant to Section 2.2 (a), Alnylam or ISIS, as applicable, shall pay to GI [***]% of their respective Sublicense Consideration received, due within 30 days after receipt.

- Subject to Section 5.5(d), in the event that Alnylam or ISIS grant a sublicense to a Third Party pursuant to Section 2.2 (a) in connection with a Drug Discovery Collaboration or Development Collaboration, Alnylam or ISIS, as applicable, shall pay to GI the following percentages of their respective Sublicense Consideration received, due within 30 days after receipt:

- Sublicense granted Percentage due to GI

- Up to, but not including, filing of an IND: [***]%
- After filing of an IND [***]%
- After initiation of Phase II Clinical Study [***]%
- After initiation of Phase III Clinical Study [***]%
- After filing of a NDA [***]%

- If Alnylam or ISIS receives any non-cash Sublicense Consideration, Alnylam or ISIS, as applicable, shall pay GI, at GI's election, either (i) a cash payment equal to the fair market value of the Sublicense Consideration, or (ii) the in-kind portion, if practicable, of the Sublicense Consideration.

- (Section 5.5(d)) If Alnylam or ISIS grant a sublicense that includes, in addition to the Patent Rights, patents or patent applications Controlled by Alnylam or ISIS, the percentage of the Sublicense Consideration due to GI shall be based on the value reasonably attributable to the Patent Rights relative to the value of the patents or patent applications Controlled by Alnylam or ISIS included in such sublicense (such relative value of the Patent Rights hereinafter the "Patent Rights Value").

- Together with the copy of any sublicense agreement to be provided to GI according to Sec. 2.2, Alnylam or ISIS, as applicable, shall suggest to GI the Patent Rights Value based on a good faith fair market value determination, together with any information reasonably necessary or useful for GI to evaluate such suggestion.

- If a "fair market value" has to be determined, the Party obliged to suggest such fair market value shall provide the other Party in due time with a good faith determination of the fair market value, together with any information necessary or useful to support such determination. The other Party shall have the right to provide the suggesting Party in due time with a counter-determination of the fair market value, which shall include any information necessary or useful to support such counter-determination.

Prosecution and Enforcement (Section 6):

- GI shall, in its sole discretion, apply for, seek issuance of, maintain, or abandon the Patent Rights during the Term.

- Alnylam, ISIS and GI shall cooperate, if necessary and appropriate, with each other in gaining patent term extension wherever applicable to the Patent Rights, and shall use reasonable efforts to agree upon a joint strategy relating to patent term extensions.

- Alnylam and ISIS shall together pay to GI [***]%, and each of Alnylam and ISIS shall pay [***]% of such [***]% share, of all fees and costs, including attorneys fees, relating to the filing, prosecution, maintenance and extension of the Patent Rights, which incur during the Term.

- If Alnylam or ISIS wish to cease payment for any of the Patent Rights, GI shall have the right to continue payment for such Patent Rights in its own discretion and at its own expense; such Patent Rights shall no longer be covered by this Agreement with respect to the ceasing party from the date Alnylam or ISIS informs GI of its cessation of payments.

- Enforcement (Section 6.3):

- Alnylam and ISIS shall each promptly inform GI in writing if they become aware of any suspected or actual infringement of the Patent Rights by any Third Party, and of any available evidence thereof.

- Subject to the right of each Alnylam and ISIS to join in the prosecution of infringements set forth below, GI shall have the right, but not the obligation, to prosecute (whether judicial or extrajudicial) in its own discretion and at its own expense, all infringements of the Patent Rights. The total costs of any such sole infringement action shall be borne by GI, and GI shall keep any recovery or damages (whether by way of settlement or otherwise) derived therefrom. In any such infringement suits, Alnylam and ISIS shall each, at GI's expense, cooperate with GI in all respects.

- Alnylam and ISIS shall each have the right at their sole discretion to join GI's prosecution of any infringements of the Patent Rights. GI and the joining Party(ies) will agree in good faith on the sharing of the total cost of any such joint infringement action and the sharing of any recovery or damages derived therefrom.

- If GI decides not to prosecute infringements of the Patent Rights, neither solely nor jointly with Alnylam or ISIS, GI shall offer to Alnylam and ISIS to prosecute (whether jointly by Alnylam and ISIS or solely by one of them) any such infringement in their own discretion and at their own expense. GI shall, at the expense of the prosecuting Party(ies), cooperate. The total cost of any such sole infringement action shall be borne by the prosecuting Party(ies), and the prosecuting Party(ies) shall keep any recovery or damages derived therefrom.

- If a Party prosecuting infringements intends to settle the infringement (such as granting a license or entering a settlement agreement), any such arrangement needs the prior written approval of the other Parties, which shall not unreasonably be withheld. Any sublicense granted by Alnylam or ISIS to a Third Party infringer shall be regarded and treated as a Naked Sublicense under this Agreement.

Term and Termination (Section 9):

- Alnylam and ISIS shall each have the right to terminate this Agreement, for any reason, upon at least 3 months prior written notice to GI. Termination of this Agreement by either Isis or Alnylam shall not be deemed to be termination by the other.

- If at least 50% of issued and outstanding shares of Alnylam or ISIS are assigned or transferred to a Third Party, Alnylam or ISIS, as applicable, shall provide GI, upon GI's request, with written reports in reasonable detail on the actual and intended future activities of Alnylam or ISIS, as applicable, to develop and commercialize Licensed Products. If the reports are not provided to GI in due time and/or in sufficient detail, after 60 days written notice from GI, such failure will be a material breach, and GI shall have the right to terminate this Agreement with respect to such breaching party in accordance with the procedures set forth in Section 9.6. Alnylam or ISIS, as applicable, shall inform GI promptly of the implementation of any such assignment or transfer.

- GI shall have the right to terminate this Agreement upon 30 days prior written notice to Alnylam or ISIS, if Alnylam or ISIS, as applicable, or any of their Affiliates, attack, or have attacked or support an attack through a Third Party, the validity of any of the Patent Rights.

- If any license granted to Alnylam or ISIS under this Agreement is terminated, any sublicense under such license granted prior to termination of said license shall remain in full

force and effect, provided that (i) the Sublicensee is not then in breach of its sublicense agreement, and (ii) the Sublicensee agrees, in writing within 30 days after the effective date of termination, to be bound to GI as licensor under the terms and conditions of the sublicense agreement, provided that GI shall have no other obligation than to leave the sublicense granted by Alnylam or ISIS in place.

Non-Use of Names (Section 4.5):

- Neither Alnylam nor ISIS, nor their Affiliates or Sublicensees, may use the name of "Max Planck Institute", "Max Planck Society", "Garching Innovation" or any variation, adaptation, or abbreviation thereof, or of any of its trustees, officers, faculty, students, employees, or agents, or any trademark owned by any of the aforementioned, in any promotional material or other public announcement or disclosure without the prior written consent of GI or in the case of an individual, the consent of that individual.

Assignment (Section 10.4):

- Neither this Agreement no any rights or obligations may be assigned or otherwise transferred by Alnylam or ISIS to a Third Party without the prior written consent of GI. Notwithstanding the foregoing, Alnylam and ISIS each may assign this Agreement to a Third Party in connection with the merger, consolidation, or sale of all or substantially all of their assets or that portion of their business to which this Agreement relates; provided, however, that this Agreement shall immediately terminate if the proposed Third Party assignee fails to agree in writing to be bound by the terms and conditions of this Agreement on or before the effective date of assignment. After the effective date of assignment, the Third Party assignee shall provide GI, upon GI's request, with written reports in reasonable detail on the actual and intended future activities of the Third Party assignee to develop and commercialize Licensed Products. If the Third Party assignee does not maintain a program to develop and commercialize Licensed Products that is substantially similar or greater in scope to the program of Alnylam or ISIS after the effective date of assignment, then GI has the right to limit the scope of the co-exclusive license granted under this Agreement to such Licensed Products actually covered by the program of the Third Party assignee.

Definitions:

"Development Collaboration" means a collaboration by Alnylam and/or ISIS with a Third Party whose purpose is the (i) further development and/or commercialization of a Licensed Product discovered by Isis or Alnylam either on their own or as part of a Drug Discovery Collaboration or (ii) further joint development and/or joint commercialization of Licensed Products, in each case, beginning after the initiation of IND-Enabling Tox Studies for such Licensed Products. Collaborations that do not include or involve the licensed Patent Rights shall not constitute Development Collaborations.

"Drug Discovery Collaboration" means a collaboration by Alnylam and/or ISIS with a Third Party whose purpose is the joint discovery, joint development and/or joint optimization of Licensed Products up to, but not including, IND-Enabling Tox Studies for such Licensed Products.

"Existing GI Licenses" means any license agreement between Alnylam and GI in force and effect prior to the Effective Date of this Agreement and relating to patents or patent applications of MPG that also cover the manufacture, use and sale of Licensed Products.

"Field" means use of Licensed Products

(i) for each Party's internal and collaborative research use, and

(ii) for all therapeutic and prophylactic uses in human diseases,

specifically excluding any commercial provision of Licensed Products as research reagents for research purposes, and any diagnostic use.

"Licensed Products" means any product, or part thereof, the manufacture, use or sale of which, absent the license granted hereunder, would infringe one or more Pending Claims or one or more Valid Claims of the Patent Rights.

"Naked Sublicenses" means any sublicense to the Patent Rights granted by Alnylam and/or ISIS to a Third Party that is not a license in connection with a Drug Discovery Collaboration, Development Collaboration or Sales Partner agreement. Licenses that do not include or involve rights to the Patents Rights shall not constitute Naked Sublicenses.

"Patent Rights" means the patents and applications listed on Exhibit A and the related patent family.

"Sales Partner" means any legal entity that is granted a sublicense to the Patent Rights by Alnylam, ISIS, their Affiliates or Sublicensees solely to market, promote, distribute or sell, or otherwise dispose of, Licensed Products in finished form.

"Sublicense Consideration" means any consideration, whether in cash (e.g. initial or upfront payments, technology access fees, annual fixed payments) or in kind (e.g. devices, services, use rights, equity), received by Alnylam or ISIS and their Affiliates from Sublicensees as consideration for the sublicense granted. Sublicense Consideration specifically excludes (i) any milestone payments relating to the achievement of certain clinical events, (ii) any running royalties on sales of products, (iii) payments specifically committed to reimburse Alnylam or ISIS for the fully-burdened cost of research and development, (iv) payments made by the Sublicensee in consideration of equity (shares, options, warrants or any other kind of securities) of Alnylam or ISIS at fair market value, and (iv) equity (shares, options, warrants or any other kind of securities) of the Sublicensee purchased by Alnylam or ISIS at fair market value.

MIT

Amended and Restated Exclusive Patent License Agreement between Massachusetts Institute of Technology ("MIT") and Alnylam, dated May 9, 2007 ("MIT Agreement")

Brief Summary of Technology Covered by License:

- M.I.T. granted Alnylam exclusive rights to develop and commercialize for human RNAi therapeutics certain technology relating to novel lipid compositions that are potential components of cationic liposomal formulations for cellular delivery of oligonucleotides. The technology was developed in the laboratory of Professor Robert Langer.

Limitations on Scope of License (Sections 2.1, 2.3 and 2.5)

- The license granted to Alnylam is limited to a exclusive (for the Exclusive Period), worldwide license under the Patent Rights to develop, make, have made, use and import Library Products and Licensed Processes to develop, make, have made, use, sell, offer to sell, lease, and import Licensed Products in the Field and to develop and perform Licensed Processes in the Field.

- Alnylam does not have the right to sell or offer for sale the Library Products separately from a sale or offer for sale of a Licensed Product.

- MIT retains the right to practice under the Patent Rights for research, teaching, and educational purposes. The U.S. federal government retains a royalty-free, non-exclusive, non-transferable license to practice any government-funded invention claimed in any Patent Rights as set forth in 35 USC 201-211, and the regulations promulgated thereunder, including the requirement that Library Products, whether or not part of Licensed Products, used or sold in the U.S. must be manufactured substantially in the U.S.

- The Patent Rights may not be asserted against non-for-profit research institutions that practice the Patent Rights for research funded by (i) the institutions themselves, (ii) not-for profit foundations, or (iii) any federal, state or municipal government. Alnylam may assert the Patent Rights against not-for-profit research institutions only if the infringement activity of the not-for-profit research institution was performed in the fulfillment of research sponsored by a for-profit entity and the assertion of infringement must be limited to those specific activities.

Restrictions on Sublicensing by Alnylam (Sections 2.1 and 2.3)

- Alnylam may grant sublicenses under commercially reasonable terms and conditions only during the Exclusive Period. Any sublicenses by Alnylam may extend past the expiration date of the Exclusive Period, but any exclusivity of such sublicense will expire upon the expiration of the Exclusive Period.

- The sublicense must incorporate terms and conditions sufficient to enable Alnylam and its Affiliates to comply with the MIT Agreement. Such sublicenses will also include provisions to provide that if Sublicensee brings a Patent Challenge against MIT (except as required under a court order or subpoena), Alnylam may terminate the sublicense.

- Upon termination of the MIT Agreement, any Sublicensee not then in default will have the right to seek a license from MIT, and MIT agrees to negotiate such licenses in good faith under reasonable terms and conditions.

- Alnylam may permit third parties (i) to use Library Products and Licensed Processes for the purpose of research with academic or nonprofit institutions and contract research, including for the conduct of clinical trials of a Licensed Product, and (ii) to sell Licensed Products under an agency, consignment or equivalent arrangement, wherein such rights are not sublicense rights.

- Alnylam will promptly furnish MIT with a fully signed photocopy of any sublicense agreement, which copy may be redacted except with respect to terms directly relevant to Alnylam's obligations under the MIT Agreement.

Diligence and Reporting (Sections 3.1 and 3.2)

- Sublicensees are required to use diligent efforts to develop Library Products and Licensed Products and to introduce Licensed Products into the commercial market; thereafter Sublicensees are required to make Licensed Products reasonably available to the public. Specifically, the following obligations must be fulfilled:

- Written reports are due within [***] days after the end of each calendar year on the progress of efforts during the immediately preceding calendar year to develop and commercialize Licensed Products. Such reports will include the number of [***], a description of [***], and the [***]that have been tested. The report will also contain a discussion of intended efforts and sales projections for the year in which the report is submitted.

- Funding for research at MIT pursuant to the Budget set forth in Attachment C of the Research Agreement.

- By [***], Library Products will be evaluated for use in [***].

- Prior to [***], at least [***] will be advanced to [***] studies in support of [***] for [***] studies.

- Filing of [***] for Licensed Product [***]by [***].

- Commencement of [***] trial for a Licensed Product within [***] years of IND filing for such Licensed Product.

- First Commercial Sale of a Licensed Product within [***] for each such Licensed Product.

- If any Sublicensee is determined to have failed to fulfill any obligation under Sections 3.1(a) and 3.1(c) - (g) above, MIT may treat such failure as a material breach, subject to any changes to such diligence requirements as may be mutually-agreed by the parties below.

• If Alnylam anticipates a failure to meet an obligation set forth in Section 3.1(c), (d), (e), (f) or (g) above will occur, Alnylam will promptly advise MIT, and representatives of each party

will meet to review the reasons for anticipated failure. Alnylam and MIT will enter into a written amendment to the MIT Agreement with respect to any mutually agreed upon change(s) to the relevant obligation. If, after good faith discussion, Alnylam and MIT are unable to agree upon an amendment to the obligation, Alnylam, at its discretion, may elect to extend the due date to meet the obligation for such diligence obligation by one year by providing written notice to MIT along with payment in the amount of $[***]. Alnylam may extend the due date of each diligence obligation set forth in Section 3.1(c), (d), (e), (f) or (g) of the MIT Agreement only once during the term.

Financial Obligations (Section 4.1)
License Maintenance Fees:

• Alnylam will pay MIT the following license maintenance fees on the dates set forth below:

Each January 1st for 2008 and 2009	$[***]
Each January 1st for 2010 and 2011	$[***]
Each January 1st for 2012 and 2013	$[***]
Each January 1st for 2014 and 2015	$[***]
Each January 1st of every year thereafter	$[***]

• The annual license maintenance fee is nonrefundable, but may be credited to running royalties subsequently due on Net Sales earned during the same calendar year, if any. License maintenance fees paid in excess of running royalties due in such calendar year will not be creditable to amounts due for future years.

Royalty Payments:
• Running royalties of [***]% of Net Sales of Licensed Products and Licensed Processes are due within [***] days of the end of each calendar quarter.

• If Alnylam or an Affiliate is legally required to pay royalties to one or more third parties in order to obtain a license or similar right necessary to practice the Patent Rights, Alnylam will be entitled to credit up to [***]% of the amounts payable to such third parties against the royalties due to MIT for the same reporting period; provided, however, that (i) in no event will the running royalties due to MIT, when aggregated with any other offsets and credits allowed under the MIT Agreement, be less than [***]% of Net Sales in any reporting period, and (ii) royalties due to third parties with respect to [***] patents (see Appendix B to MIT Agreement) will not qualify for purposes of the foregoing offset against royalties.

Milestone Payments:
• Alnylam will pay MIT the amounts set forth below upon achievement by Alnylam or any of its Affiliates or Sublicensees of certain milestone events as set forth below. Payments will be due in respect of the achievement of such milestone events for each first Licensed Product containing an miRNA Therapeutic(s) and/or an siRNA Therapeutic(s) towards a specific Target or a specific combination of Targets; provided, however, that if in the course of development a given Licensed Product is discontinued and replaced with a different Licensed Product for the same therapeutic indication containing an miRNA Therapeutic(s) and/or an siRNA Therapeutic(s) towards at least one Target that was also a Target of the discontinued Licensed

Product, milestone payments already paid for the discontinued Licensed Product will not be due for achievement of the same milestone event(s) by the substituted Licensed Product.

Milestone Event	Payment
Filing of an Investigational New Drug Application (or equivalent)	$[***]
Dosing of first patient in a Phase 2 clinical trial (or equivalent)	$[***]
Dosing of first patient in a Phase 3 clinical trial (or equivalent)	$[***]
First Commercial Sale	$[***]

• In the event of an assignment as described in Article 10 of the MIT Agreement, the milestone payments set forth above that have not yet come due, will instead be replaced with the milestone events and payments set forth below.

Milestone Event	Payment
Filing of Investigational New Drug Application (or equivalent)	$[***]
Dosing of first patient in a Phase 2 clinical trial (or equivalent)	$[***]
Dosing of first patient in a Phase 3 clinical trial (or equivalent)	$[***]
First Commercial Sale	$[***]

- The milestone events set forth in the two tables above are intended to be successive. In addition and notwithstanding the foregoing, if any milestone is reached without achieving a preceding milestone, then the amount which would have been payable on achievement of the preceding milestone will be payable upon achievement of the next successive milestone. Alnylam will notify MIT within ten (10) days of the achievement of any of the above milestones by Alnylam or any of its Affiliates or Sublicensees.

Sublicense Income:

- If Alnylam or an Affiliate grants a sublicense of its rights under Section 2.1 of the MIT Agreement, Alnylam will pay MIT, as applicable:

- [***]% of all Sublicense Income received by Alnylam or Affiliates from Sublicensees which are also receiving rights to substantial technology and/or patent rights owned or controlled by Alnylam or Affiliates related to the development of Licensed Products, whether such Sublicense Income is received under the same agreement as the sublicense to Alnylam's rights under Section 2.1 of the MIT Agreement and/or in a separate agreement. (To the extent that the only other patents and/or technology rights received by Sublicensees are sublicense rights under

the patent rights listed in Appendix B, then any sharing of Sublicense Income will fall under clause (b) below); and

- [***]% of all Sublicense Income received by Alnylam or Affiliates from Sublicensees if such Sublicensees are receiving a sublicense to Alnylam's rights under Section 2.1 of the MIT Agreement alone or with a sublicense to the patent rights listed in Appendix B, without substantial additional technology and/or other patent rights from Alnylam or Affiliates, whether or not in the same agreement, as part of the same business arrangement related to Licensed Products.

- Such amount will be payable for each reporting period and will be due to MIT within [***] days of the end of each reporting period.

Reports (Sections 5.1 and 5.2)

- Prior to First Commercial Sale of a Licensed Product or first commercial performance of a Licensed Process, Alnylam is required to deliver annual reports within [***] days of the end of each calendar year, containing information concerning the immediately preceding year, as further described in Section 5.2 of the MIT Agreement (see below). The date of First Commercial Sale of a Licensed Product or commercial performance of a Licensed Process must be reported to MIT within [***] days of its occurrence.

- After First Commercial Sale of a Licensed Product or commercial performance of a Licensed Process, reports are required to be delivered to MIT within [***] days of the end of each reporting period containing information concerning the immediately preceding reporting period, as further described in Section 5.2 of the MIT Agreement (see below).

- Section 5.2 states that reports must include at least the following information for the immediately preceding reporting period:

- the number of Licensed Products sold, leased, or distributed to independent third parties in each country and, if applicable, the number of [***] used in the provision of services in each country;

- a description of Licensed Processes performed in each country as may be pertinent to a royalty accounting under the MIT Agreement;

- gross price charged in each country and, if applicable, the gross price charged for each Licensed Product used to provide services in each country; and the gross price charged for each Licensed Process performed in each country;

- calculation of Net Sales in each country, including a listing of applicable deductions;

- total royalty payable on Net Sales in U.S. dollars, together with the exchange rate used for conversion;

- the amount of Sublicense Income received by Alnylam and its Affiliates and the amount due to MIT from such sublicense income, including an itemized breakdown of the sources of income comprising the Sublicense Income;

- [***] categorized by rights relating to [***];

- the dates on which milestone events are achieved and the milestone payments due; and

- [***] in accordance with the requirements of Article [***] of the MIT Agreement.

If no amounts are due to MIT for any reporting period, the report will so state.

Recordkeeping and Audit Rights (Section 5.4)

- Sublicensees are required to maintain complete and accurate records reasonably relating to (i) the rights and obligations under the MIT Agreement, and (ii) any amounts payable to MIT in relation to the MIT Agreement, which records will contain sufficient information to permit MIT to confirm the accuracy of any reports and payments delivered to MIT and compliance in other respects with the MIT Agreement. Such records will be retained for at least [***] years following the end of the calendar year to which they pertain, during which time a certified public accountant selected by MIT (who will be required to enter into a confidentiality obligation with Sublicensee) may inspect such records upon advance notice and during normal business hours solely for the purpose of verifying any reports and payments or compliance in other respects with the MIT Agreement.

Prosecution and Enforcement (Sections 6.1, 7.1-7.3 and 7.7)

- MIT will prepare, file, prosecute, and maintain all of the Patent Rights. Alnylam will cooperate with MIT in such filing, prosecution and maintenance.

- So long as Alnylam remains the exclusive licensee of the Patent Rights in the Field, Alnylam, to the extent permitted by law, will have the right, under its own control and at its own expense, to prosecute any third party infringement of the Patent Rights in the Field, subject to Sections 2.5(c) (Non-assert), 7.4 (Offsets) and 7.5 (Recovery) of the MIT Agreement. Prior to commencing any such action, Alnylam will consult with MIT and will consider the views of MIT regarding the advisability of the proposed action and its effect on the public interest.

- If Alnylam is unsuccessful in persuading the alleged infringer to desist or fails to have initiated an infringement action within a reasonable time after Alnylam first becomes aware of the basis for such action, MIT will have the right, at its sole discretion, to prosecute such infringement under its sole control and at its sole expense, and to keep any recovery.

- If a Patent Challenge is brought against Alnylam by a third party, MIT, at its option, will have the right within 20 days after commencement of such action to take over the sole defense of the action. If MIT does not exercise this right, Alnylam may take over the sole defense of such action.

- So long as Alnylam remains the exclusive licensee of the Patent Rights in the Field, Alnylam will have the sole right to sublicense any alleged infringer in the Field for future use of the Patent Rights in accordance with Alnylam's rights under and the terms and conditions of this

Agreement. Any upfront fees as part of such sublicense will be shared equally between Alnylam and MIT; other revenues to Alnylam pursuant to such sublicense will be treated as set forth in Article 4 of the MIT Agreement.

Consequences of a Patent Challenge by Sublicensee (Sections 12.5 and 4.3)

- If a Sublicensee brings a Patent Challenge against MIT (except as required under a court order or subpoena), MIT may send a written demand to Alnylam to terminate the sublicense. If Alnylam fails to so terminate such sublicense within 30 days of MIT's demand, MIT may immediately terminate the MIT Agreement and/or the license granted thereunder.

- Notwithstanding the foregoing, if MIT decides not to terminate the MIT Agreement and the Patent Challenge is successful, Alnylam will have no right to recoup any royalties paid during the period of challenge. If the Patent Challenge is unsuccessful, Alnylam will reimburse MIT for all of its costs and expenses it incurred as a result of such Patent Challenge, including without limitation attorneys fees, court costs, litigation related disbursements, and third party and expert witness fees (collectively, "Litigation Costs"). Reimbursement for Litigation Costs will be made within thirty (30) days of receipt of one or more invoices from MIT for such Litigation Costs.

Certain Termination Rights (Sections 12.1, 12.2 and 12.4)

- Alnylam has the right to terminate the MIT Agreement for any reason upon at least 6 months' prior written notice to MIT and payment of all amounts due to MIT through the effective date of termination.

- If Alnylam ceases to carry on its business related to the MIT Agreement, MIT will have the right to terminate the MIT Agreement immediately upon written notice to Alnylam.

- MIT, at its sole discretion, may terminate the Exclusive Period upon ten (10) days written notice to Alnylam if any of the following events occurs: (a) Alnylam is in uncured material default under the Research Agreement, including uncured failure to make any payments due thereunder; or (b) the Research Agreement is terminated for any reason other than for (i) material breach by MIT, (ii) the inability of Dr. Robert Langer to continue to serve as Principal Investigator, and the inability of the parties to agree upon a replacement Principal Investigator, an interim Principal Investigator, or an alternate arrangement for the performance of the Research after Dr. Langer is no longer able to serve as Principal Investigator (capitalized terms used in the foregoing clause have the meanings ascribed to them in the Research Agreement); or (iii) circumstances beyond MIT's reasonable control that preclude the continuation of the Research, as provided for under the Research Agreement.

Definitions

"Development Candidate" means a pre-clinical Licensed Product which possesses desirable properties of a therapeutic agent for the treatment of a clinical condition based on *in vitro* and animal proof-of-concept studies.
"Exclusive Period" means the term of the MIT Agreement.
"Field" means therapeutic use in humans.
"Immunomodulatory Nucleic Acid" means a nucleic acid molecule that (i) stimulates or blocks immune system functions, and (ii) the nucleotide sequence of which does not specifically target

and modulate gene expression. Immunomodulatory Nucleic Acid specifically excludes siRNA, miRNA and nucleic acids that function through an RNA interference mechanism.
"Library Component" means a Library Product which is a set of reaction products formed by an addition reaction between two individual monomers, which set will include all reaction products and combinations within such set, including all isomers; and any compounds identical to any of the foregoing, including individual reaction products within such set, regardless of the means by which said compounds are prepared, manufactured or synthesized.
"Library Product" means any product that, in whole or in part: (i) absent the license granted hereunder, would infringe one or more Valid Claims of the Patent Rights; or (ii) is manufactured by using a Licensed Process or that, when used, practices a Licensed Process.
"Licensed Process" means any process that, in whole or in part: (i) absent the license granted hereunder, would infringe one or more Valid Claims of the Patent Rights; or (ii) when practiced, uses a Library Product.

"Licensed Product" means any product that contains both (i) an RNAi Product and (ii) a Library Product. Licensed Product specifically excludes any products containing or incorporating any other therapeutically or pharmaceutically active agents, including without limitation proteins or peptides, antibodies, Small Molecules, non-siRNA and non-miRNA nucleic acids, and Immunomodulatory Nucleic Acids.
"miRNA" ("microRNA") means a class of endogenous, non-coding, sequence specific ribonucleic acid (RNA) between 21 to 25 nucleotides in length that modulates gene expression. miRNA specifically excludes messenger RNA, and any other RNA that encodes a polypeptide, and Immunomodulatory Nucleic Acids.
"miRNA Therapeutic" means a therapeutic containing, composed of or based on oligomers of native or chemically modified RNA designed to either modulate an miRNA and/or provide the function of an miRNA.
"ND98 Library Component" means the Library Component which is described in Appendix C of the MIT Agreement.
"Patent Rights" means the patent applications listed on Appendix A to the MIT Agreement entitled "Amine-Containing Lipids and Uses Thereof" and "A Combination Library of Lipidoids: Efficient Systemic siRNA Delivery", and resulting patents and patent applications.
"Research Agreement" means the sponsored research agreement between MIT and Alnylam effective on May 8, 2007.
"Research Support Payment" means payments to Alnylam or an Affiliate from a Sublicensee for the purposes of funding the costs of *bona fide* research and development of Licensed Products and/or Library Products under a jointly prepared research plan and only to the extent such payments were spent on such research and development of Licensed Products and/or Library Products, and only to fund or pay for direct and indirect costs and fully loaded personnel costs, all as calculated under GAAP. For the avoidance of doubt, Research Support Payments will mean payments that are expressly intended only to fund or pay for (i) equipment, supplies, products or services, and (ii) the use of employees and/or full time consultants, incurred or to be incurred on behalf of such Sublicensee to achieve a research or development goal for Licensed Products and/or Library Products.
"RNAi Product" means a product containing one or more siRNA Therapeutics and/or miRNA Therapeutics towards one or more Targets. For the avoidance of doubt, RNAi Product specifically includes siRNA Therapeutics and miRNA Therapeutics in association with other molecules which are not therapeutically or pharmaceutically active, but which function to

improve delivery to cells, including, without limitation, siRNA and miRNA Therapeutics which are covalently linked to, or otherwise associated with, lipids, carbohydrates, peptides, proteins, aptamers and Small Molecules.
"siRNA" ("small interfering RNA") means a double-stranded ribonucleic acid (RNA) molecule designed to act through an RNA interference mechanism that consists of either (a) two separate oligomers of native or chemically modified RNA that are hybridized to one another along a substantial portion of their lengths, or (b) a single oligomer of native or chemically modified RNA that is hybridized to itself by self-complementary base-pairing along a substantial portion of its length to form a hairpin. siRNA specifically excludes messenger RNA, and any other RNA that encodes a polypeptide, and Immunomodulatory Nucleic Acids.
"siRNA Therapeutic" means a therapeutic containing, composed of or based on siRNA and designed to modulate the function of particular genes or gene products by causing degradation of a messenger RNA to which such siRNA is complementary, and that is not an miRNA Therapeutic.
"Small Molecule" means a non-polymeric bioactive molecule that is not a peptide, protein, DNA, RNA or a complex carbohydrate.
"Sublicense Income" means any payments that Alnylam or an Affiliate receives from a Sublicensee in consideration of the sublicense of the rights granted Alnylam and Affiliates under Section 2.1 of the MIT Agreement, including without limitation equity, license fees, milestone payments (net of any sums due to MIT under this Agreement for the same milestone event), license maintenance fees, and other payments, but specifically excluding:

- royalties on Net Sales;
- minimum royalty upfront payments only to the extent such payments equal actual royalties due to Alnylam;
- fair market value of equity investments in Alnylam or an Affiliate by a Sublicensee;
- reimbursement of out of pocket patent expenses for the Patent Rights;
- Research Support Payments;
- loan proceeds paid to Alnylam by a Sublicensee in an arms length, full recourse debt financing; and
- any amounts received under an indemnification obligation.

For clarity, the amounts received by Alnylam or its affiliates related to the development of Licensed Products will be considered Sublicense Income.

"Target" means (a) a single gene, as defined in the NCBI Entrez Gene database or any successor database thereto, or a product of such gene, that is a site or potential site of therapeutic intervention by an siRNA Therapeutic and/or an miRNA Therapeutic; (b) naturally occurring variants of a gene or gene product described in clause (a); or (c) a naturally occurring interfering RNA or miRNA or precursors thereof; provided that for the purposes of this definition a viral

genome will be regarded as a single gene, and that the DNA sequence encoding a specific miRNA precursor will also be regarded as a single gene.

TEKMIRA/UBC

The Sublicense Agreement between Tekmira and Alnylam, dated January 8, 2007 ("UBC Sublicense Agreement")
Brief Summary of Technology Covered by License: See Tekmira-Alnylam Agreement above.
Limitations on Scope of License (Sections 3.1 and 3.3)

- The sublicense granted to Alnylam is limited to an exclusive, worldwide license under the rights granted to Tekmira in the University License Agreement (see below) with respect to Technology to research, develop, manufacture, have made, distribute, import, use, sell and have sold Products in and for the Alnylam Field. In addition, any sublicense granted by Tekmira to Alnylam would be subject to Tekmira's sublicense to Esperion Technologies, Inc. of certain technology relating to liposome compositions and methods for the treatment of atherosclerosis.

- Under the University License Agreement, Tekmira obtained from the University an exclusive, worldwide license to use and sublicense the Technology and to make, have made, distribute, import and use goods, the manufacture, use or sale of which would, but for the license granted herein, infringe a Valid Claim of any Patent, including a license to use and sublicense the Technology for (a) the delivery of and use with nucleic acid constructs, and (b) the treatment, prophylaxis and diagnosis of diseases in humans using an RNAi Product or miRNA Product, and to research, develop, make, have made, distribute, import, use, sell and have sold RNAi Products and miRNA Products.

- University retains the right to use the Technology without charge in any manner whatsoever for non-commercial research, scholarly publication, educational or other non-commercial use.

Restrictions on Sublicensing by Alnylam (Sections 3.2 and 4.2)

- Any further sublicense granted by Alnylam to a third party would be subject to the grant of the following licenses by Alnylam to Tekmira under Alnylam's rights in the Technology: (a) to perform Tekmira's obligations under the Collaboration with respect to Products, and the Manufacturing Activities, on a non-exclusive basis, and (b) to develop, manufacture and commercialize Inex Royalty Products for the treatment, prophylaxis and diagnosis of diseases in humans, on an exclusive basis.

- Alnylam may grant sublicenses to third parties with respect to the Technology only upon written notice to Tekmira and the University, and provided that the Sublicensee agrees (i) to perform the terms of the UBC Sublicense Agreement as if such Sublicensee were Alnylam under the UBC Sublicense Agreement; (ii) to represent that Sublicensee is not, as of the effective date of the relevant sublicense agreement, engaged in a dispute with the University; and (iii) to be subject to a written sublicense agreement that contains terms consistent with "the terms of this Agreement" described in Section 4.2(c) of the UBC Sublicense Agreement (see below) and that provides that the University is a third party beneficiary of, and has the right to enforce directly against the sublicensee, the terms in such sublicense agreement that are consistent with the terms listed in Section 4.2(c)(ii) of the UBC Sublicense Agreement.

- Section 4.2(c)(ii) of the UBC Sublicense Agreement states that the "terms of this Agreement" means (i) the terms set forth in the UBC Sublicense Agreement; (ii) terms in such

sublicense agreement consistent with Sections 1.3 (Alnylam Consent to Certain Disclosures to the University), 1.7 (Rights of the University), 2.1 (Limited Warranties), 2.2 (Disclaimer of Product Liability), 2.3 (Indemnification of the University), 2.4 (Monetary Cap Respecting UBC License), 2.5 (Disclaimer of Consequential Losses by the University), 2.6 (Litigation), 2.7 (UBC Trademark), 2.8 (Confidentiality of Terms) and 2.13 (Alnylam Warranties) of the Consent Agreement among Alnylam, Tekmira and the University of even date with the UBC Sublicense Agreement ("Consent Agreement"); and (iii) other customary and reasonable terms, including but not limited to terms relating to breach and termination, that are consistent with Alnylam's obligations to Tekmira under the UBC Sublicense Agreement and the Tekmira Agreement.

- Any sublicense granted by Alnylam under the UBC Sublicense Agreement will survive termination of the licenses or other rights granted to Alnylam under the UBC Sublicense Agreement, and be assumed by Tekmira, as long as (i) the sublicensee is not then in breach of its sublicense agreement, (ii) the sublicensee agrees in writing to be bound to Tekmira as a sublicensor and to the University under the terms and conditions of the UBC Sublicense Agreement, and (iii) the sublicensee agrees in writing that in no event will Tekmira assume any obligations or liabilities, or be under any obligation or requirement of performance, under any such sublicense extending beyond Tekmira's obligations and liabilities under the UBC Sublicense Agreement.

- Alnylam is required to furnish Tekmira with a copy of each sublicense granted within 30 days after execution. Any such copy may contain reasonable redactions as Alnylam may make, provided that such redactions do not include provisions necessary to demonstrate compliance with the requirements of the UBC Sublicense Agreement. If University requests of Tekmira that a less redacted version of any sublicense be provided to University, Alnylam agrees to discuss in good faith with Tekmira and the University the University's concerns.

Financial Obligations (Section 5.0)

- The consideration for the rights granted to Alnylam to the Technology under the UBC Sublicense Agreement, and the consideration for the rights granted by Tekmira to Alnylam to other technologies under the Tekmira Agreement, is the payment by Alnylam of milestones and royalties in accordance with Article 7 of the Tekmira Agreement.

Prosecution and Enforcement (Section 7.7)

- Tekmira will have the right, with reasonable input from Alnylam, to identify any process, use or products arising out of the Technology that may be patentable and will take all reasonable steps to apply for a patent in the name of the University, provided that Tekmira pays all costs of applying for, registering, and maintaining the patent in those jurisdictions in which Tekmira determines that a Patent is required.

- On the issuance of a patent for the Technology, Tekmira will have the right to become, and will become the licensee of the same, all pursuant to the terms contained in the University License Agreement, and Alnylam will have the right to become, and will become the sublicensee of such rights pursuant to the terms contained in the UBC Sublicense Agreement.

- Should Tekmira:

- discontinue pursuing one or more patent applications, patent protection or patent maintenance in relation to the Patent(s) or any continuation, continuation in-part, division, reissue, re-examination or extension thereof; or

- not pursue patent protection in relation to the Patent(s) in any specific jurisdiction; or

- discontinue or not pursue patent protection in relation to any further process, use or products arising out of the Technology in any jurisdiction;|

- then Tekmira will provide Alnylam with notice of its decision to discontinue or not to pursue such patent protection concurrently with the notice provided to the University by Tekmira pursuant to Section 6.6 of the University License Agreement.

- In the event of an alleged infringement by a third party of the Technology or any right with respect to the Technology, or any complaint by Alnylam alleging any infringement by a third party with respect to the Technology or any right with respect to the Technology, in each case that is licensed to Alnylam under the UBC Sublicense Agreement, Alnylam will, subject to Tekmira having first obtained the University's consent as required by Article 7 of the University License Agreement, have the right to prosecute such litigation at Alnylam's expense.

- In the event of any litigation, Alnylam will keep Tekmira fully informed of the actions and positions taken or proposed to be taken by Alnylam (on behalf of itself or a sublicensee) and actions and positions taken by all other parties to such litigation.

- In the event of an alleged infringement of the Technology or any third party use of the Technology which is Confidential Information, Alnylam and Tekmira agree that they will reasonably cooperate to enjoin such third party's use of the Technology.

- If any complaint alleging infringement or violation of any patent or other proprietary rights is made against Alnylam (or a sublicensee of Alnylam) with respect to the manufacture, use or sale of Product, then:

- Alnylam will promptly notify Tekmira upon receipt of any such complaint and will keep Tekmira fully informed of the actions and positions taken by the complainant and taken or proposed to be taken by Tekmira (on behalf of itself or a sublicensee);

- Alnylam (or any sublicenseee, as the case may be) will pay all costs and expenses incurred by Alnylam (or any sublicensee of Alnylam) in investigating, resisting, litigating and settling such a complaint, including the payment of any award or damages and/or costs to any third party; and

- if as a result of such suit it is decided that a Product infringes any valid claim on a patent owned by another, Tekmira will consider fair distribution of Royalty Income.

Diligence and Reporting (Section 10.2)

- Alnylam is required to use its reasonable commercial efforts to promote, market and sell the Products and utilize the Technology and to meet or cause to be met the market demand for the Products and the utilization of the Technology.

- Alnylam is required to deliver to Tekmira an annual report, due on December 31 of each year, which summarizes the major activities Alnylam has undertaken in the course of the preceding 12 months to develop and commercialize and/or market the Technology. The report must include an outline of the status of any Products in clinical trials and the existence of any sublicenses of the Technology.

Certain Termination Rights (Section 16.1)

- If Alnylam's rights to Inex Technology are terminated under the Tekmira Agreement, the UBC Sublicense Agreement and the license granted to Alnylam thereunder also terminates.

Definitions

Capitalized terms not otherwise defined below have the meanings given to them under the Tekmira Agreement.

"1999 CRA" means the Collaborative Research Agreement between Tekmira and the University dated effective January 1, 1999 and successor agreements to such Know-How.

"2007 CRA" means the Collaborative Research Agreement between Tekmira and the University dated effective January 1, 2007 and successor agreements to such Know-How.

"Alnylam Field" means the use of Products for the treatment, prophylaxis and diagnosis of diseases in humans.

"Improvements" means, generally (i) any and all patents and any and all patent applications that claim priority to Patents; and (ii) any and all inventions arising therefrom. Notwithstanding anything to the contrary in the University License Agreement, ownership of all Improvements (A) that fall within clause (i) above will be assigned to the University; and (B) that fall within clause (ii) above will follow inventorship as determined by U.S. patent law, except that the University will own all Improvements made by its employees, whether alone or jointly with Tekmira, under the 1999 CRA or 2007 CRA.

"miRNA Product" means a product containing, comprised of or based on native or chemically modified RNA oligomers designed to either modulate a micro RNA transcript and/or provide the function of a micro RNA transcript.

"Patent(s)" means, generally, the patents and patent applications, including certain "Wheeler Patents," listed on Schedule A to the UBC Sublicense Agreement, and any claims of CIPs and of resulting patents which are to the UBC Sublicense Agreement, and any reissues of such patents.

"Product(s)" means any RNAi Product or miRNA Product that, the manufacture, use or sale of which would, but for the license granted herein, infringe a Valid Claim of one or more of the Patent(s).

"RNAi Product" means a product containing, comprised of or based on small interfering RNAs or small interfering RNA derivatives or other moieties effective in gene function modulation and designed to modulate the function of particular genes or gene products by causing degradation of a target mRNA to which such small interfering RNAs or small interfering RNA derivatives are complementary, and that is not an miRNA Product.

"Technology" means the Patent(s) and any and all knowledge, know-how and/or technique or techniques invented, developed and/or acquired, being invented, developed and/or acquired by the University solely or jointly with Tekmira relating to the Patent(s), including, without

limitation, all research, data, specifications, instructions, manuals, papers or other materials of any nature whatsoever, whether written or otherwise, relating to same.

"University License Agreement" means the License Agreement dated effective July 1, 1998, as amended, pursuant to which Tekmira is the exclusive licensee of certain Patents owned by the University of British Columbia (the "University").

Isis Pharmaceuticals, Inc. requests that the marked portions of the exhibit be granted confidential treatment pursuant to Rule 24b-2 of the Securities Exchange Act of 1934.	Exhibit 10.3

LIMITED LIABILITY COMPANY AGREEMENT
OF
REGULUS THERAPEUTICS LLC

A DELAWARE LIMITED LIABILITY COMPANY

DATED AS OF SEPTEMBER 6, 2007

TABLE OF CONTENTS

Schedules and Exhibits

LIMITED LIABILITY COMPANY AGREEMENT
OF
REGULUS THERAPEUTICS LLC

This LIMITED LIABILITY COMPANY AGREEMENT (this "**Agreement**") of Regulus Therapeutics LLC, a Delaware limited liability company (the "**Company**"), is entered into as of September 6, 2007 (the "**Effective Date**") by and among the Company, Alnylam Pharmaceuticals, Inc., a Delaware corporation ("**Alnylam**"), and Isis Pharmaceuticals, Inc., a Delaware corporation ("**Isis**," and together with Alnylam, the "**Members**").

W I T N E S S E T H:

WHEREAS, the Members desire to form a joint venture to discover, develop manufacture and commercialize miRNA Therapeutics (the "**Joint Venture**");

WHEREAS, in connection therewith and on the Effective Date, the Members and the Company are entering into the following agreements, in each case as more particularly and more fully set forth therein: (a) the License Agreement; and (b) the Services Agreement;

WHEREAS, a Certificate of Formation for the Company, a limited liability company organized under the laws of the State of Delaware, was filed with the Delaware Secretary of State on September 5, 2007 (the **"Certificate"**); and

WHEREAS, the Members desire to enter into this Agreement to provide for their respective rights, powers, duties and obligations as Members, as well as for the management, operations and activities of the Company going forward;

NOW, THEREFORE, the Members by this Agreement set forth the limited liability company agreement for the Company under the Delaware Limited Liability Company Act (6 Del. C. § 18-101 et seq. – as amended from time to time, the "**Act**"), upon the following terms and conditions:

ARTICLE 1

Definitions; Representations and Warranties

Except as otherwise defined throughout this Agreement, as used herein the capitalized terms appearing in **Schedule 1** will have the meanings set forth therein. Each Member represents and warrants to the other Member and the Company that the statements set forth in **Schedule 2** with respect to such Member are true and correct as of the Effective Date.

ARTICLE 2

Organization and Description

2.1 Name.

The name of the Company will be "Regulus Therapeutics LLC." The Company may from time to time do business under any other name under which it is qualified to do business. The business of the Company will be conducted in compliance with all applicable laws.

2.2 Term.

The term of the Company commenced on the date of the filing of the Certificate in the office of the Secretary of State of the State of Delaware and will continue until dissolved in accordance with Article 10.

2.3 Registered Office and Statutory Agent.

The registered office and statutory agent in Delaware required by the Act will be as set forth in the Certificate until such time as the registered office or statutory agent is changed in accordance with the Act.

2.4 Principal Executive Office.

The principal executive office for the transaction of the Company's business initially will be 1896 Rutherford Road, Carlsbad, California 92008. At any time, the Managing Board may change its location within the United States of America, whether within or without the State of Delaware.

2.5 Business.

The Company's business (the "**Business**") will be to (a) discover, develop, manufacture and commercialize miRNA Therapeutics and undertake all activities necessary or incidental thereto, and (b) subject to approval of the Managing Board, to conduct and carry on any other lawful business, purpose or activity which is permitted to be carried on by a limited liability company under the Act.

2.6 Qualification in Other Jurisdictions.

The Company will execute, deliver and file any certificates (and any amendments or restatements thereof) necessary for the Company to qualify to do business in any jurisdiction in which the Company conducts business and in which such qualification or registration is required by law or deemed advisable by the Managing Board.

2.7 Filings, Reports and Formalities.

The Company will make all filings and submit all reports required to be filed or submitted under the Act with respect to the Company. Throughout the term of the Company, the

Company will comply with all requirements necessary to maintain the limited liability status of the Company and the limited liability status of the Members under the laws of the State of Delaware and of each other jurisdiction in which the Company does business.

2.8 Limited Liability.

Except as otherwise required by the Act, the debts, obligations and liabilities of the Company, whether arising in contract, tort or otherwise, will be solely the debts, obligations and liabilities of the Company, and no Member, Director or Officer of the Company will be obligated personally for any such debt, obligation or liability of the Company solely by reason of being a member, director, manager or officer of the Company.

ARTICLE 3

Members; Voting Rights; Meetings; Withdrawal

3.1 Members.

Each Person who is or becomes a Member will be and remain a member of the Company until such Person ceases to be a member in accordance with the provisions of the Act, the Certificate or this Agreement. The names and addresses of the Members, and their respective Percentage Interests and Capital Accounts as of the Effective Date, are set forth on **Schedule 3.1** hereto, as the same may be amended (or, with respect to the addresses of Members, noticed under Section 13.9) or adjusted from time to time pursuant to this Agreement.

3.2 Powers of Members.

Except as otherwise provided herein and in the Ancillary Agreements, no Member will have any power to transact any business in the Company's name nor have the power to sign documents, act for or on behalf of or otherwise bind the Company. Subject to the provisions of this Agreement and unless otherwise required by the Act or the Certificate, the Members hereby delegate any and all such powers to the Managing Board to carry out the business affairs of the Company on the Members' behalf.

3.3 Member Voting Rights.

The Members will have no voting rights except as to those matters which, pursuant to this Agreement, the Certificate or non-waivable provisions of the Act, require the authorization or approval of the Members. Any authorization or approval required pursuant to this Agreement, the Certificate or non-waivable provisions of the Act will be effected by the unanimous affirmative vote of the Members. Such vote may be by voice vote or by ballot.

3.4 Meetings of Members.

(a) Annual Meeting. The Members will convene at least one meeting every year during the fourth quarter of the Fiscal Year of the Company at the same location (or by the same remote communication) as the meeting of the Managing Board held during the fourth quarter of

the same Fiscal Year pursuant to Section 4.2(b) and on the same day of such Managing Board meeting, or the immediately preceding or immediately following day.

(b) Special Meetings. A special meeting of the Members may be called at any time by any Director or the President by written request to the Chairperson, who will consult with the Members to set a date approved by the Members (which approval will not be unreasonably withheld or delayed).

(c) Notice and Minutes.

(i) Written notice of all meetings of the Members will be given to each Member not less than five (5) nor more than thirty (30) days before the meeting. Such notices will state (A) the place, date and hour of the meeting and (B) those matters which, at the time of the mailing of the notice, are intended to be presented for action. Only Persons whose names are listed as Members on the records of the Company at the close of business on the Business Day immediately preceding the day on which notice of the meeting is given or, if such notice is waived, at the close of business on the Business Day immediately preceding the day on which the meeting of Members is held will be entitled to receive notice of and to vote at such meeting, and such day will be the record date for such meeting (except that the record date for Members entitled to give consent to action without a meeting will be determined in accordance with Section 3.5 hereof).

(ii) The Members will appoint a representative to act as secretary for the meeting who will keep minutes of all proceedings of the meeting, which minutes will be distributed to each of the attending Members. The attending Members will consider the minutes for approval at or prior to the next meeting of the Members. The acting secretary will sign the final minutes of Member meetings and cause all such minutes and unanimous written consents of the Members executed pursuant to Section 3.5 hereof to be entered into a minute book maintained for such purpose.

(d) Place of Meetings. Annual meetings of the Members will be held at a place determined in accordance with Section 3.4(a) hereof, and special meetings of the Members will be held at such place as may be designated by the Chairperson or, if not so designated, at the principal executive office of the Company.

(e) Quorum. The presence at any meeting in person or by proxy of an authorized representative of both Alnylam and Isis will constitute a quorum for the transaction of business (without prejudice to the vote required for the approval of any particular action).

(f) Waiver of Notice.

(i) The actions of any meeting of Members, however called and noticed and wherever held, will be as valid as if taken at a meeting duly held after regular call and notice, if a quorum be present either in person or by proxy and, if notice has not been given in compliance with Section 3.4(c), each Member entitled to vote has waived notice pursuant to Section 3.4(f)(ii) or, either before or after the meeting, has signed a written waiver of notice or a written consent to a holding of the meeting, or a written approval of the minutes thereof. The waiver of notice, consent or approval need not specify either the business to be transacted or the purpose of any

meeting. All such waivers, consents or approvals will be filed with the Company records and made a part of the minutes of the meeting.

(ii) Attendance of a Member at a meeting, in person or by proxy, without protesting the lack of notice of such meeting at the beginning of such meeting, will constitute a waiver of notice by such Member, provided that such Member has been given an adequate opportunity at the meeting to protest such lack of notice.

(g) Attendance by Telephone Conference, Etc. The Members may participate in a meeting of the Members by means of telephone conference or similar communications equipment by means of which all Persons participating in the meeting can hear each other, and such participation will constitute presence in person at such meeting, subject to a Member's right to protest lack of notice pursuant to Section 3.4(f)(ii) above.

3.5 Action by Members Without a Meeting.

(a) Any action that under any provision of the Act, the Certificate or this Agreement may be taken at a meeting of the Members may be taken without a meeting and without prior notice, if a consent in writing, setting forth the action so taken, is delivered to and signed by the Members necessary to authorize or take such action at a meeting at which all Members entitled to vote thereon were present and voted.

(b) A telecopy, electronic mail, or other electronic transmission (each, an **"electronic transmission"**) consenting to an action to be taken and transmitted by a Member or the Member's proxyholder will be deemed to be written, signed and dated for purposes of this Section 3.5, provided that any such electronic transmission sets forth or is delivered with information from which the Company can determine (A) that the electronic transmission was transmitted by such Member or proxyholder, and (B) the date on which such Member or proxyholder transmitted such electronic transmission. The date on which such electronic transmission was transmitted will be deemed to be the date on which such consent was signed. No consent in the form of an electronic transmission will be deemed to have been delivered until its receipt by the Company at its principal executive office.

(c) Unless a record date has been fixed for the determination of Members entitled to notice of and to give such written consent, the record date for such determination will be the day on which the first written consent is given. Any Member giving a written consent, or the Member's proxyholder, may revoke the consent by a writing (including electronic transmission) received by the Company prior to the time that written consents of the Members required to authorize the proposed action have been filed with the Company, but may not do so thereafter. Such revocation is effective upon its receipt by the Company.

3.6 Corporate Opportunities.

(a) Except as otherwise set forth in any Ancillary Agreement, no Director or Member or its Affiliates will be prohibited from engaging in, or carrying on, any business or activity that is similar to or in competition with another Member or the Company or any of their respective Affiliates. Except as otherwise set forth in any Ancillary Agreement, (i) neither the Company nor any other Member will have any right in or to any such businesses or activities or the income

or profits derived therefrom as a result of entering into this Agreement, and (ii) no Director, Officer or Member or its Affiliates will have any obligation to present, or disclose the existence of, any such activities or businesses or the opportunity to participate in any of them to the Company, any of its subsidiaries or to any other Member or any other Member's Affiliates, except as such information may be required to satisfy reporting obligations under law, including without limitation, the rules and regulations of the SEC. *Notwithstanding the foregoing*, the Parties acknowledge that the disclosure of such information may be required in connection with obtaining and maintaining appropriate directors' and officers' insurance.

(b) Except as otherwise set forth in any Ancillary Agreement, in the event that a Member or Director acquires knowledge of a potential transaction or matter that may be a corporate opportunity for a Member and the Company, such Member or Director will have no duty to communicate or present such corporate opportunity to the Company, and the Company hereby renounces any interest or expectancy it may have in such corporate opportunity, with the result that such Member or Director will not be liable to the Company or the other Members for breach of any fiduciary duty, including for breach of any fiduciary duty as a Member or Director of the Company by reason of the fact that such Member or Director pursues or acquires such corporate opportunity for itself, directs such corporate opportunity to another Person, or does not present such corporate opportunity to the Company.

3.7 No Priority, Etc.

Except as otherwise provided herein, no Member will have priority over any other Member either as to the return of the amount of its Capital Contribution to the Company, as to any distribution by the Company, or as to any other economic or other right comprising part of Membership Interests.

3.8 No Withdrawal.

No Member may withdraw or resign from the Company.

3.9 Additional Members.

No additional Persons may be admitted as Members, unless admitted pursuant to and in accordance with Article 8 or Section 4.3, as applicable.

ARTICLE 4

Management

4.1 Managing Board of Directors.

The Members will establish a Managing Board of Directors of the Company ("**Managing Board**") as of the Effective Date.

(a) Directors. The Managing Board will consist of up to [***] directors (each, a "**Director**"). Alnylam will have the right to designate [***] Directors who need not be Independent Directors (the "**Alnylam Directors**") and [***] Director who must be an

Independent Director. Isis will have the right to designate [***] Directors who need not be Independent Directors (the "**Isis Directors**") and [***] Director who must be an Independent Director. The President of the Company will, at all times while in office, be a Director. Other than the President, each Director will serve at the pleasure of the designating Member until such Director's removal by the designating Member or such Director's resignation. If there is a vacancy on the Managing Board, the vacancy will be filled by the Member, if any, who initially designated the Director. Any Member may remove, at any time and for any reason, any or all of the Directors designated by such Member and, subject to the Independent Director requirements, designate in lieu thereof any individual(s) to serve the remainder of the relevant term.

(b) Chairperson. The Chairperson of the Managing Board ("**Chairperson**") will be the President, unless otherwise designated from among the Directors by the Directors.

(c) Observers. The right to attend all or particular meetings of the Managing Board ("**Observer Rights**") may be granted to any Person designated by a Member upon the approval of the other Member (such approval not to be unreasonably withheld or delayed); provided, however, that any Person granted Observer Rights, and/or any representative of such Person attending meetings of the Managing Board, will agree in writing to be subject to appropriate confidentiality obligations if requested by a Director; provided, further, that such holder of Observer Rights may be excluded from any meeting or any portion of a meeting for which any Director believes (i) such meeting or portion will involve a discussion of information that the Company or the Member designating such Director considers to be a trade secret or of a confidential or proprietary nature, (ii) exclusion of such holder of Observer Rights is desirable in order to preserve the attorney client-privilege or (iii) exclusion is otherwise merited.

(d) Other Attendees. Any Director may invite a subject matter expert to attend any meeting of the Managing Board; provided, however, that any Person granted attendance rights will agree in writing to be subject to appropriate confidentiality obligations if requested by a Director and provided further that no other Director objects to such expert's presence. Upon such objection, the expert will be excluded from any meeting or any portion of a meeting.

4.2 Power and Authority of the Managing Board.

(a) The business and affairs of the Company will be managed by or under the direction of the Managing Board, except as may otherwise be provided in this Agreement. The Managing Board is hereby designated as a "manager" within the meaning of the Act and will have the power on behalf and in the name of the Company to carry out any and all objectives and purposes of the Company contemplated by this Agreement, the Act or the Certificate and to perform all acts which it may deem necessary, advisable or appropriate in connection therewith. *Notwithstanding any other provision of this Agreement, the Act or the Certificate*, the Managing Board will not have the power or authority to do or perform, or cause the Company or any Member to do or perform, any act with respect to a Major Decision unless such Major Decision has been approved in accordance with Section 4.3.

(b) Except as otherwise provided in this Agreement, the Members agree that all determinations, decisions and actions made or taken by the Managing Board will be conclusive and absolutely binding upon the Company, the Members (but only in their capacity as such) and

their respective successors, assigns and personal representatives; provided, however, that the foregoing will not affect the rights of the Company or any Member with respect to any matter involving a breach by a Director of Section 10.1 of this Agreement.

(c) The Managing Board may establish operating committees of the Managing Board to which the Managing Board delegates various aspects of its authority. Each such operating committee will consist of an equal number of Directors designated by each Member, and vacancies in the membership of an operating committee will be filled by the Member that designated the Director whose seat is vacated. No delegation of authority to an operating committee will be to the exclusion of the authority of the Managing Board to act with respect to the matters for which authority is so delegated. All requirements with respect to meetings of the Managing Board will apply, *mutatis mutandis*, to meetings of operating committees thereof.

4.3 Major Decisions.

(a) *Notwithstanding any other provision of this Agreement, the Act or the Certificate to the contrary* and in addition to any other requirement under this Agreement, the Act or the Certificate, the Company may not do or perform any of the actions set forth below (each a **"Major Decision"**) without first obtaining the approval of an authorized representative of both Alnylam and Isis:

(i) appoint or remove any Officer;

(ii) determine the compensation of the President and Chief Scientific Officer;

(iii) appoint or remove any member of the Scientific Advisory Board or remove or appoint the Chairperson of the Scientific Advisory Board

(iv) amend any existing Operating Plan or approve any Proposed Operating Plan;

(v) create, incur, guarantee or assume any indebtedness, except for trade payable, on behalf of the Company (including obligations in respect of capital leases), in excess of $[***].

(vi) make or obligate the Company to make any single or aggregate capital expenditure outside of the Approved Operating Budget in excess of $[***];

(vii) license, sublicense or otherwise transfer, grant a security interest in or otherwise encumber, any of the Intellectual Property owned by or licensed to the Company, other than as provided in the Ancillary Agreements;

(viii) license, sublicense or otherwise obtain rights to Intellectual Property owned by a Third Party or a Member or Member's Affiliate, except as contemplated by Sections 2.2 and 2.4 of the License Agreement;

(ix) declare, set aside or pay any dividend or other distribution (whether in cash, stock or property or any combination thereof), other than tax distributions pursuant to Section 7.2(a) or as provided in the Ancillary Agreements;

(x) enter into any partnering activities and/or collaborations;

(xi) repurchase any Membership Interests of the Company;

(xii) admit a new Member to the Company, except as permitted by Article 8;

(xiii) Transfer any Membership Interests of the Company, except in accordance with the provisions of Article 8;

(xiv) reclassify or reorganize the Membership Interests;

(xv) cause or approve any (i) merger or consolidation of the Company, (ii) acquisition of any other entity or assets of any other entity, if the value of the acquisition exceeds $[***] or (iii) sale of the Company's assets if the value of such assets exceeds $[***];

(xvi) amend, modify, waive or avoid any provision of this Agreement or the Certificate, except as expressly authorized herein or therein;

(xvii) expect as provided in Article 10, liquidate, dissolve, wind up or declare the Company bankrupt;

(xviii) amend any Ancillary Agreement;

(xix) cause or approve the bringing of an action, suit or proceeding against a Member, an Affiliate of a Member or a Third Party; or

(xx) amend this Section 4.3.

4.4 Meetings of the Managing Board.

(a) Agendas. The Chairperson will prepare or direct the preparation of the agenda for, and preside over, meetings of the Managing Board. The Chairperson will deliver such agenda to each Director as soon as practicable in advance, and any Director may add items to an agenda at any time.

(b) Timing; Place; Notice.

(i) Regular Meetings. The Managing Board will convene at least one meeting during each quarter of each Fiscal Year of the Company, with the place of the meeting, if any, alternating between the principal offices of Alnylam and the principal offices of Isis, unless otherwise agreed to by a majority of the Directors, including at least one Alnylam Director and one Isis Director.

(ii) Special Meetings. Special meetings of the Managing Board may be called by the Chairperson or at the written request of at least one (1) Director. Within three (3) days

after determining to call or receiving a proposal for a special meeting by at least one (1) Director, the Chairperson will consult with the other Directors to determine a mutually convenient time within the following thirty (30) day period to convene such meeting; provided, however, that the decision as to time and place will be made by the Chairperson. Any special meeting of the Managing Board will not be held more than thirty (30) days from the date of the receipt of the request.

(iii) Notice. Written notice of the time and place of each meeting of the Managing Board will be given by or at the direction of the Chairperson to each Director, at least five (5) Business Days before such meeting.

(iv) Waiver of Notice. The required notice to any Director may be waived by such Director in writing. Attendance by a Director at a meeting will constitute a waiver of any required notice of such meeting by such Director, except when such Director attends such meeting for the express purpose of objecting, at the beginning of the meeting, to the transaction of any business because the meeting is not properly called or convened.

(c) Attendance by Telephone Conference, Etc. Directors may participate in a meeting of the Managing Board by means of telephone conference or similar communications equipment by means of which all Persons participating in the meeting can hear each other, and such participation will constitute presence in person at such meeting, subject to such Director's right to protest lack of notice pursuant to Section 4.4(b)(iv).

(d) Quorum. A quorum of any meeting of the Managing Board will require the presence of a majority of the Directors, including at least one Alnylam Director and at least one Isis Director.

(e) Action at a Meeting. At any meeting of the Managing Board at which a quorum is present, the vote of a majority of those present will be sufficient to take any action, unless a different vote is required by this Agreement, the Certificate or the Act. *Notwithstanding the foregoing, or any other provision in this Agreement*, neither the Company, the Managing Board nor any Director or Officer will have any power or authority to do or perform any act with respect to any Major Decision unless such matter has been approved in accordance with the provisions of Section 4.3.

(f) Minutes. In order to facilitate each meeting, a Director or another appropriately qualified Person, in either case designated by the Chairperson, will act as the secretary of the meeting. The responsibilities of the secretary are to keep minutes of the meeting and to record and collect documents related to the meeting. The secretary will also distribute the above documents to each Director and will cause the minutes and other documents related to the meetings to be kept on file by the Company. The Directors who attended the meeting will consider the minutes for approval at or prior to the next meeting.

(g) Action by Written Consent. Any action required or permitted to be taken at a meeting of the Managing Board may be taken without a meeting if all Directors consent to the action in writing or by electronic transmission, and the written consents and hard copies of the electronic transmissions are filed with the minutes of the proceedings of the Managing Board.

4.5 Compensation.

(a) The Alnylam Directors and Isis Directors will serve without compensation from the Company and each Member will reimburse its own Directors' out-of-pocket expenses incurred in connection with such Directors' service on the Managing Board. The foregoing sentence will have no effect with regard to the Director's right to indemnification pursuant to Article 11.

(b) The Independent Directors will be compensated, as determined by the Managing Board, in cash by the Company for service on the Managing Board and attendance at meetings of the Managing Board or its committees. The Company will reimburse the President and the Independent Directors for their out-of-pocket expenses incurred in connection with their service on the Managing Board.

(c) Each Independent Director will also enter into a consulting agreement (a **"Director Consulting Agreement"**) with the Company, Alnylam and Isis, pursuant to which such Independent Director will provide advisory, educational and other services to the Company, and pursuant to which such Independent Director will provide advisory and educational services to each Member. Each such Director Consulting Agreement will be in substantially the form attached hereto as **Schedule 4.5** and will provide for, among other things, the provision of stock options to purchase common stock of the Members. Pursuant to the Director Consulting Agreement, the Managing Board will recommend to each Member's Board of Directors the stock options to be granted by such Member to the Independent Directors pursuant to and consistent with such Member's equity incentive plan. To the extent either Member's Board of Directors does not approve, or a Member does not make, such stock option grant recommended by the Managing Board, such Member will be required to compensate the Independent Director to whom the grant is not approved or made with cash, such that the Option Value of the stock options granted, if any, and cash paid to the Independent Director by the Member is equal to the Option Value of the stock options recommended to be issued by that Member to such Independent Director by the Managing Board.

4.6 Initial Designation.

The Directors designated as of the Effective Date are set forth on **Schedule 4.6** hereto.

4.7 Directors Bound.

(a) Each person elected to serve as a Director of the Company shall sign this Agreement, or a counterpart hereof or amendment hereto, or other writing pursuant to which such person (i) acknowledges receipt of a copy of this Agreement as amended and in effect as of the date of such writing, (ii) agrees that such person is a party to and bound by this Agreement, including the power of attorney set forth below, (iii) agrees to perform the duties of a Director hereunder, and (iv) agrees to execute and deliver such additional agreements, instruments, certificates and documents as may be necessary, appropriate or convenient to reflect the foregoing matters and the election of such person as a Director of the Company.

(b) Upon the death, resignation, removal or expiration of the term of any Director (a "**Terminated Director**"), (i) such Terminated Director shall have no further authority under this

Agreement, (ii) such Terminated Director shall have no further obligations or rights under this Agreement (except for liabilities and rights accruing prior to the date of death, resignation, removal or expiration of such Terminated Director's term, including rights to exculpation and indemnification under Article 11 hereof which relate to actions or omissions occurring during such person's service as a Director), and (iii) no writing or instrument shall be required to be executed by the Company or the Terminated Director to reflect such cessation of service, except that the Terminated Director (or his legal representative or attorney-in-fact, as provided in the following paragraph) shall execute and deliver any agreement, instrument, certificate or document which may be reasonably required to reflect that the Terminated Director is no longer a Director of the Company.

(c) Each person now or hereafter serving as a Director of the Company, by execution of this Agreement, an amendment hereto, or other writing acknowledging that such person is bound hereby, hereby constitutes and appoints each other person who may from time to time be serving as an Officer, and each of them acting singly, such Director's agent and attorney-in-fact for the purpose of executing and delivering any and all agreements, instruments and other documents as are necessary or appropriate to reflect that such person is no longer a Director of the Company following the death, resignation, removal or expiration of the term of such Director, which power of attorney is hereby agreed and acknowledged to be and irrevocable and shall survive the death, resignation, removal, expiration of the term, bankruptcy or incapacity of any Director until such time as the cessation of such Director's service in such capacity has been reflected by all necessary or appropriate agreements, instruments and other documents.

ARTICLE 5

Employees; Operating Plan and Budget; Scientific Advisory Board

5.1 Employees.

(a) Number; Duties and Power. There will be such number of employees of the Company (including for such purpose employees of a Member who are seconded thereby to the Company), including a President, Chief Scientific Officer and such other senior management, as may be determined from time to time by the Managing Board. The Managing Board will have the right to confer upon any employee such titles and delegate thereto such specifically defined duties as the Managing Board deems appropriate. *Notwithstanding the foregoing or any other provision of this Agreement, the Act or the Certificate to the contrary*, no employee of the Company will have the power or authority to do or perform any act with respect to a Major Decision unless such Major Decision has been approved in accordance with Section 4.3.

(b) Secondment and Reimbursement.

(i) Until such time as the Members mutually agree that the Company may directly employ employees, all employees of the Company will be employed by either Alnylam or Isis. Alnylam and Isis will each determine which of its own employees will perform such Member's research, development and other obligations required by the Approved Operating Plan and/or Services Agreement, each Member will second such employees to the Company. The

Company will reimburse each Member for the cost of such employees as set forth in the Approved Operating Plan and/or Services Agreement.

(ii) After such time as the Members mutually agree that the Company may directly employ employees, at the discretion of the employing Member and the approval of the President of the Company, employees seconded to the Company may become full-time employees of the Company.

(c) Appointment and Removal. Subject to Section 4.3, the Managing Board will have the right to appoint and the right to remove (with or without cause), any Officer or employee and the President will have the right to appoint and remove (with or without cause) any employee who is directly employed by the Company and is not an Officer. Each Officer will hold office until a successor has been designated by the Managing Board and qualified or until his or her earlier death, resignation or removal.

(d) Officers.

(i) The Managing Board, with the approval of the Members pursuant to Section 4.3, will appoint a President and Chief Scientific Officer. Until such time as the Members mutually agree otherwise, each such Officer will be employed by either Alnylam or Isis (and to the extent not an employee of Alnylam or Isis, as the case may be, then such Officer will enter into a consulting arrangement with such Member), but will be seconded to the Company by such Member and dedicated full time to activities relating to the Company. The Company will reimburse the Member employing the President

and/or Chief Scientific Officer as set forth in the Approved Operating Plan, or as otherwise determined by the Managing Board and Members in accordance with Section 4.3.

(ii) The President and Chief Scientific Officer, as well as any other employee designated by the Managing Board as an officer of the Company (each, an "**Officer**"), if required to do so by the Managing Board, will enter into employment and/or consulting agreements with the Company and/or the Members that include customary assignment of inventions, non-disclosure and "non-compete" provisions (to the extent enforceable under the laws of the jurisdiction in which the Officer performs services for the Company) and other customary provisions approved by the Managing Board.

(e) Compensation.

(i) Any material compensation program or material benefit plans of the Company, as they may be amended from time to time, are subject to approval by the Managing Board and, in the case of Officers, by the Members in accordance with Section 4.3.

(ii) Subject to the approval requirements of this Agreement, the Officers will receive such compensation as the Managing Board may determine, including equity compensation in the form of stock options grants from both Members. To the extent either Member's Board of Directors does not approve, or the Member does not make, such stock option grant in the full amount recommended, or at all, such Member will be required to compensate the Officer to whom the grant is not approved or made with cash such that the Option Value of the

stock options granted and cash paid to the Officer from such Member is equal to the Option Value of the stock options recommended by the Managing Board.

(iii) Subject to approval of the relevant Member's Board of Directors, employees other than Officers will receive equity compensation in the form of stock option grants from the Member seconding such employee to the Company. The terms and conditions of such stock option grants will be consistent with the stock option grants made by such Member to similarly situated employees dedicated full time to activities of the Member.

(f) Services. For the Initial Commitment Period, each Member will provide services to the Company, the cost of which is included in the FTE rate and set forth in the Services Agreement, with no resulting change to the Members' Capital Accounts. The individuals providing such services need not be dedicated full time to activities of the Company.

(i) Isis will provide general and administrative support services, other than business development services, on an as needed basis.

(ii) Alnylam will provide business development services to the Company, on an as needed basis.

(iii) Each of Alnylam and Isis will provide Intellectual Property prosecution and enforcement services to the Company on an as needed basis and as determined by the Collaboration Working Group.

5.2 Operating Plan.

(a) The initial Operating Plan, dated as of the Effective Date attached hereto as **Exhibit A** (the **"Initial Operating Plan"**), will be deemed the "Approved Operating Plan" for the period beginning on the Effective Date and ending on [***] (such period, the **"Initial Commitment Period"**). No later than [***], the Parties will review and consider, together with the Collaboration Working Group, whether to revise the Initial Operating Plan.

(b) No later than September 30, [***], and no later than September 30 in each Fiscal Year thereafter, the Collaboration Working Group will submit to the Managing Board a proposal for revising the Approved Operating Plan then in effect ("**Proposed Operating Plan**"), which will include a proposed Development Plan (**"Proposed Development Plan")**, proposed Operating Budget **("Proposed Operating Budget"**) and proposed Capital Contribution Schedule (**"Proposed Capital Contribution Schedule"**).

(c) Each Proposed Operating Plan will be considered at the first meeting of the Managing Board following its submission and will be subject to the approval of the Managing Board and the Members in accordance with Section 4.3. The Chairperson will call a special meeting of the Managing Board for this purpose at the request of any Director if the next scheduled regular meeting is later than December 31 of the year in which submission is made. Any such Proposed Operating Plan (or any amendment thereto) that is approved by the Managing Board will be considered the "**Approved Operating Plan**" for all purposes of this Agreement until amended or replaced.

(d) In the event that, during the Initial Commitment Period, funding in addition to that set forth in the Initial Capital Contribution Schedule is required to continue to carry out the Development Plan, the Members agree to use their best efforts to negotiate and approve a Proposed Operating Plan for the remainder of the Initial Commitment Period.

(e) If, after the Initial Commitment Period, the Managing Board and the Members in accordance with Section 4.3 are unable to [***] (a "**Stalemate**"), either Member may initiate a Buy-Out; provided, however, that in the event sufficient funding is available to the Company to continue to carry out the Development Plan after the Initial Commitment Period, a Stalemate will not be deemed to have occurred, and neither Member may initiate a Buy-Out, until a date [***] days prior to the date on which all of the Company's funds are expected to be depleted as determined based on the Approved Operating Plan then in effect.

5.3 Scientific Advisory Board.

(a) The Company will establish a Scientific Advisory Board (**"SAB"**) consisting of at least three (3) members. The initial members and chairperson of the SAB will be as set forth on **Schedule 5.3**. Any changes to the composition of the Scientific Advisory Board, including the removal or appointment of the chairperson, will be made in accordance with Section 4.3.

(b) Each member of the SAB will also enter into a consulting agreement with the Company (a **"SAB Consulting Agreement"**) pursuant to which such member of the SAB will provide advisory, educational and other services to the Company, and pursuant to which such SAB member will provide advisory and educational services to each Member. Each such SAB Consulting Agreement will be in substantially the form attached hereto as **Schedule 4.5** and will provide for, among other things, the provision of stock options to purchase common stock of the Members. Pursuant to the SAB Consulting Agreement, the Managing Board will recommend to each Member's Board of Directors the stock options to be granted by such Member to the members of the SAB pursuant to and consistent with such Member's equity incentive plan. To the extent either Member's Board of Directors does not approve, or the Member does not make, such stock option grant as recommended by the Managing Board, such Member will be required to compensate each SAB member to whom the grant is not approved or made with cash, such that the Option Value of the stock options granted, if any, and cash paid to the SAB member by the Member is equal to the Option Value of the stock options recommended to be issued by such Member to the SAB member by the Managing Board.

(c) The SAB will meet at least quarterly until December 31, 2009 and will initially be responsible for:

(i) advising the Company as to research goals and plans;

(ii) reviewing research data and advising the Company with respect to interpretation of such research data, as requested by the Managing Board, President or Chief Scientific Officer; and

(iii) advising the Company with respect to research and development decisions, as requested by the Managing Board, President or Chief Scientific Officer.

ARTICLE 6

Capital Contributions and Percentage Interests

6.1 Capital Contributions.

(a) In consideration for Alnylam's initial Membership Interest in the Company, Alnylam is contributing to the Company the Intellectual Property as set forth in Sections 2.1 and 2.2 of the License Agreement (the **"Alnylam Initial IP Contribution"**). In addition, Alnylam agrees to contribute in cash an aggregate of $10,000,000 to the Company within five (5) days following the Effective Date. Such cash contribution by Alnylam is intended by the Parties to be used by the Company to fund the Approved Operating Plan. The Parties agree that the aggregate fair market value of the rights, assets and cash contributed by Alnylam as described in this Section 6.1(a) will be equal to $[***] as of the date of their contribution.

(b) In consideration for Isis' initial Membership Interest, Isis is contributing to the Company the Intellectual Property as set forth in Sections 2.1 and 2.2 of the License Agreement (the **"Isis Initial IP Contribution"**). The Parties agree that the aggregate fair market value of the rights and assets contributed by Isis as described in this Section 6.1(b) will be equal to $[***] as of the date of their contribution.

(c) Operating Plan Contributions. Each of the Members agrees to make the additional Capital Contributions set forth in the Initial Capital Contribution Schedule, which is contained in the Initial Operating Plan (**"Initial Operating Plan Contributions**"). Each Member also agrees to make any additional Capital Contributions as set forth in any Capital Contribution Schedule contained in an Approved Operating Plan (**"Future Operating Plan Contributions"** and together with Initial Operating Plan Contributions, **"Operating Plan Contributions"**).

(d) Pro Rata Contributions. The Members will be responsible, pro rata in accordance with their Percentage Interests, for any Capital Contributions required to be made pursuant to Section 6.1(c); provided, however, that in the event a Member fails to make any Operating Plan Contribution in accordance with Section 6.1(c), then until such time as the defaulted amount of capital has been paid by such Member (the "**Defaulting Party**"), interest will accrue thereon (at the rate of [***] percent ([***]%) per annum or, if lower, the highest interest rate permitted by applicable law), and will be due to the Company; provided further that, in the event the Defaulting Party has not paid such defaulted amount of capital, plus accrued interest thereon, within thirty (30) days of the Managing Board's request for such Capital Contribution, the other Member (the "**Non-Defaulting Party**") will have the right to elect to initiate a Buy-Out.

(e) Additional Capital. Any funds contributed by the Members to the Company pursuant to this Agreement (other than the Members' Initial Capital Contributions), will be referred to as an "**Additional Capital Contribution**" and will constitute additional Capital Contributions to the Company.

(f) Percentage Interests. The Members hereby agree that the Percentage Interests of each Member as of the Effective Date are as set forth on **Schedule 3.1**.

(g) Adjustments to Capital Contributions. Except as provided in Section 6.1(c), in no event and at no time will a Member be required or permitted to make a Capital Contribution other than in accordance with Section 6.1(a) and (b).

(h) Capital Account. Each Member's Capital Account will be determined in the manner described in Section 6.4 of this Agreement.

(i) Transfer Taxes. Each Member will pay all sales, use, transfer, real property transfer, recording, gains, stock transfer and other similar taxes and fees ("**Transfer Taxes**") incurred in connection with its Capital Contributions to the Company and will be responsible for filing all necessary documentation and tax returns with respect to such Transfer Taxes. Each Member will be responsible for any and all Taxes imposed upon such Member or its Affiliates in connection with their respective Capital Contributions to the Company or in connection with any distribution of property from the Company.

6.2 Withdrawal or Reduction of Capital Contributions.

Except as expressly provided in this Agreement, no Member will have the right to withdraw from the Company or be repaid all or any part of such Member's Capital Contribution or any other payment in respect of its Membership Interests (including any payment contemplated by Section 18-604 of the Act), and this Section 6.2 will expressly constitute a "provision otherwise" for purposes of Section 18-604.

6.3 No Interest on Capital Contributions.

No interest will be payable by the Company on or with respect to the Capital Contributions or Capital Accounts.

6.4 Capital Accounts.

(a) A single Capital Account will be maintained for each Member (regardless of the time or manner in which such interest was acquired) in accordance with the capital accounting rules of section 704(b) of the Code, and the regulations thereunder (including Treasury Regulations section 1.704-1(b)(2)(iv)) (a "**Capital Account**"). In general, under such rules, a Member's Capital Account will be:

(i) increased by (A) the amount of money contributed by the Member to the Company (including the amount of any Company liabilities that are assumed by such Member other than in connection with a distribution of Company property), (B) the Fair Market Value of property contributed by the Member to the Company (net of liabilities secured by such contributed property that under section 752 of the Code the Company is considered to assume or take subject to), and (C) allocations to the Member of Company income and gain (or any item thereof), including income and gain exempt from tax; and

(ii) decreased by (A) the amount of money distributed to the Member by the Company (including the amount of such Member's individual liabilities that are assumed by the Company other than in connection with a contribution of property to the Company), (B) the Fair Market Value of property distributed to the Member by the Company (net of liabilities secured

by such distributed property that under section 752 of the Code such Member is considered to assume or take subject to), (C) allocations to the Member of expenditures of the Company not deductible in computing its taxable income and not properly chargeable to capital account, and (D) allocations to the Member of Company loss and deduction (or any item thereof).

Except as otherwise required by the Treasury Regulations, the transferee of any Membership Interest in the Company will succeed to the Capital Account of the transferor to the extent it relates to the transferred Membership Interest.

(b) Where section 704(c) of the Code applies to Company property or where Company property is revalued pursuant to paragraph (b)(2)(iv)(f) of Treasury Regulations section 1.704-1, each Member's Capital Account will be adjusted in accordance with Treasury Regulations sections 1.704-1(b)(2)(iv)(g) and 1.704-3(d)(2) as to allocations to the Members of depreciation, depletion, amortization and gain or loss, as computed for book purposes with respect to such property.

(c) When Company property is revalued pursuant to Treasury Regulations section 1.704-1(b)(2)(iv)(f), or where Company property is distributed in kind (whether in connection with liquidation and dissolution or otherwise), the Capital Accounts of the Members will first be adjusted to reflect the manner in which the unrealized income, gain, loss and deduction inherent in such property (that has not been reflected in the Capital Account previously) would be allocated among the Members if there were a taxable disposition of such property for the Fair Market Value of such property (taking into account section 7701(g) of the Code) on the date of distribution.

(d) It is intended that the Capital Accounts of the Members will be determined and maintained throughout the term of the Company in accordance with, and will be adjusted as may be required under, section 704 of the Code and the Treasury Regulations promulgated thereunder. The foregoing provisions of this Section 6.4 and certain other provisions of this Agreement are intended to comply with the Treasury Regulations promulgated under section 704 of the Code and will be interpreted and applied in a manner consistent with said Treasury Regulations. The Tax Matters Partner will make or cause to be made all necessary adjustments in each Member's Capital Account, or the manner in which the Capital Accounts, or any debits or credits thereto, are computed, as required by the capital accounting rules of section 704 of the Code and the regulations thereunder.

(e) No Member will be required to pay the Company or to any other Member the amount of any negative balance which may exist from time to time in such Member's Capital Account.

ARTICLE 7

Allocation of Profits and Losses; Distributions; Tax and Accounting Matters

7.1 Allocations.

Each Member's distributive share of the Company's total income, gain, loss, deduction or credit (or items thereof), which total will be as shown on the annual federal income tax return prepared by or at the direction of the Tax Matters Partner or as finally determined by the United States Internal Revenue Service or the courts, and as modified by the capital accounting rules of section 704(b) of the Code and the Treasury Regulations thereunder, as implemented by Section 6.4 hereof, as applicable, will be determined as follows:

(a) General Allocation. Except as otherwise provided in this Article 7, all of the Company's items of income, gain, loss, deduction or credit (or items thereof) will be allocated to the Members pro rata in accordance with their Percentage Interests.

(b) Regulatory Allocations. The following provisions are intended to comply with certain regulatory requirements for allocations set forth in section 704(b) of the Code. It is the intent and understanding of the parties that the allocations required by this Section 7.1(b) will be offset by future,

offsetting allocations pursuant to this Section 7.1(b).

(i) Limitation. *Notwithstanding anything in this Section 7.1 to the contrary*, items of loss and deduction allocated to any Member pursuant to this Section 7.1 with respect to any taxable year will not exceed the maximum amount of such items that can be so allocated to such Member without causing such Member to have a deficit balance in its Capital Account in excess of the amount of such Member's obligation, if any, to restore such deficit Capital Account, computed in accordance with the rules of Treasury Regulations section 1.704-1(b)(2)(ii)(d). Any such items of loss or deduction in excess of the limitation set forth in the preceding sentence will be allocated as follows and in the following order of priority:

(A) first, to those Members who would not be subject to such limitation, proportionately in accordance with their Percentage Interests; and

(B) second, any remaining amount to the Members in the manner required by the Code and Treasury Regulations.

(ii) Minimum Gain Chargeback. *Notwithstanding anything to the contrary in this Section 7.1*, if there is a net decrease in "minimum gain" or "partner nonrecourse debt minimum gain" (as such terms are defined in Treasury Regulations sections 1.704-2(b) and 1.704-2(i)(2)) during a taxable period of the Company, then each Member will be allocated items of income and gain for such year (and, if necessary, for subsequent years) in the manner provided in Treasury Regulations section 1.704-2. This provision is intended to be a "minimum gain chargeback" and "partner nonrecourse debt minimum gain chargeback" within the meaning of Treasury Regulations sections 1.704-2(f) and 1.704-2(i)(4) and will be interpreted and implemented as therein provided.

(iii) Qualified Income Offset. *Subject to the provisions of Section 7.1(b)(ii), but otherwise notwithstanding anything to the contrary in this Section 7.1*, if any Member's Capital Account has a deficit balance in excess of such Member's obligation to restore its Capital Account balance, computed in accordance with the rules of paragraph (b)(2)(ii)(d) of Treasury Regulations section 1.704-1, then sufficient amounts of income and gain (consisting of a pro rata portion of each item of Company income, including gross income, and gain for such year) will be allocated to such Member in an amount and manner sufficient to eliminate such deficit as quickly as possible. This provision is intended to be a "qualified income offset" within the meaning of Treasury Regulations section 1.704-1(b)(2)(ii)(d) and will be interpreted and implemented as therein provided.

(iv) Effect of Special Allocations on Subsequent Allocations. Any special allocation pursuant to Sections 7.1(b)(i), 7.1(b)(iii) and 7.1(b)(vi) hereof will be taken into account in computing subsequent allocations of income and gain pursuant to this Section 7.1 so that the net amount of all such allocations to each Member will, to the extent possible, be equal to the net amount that would have been allocated to each such Member pursuant to the provisions of this Section 7.1 if such special allocations had not occurred. It is anticipated that all allocations pursuant to Section 7.1(b)(v) will be offset by allocations pursuant to Section 7.1(b)(ii) hereof. To the extent the Tax Matters Partner determines that any amount allocated pursuant to Section 7.1(b)(v) hereof is unlikely to be offset by a countervailing allocation of income from Section 7.1(b)(ii) hereof, then so much of such allocation as the Tax Matters Partner has determined is unlikely to be offset will also be taken into account in computing subsequent allocations of income and gain pursuant to this Section 7.1 so that the net amount of all such allocations will, to the extent possible, equal the net amount that would be allocated to such Member in the absence of such special allocation.

(v) Nonrecourse Debt. Items of deduction and loss attributable to "partner nonrecourse debt" within the meaning of Treasury Regulations Section 1.704-2(b)(4) will be allocated to the Members bearing the economic risk of loss with respect to such debt in accordance with Treasury Regulations section 1.704-2(i)(1). Items of deduction and loss attributable to "nonrecourse liabilities" of the Company within the meaning of Treasury Regulations section 1.752-1 will be allocated to the Members in proportion to their respective Percentage Interests.

(vi) Recourse Debt. Items of deduction and loss attributable to "recourse debt" within the meaning of Treasury Regulations section 1.752-1 (but excluding "partner nonrecourse debt" as defined in Section 7.1(b)(v) hereof), will be allocated to the Members bearing the economic risk of loss with respect to such debt.

(c) Allocations With Respect to Certain Property and Income.

(i) In determining each Member's allocable share of the taxable income or loss of the Company, depreciation, depletion, amortization and gain or loss with respect to any contributed property, or with respect to property which has been revalued as provided in Treasury Regulations section 1.704-1(b)(2)(iv)(f), will be allocated among the Members in accordance with the principles of section 704(c) of the Code, as set forth in the Treasury Regulations thereunder and under section 704(b) of the Code. Such allocation will be made in

accordance with the remedial method described by Treasury Regulations section 1.704-3(d) unless another method or combination of methods as permitted under Treasury Regulations section 1.704-3 is selected by the Tax Matters Partner.

(ii) Solely for tax purposes, a Member's share of the Company's depreciation recapture recognized for tax purposes upon the disposition of Company property will be computed in the manner provided for in Treasury Regulations sections 1.704-3(a)(11), 1.1245-1(e) and 1.1250-1(f). The allocations provided for in this Section 7.1(c)(ii) are required to be made solely for tax purposes and will not affect any Member's Capital Account.

(iii) Subject to Sections 7.1(b) and 7.1(c)(i) hereof, if and to the extent any transaction between the Company and a Member results in any adjustment being made to the income of the Company under section 482 or 7872 of the Code, or any similar provision now or hereafter in effect, any corresponding resulting item of Company income, gain, loss or deduction will be allocated in its entirety to the affected Member.

(d) Change in Percentage Interests. Except as otherwise required by law, if the Percentage Interests of the Members of the Company are changed during any taxable year, all items to be allocated to the Members for such entire taxable year will be prorated on the basis of the portion of such taxable year which precedes each such change and the portion of such taxable year on and after each such change by closing the books of the Company

effective as of the close of business on the date of such change, and the items so allocated for each such portion will be allocated to the Members in the manner in which such items are allocated as provided in Section 7.1(a) hereof during each such portion of the taxable year in question.

(e) State and Local Items. Items of income, gain, loss, deduction, credit and tax preference for state and local income tax purposes will be allocated to and among the Members in a manner consistent with the allocation of such items for federal income tax purposes in accordance with the foregoing provisions of this Section 7.1.

7.2 Distributions.

(a) Tax Distributions.

(i) With respect to each fiscal quarter, subject to the limitations provided in subsection (ii) below and in Section 7.4(b), and after making payment or provision for current obligations and operating expenses of the Company, but *otherwise notwithstanding anything to the contrary provided for in this Section 7.2*, the Company, to the extent of its available cash, will make distributions of cash to the Members pro rata in accordance with their respective Percentage Interests during such fiscal quarter, as promptly as practicable and in any event by the Tax Distribution Date for such fiscal quarter, so that each Member will receive an amount (a "**Tax Distribution**") equal to its federal, state and local income taxes (including obligations for estimated tax) on the taxable income that it derives as a Member of the Company for such fiscal quarter (based upon an assumed combined marginal rate of federal, state and local taxation of forty-two percent (42%), or as the Managing Board will otherwise reasonably determine). In determining the taxable income of a Member with respect to any fiscal quarter, to the extent that actual taxable income for the relevant period is not available as of the Tax Distribution Date, the

determination will be made by the Company based upon a good faith estimate of actual taxable income for such period and may be based upon the methodology permitted by the Code which results in the lowest estimated tax liability for such Members. In determining the Tax Distribution for any fiscal quarter, the cumulative amount of taxable income or loss for prior fiscal quarters in the same Fiscal Year and the Tax Distributions with respect to such prior fiscal quarters can be taken into account. To the extent the amount based upon estimates is more or less than the actual taxable income for such period as subsequently determined, the Managing Board may appropriately decrease or increase, respectively, subsequent distributions to take into account such variance. In the event that the Percentage Interest of any Member changes during the fiscal quarter, the appropriate Percentage Interests to be used in determining the amount of any Tax Distribution with respect to such fiscal quarter will be determined in a manner consistent with Section 7.1(d). To the extent cash is not available to make any Tax Distribution in full, the undistributed amount thereof will be carried forward on a cumulative basis and distributed from available cash as soon as reasonably practicable thereafter.

(ii) The aggregate amount of Tax Distributions may be reduced with respect to any fiscal quarter (x) to reflect a reduction in the applicable U.S. federal income tax rate; or (y) if and to the extent that the Managing Board determines that the Company's cash reserves are inadequate for such purpose in view of identifiable Company expenses and projected investment activities.

(iii) "**Tax Distribution Date**" will mean a date in each fiscal quarter by which timely quarterly estimated tax payments can be filed.

(b) Tax Withholding on Distributions. The Company will at all times be entitled to make payments required to discharge any obligation of the Company to withhold or make payments to any governmental authority with respect to any United States federal, state or local tax liability or any other tax liability of any Member liable for such Taxes arising out of such Members' interest in the Company. For purposes of this Agreement, any such payments or withholdings will be treated as a distribution to the Member on behalf of whom the withholding or payment was made.

(c) Distributions on Liquidation. Distributions pursuant to liquidation of the Company will be made in accordance with Section 10.3 hereof.

(d) Ordinary Course Distributions. Subject to the other provisions of this Agreement, including Section 4.3 and Section 9, and Section 5 of the License Agreement, prior to the dissolution of the Company, the Company shall distribute cash or assets to the Members in such amounts, at such times and as of such record dates as the Managing Board determines, as long as such distributions are in accordance with the Members' respective Percentage Interests.

7.3 Accounting Matters.

(a) The Company will cause to be maintained complete books and records accurately reflecting the accounts, business and transactions of the Company on a calendar-year basis and with sufficient detail and completeness customary and usual for businesses of the type engaged in by the Company. The Company's books and records and financial statements will be kept

using the accrual method of accounting and in accordance with U.S. generally accepted accounting principles. The books and records with respect to the Company's capital accounts and allocations of income, gain, loss, deduction or credit (or items thereof) will be kept under United States federal income tax accounting principles as applied to entities taxable as partnerships. The Company's financial statements will be audited annually by an independent nationally recognized public accounting firm. At a minimum, the Company will keep such books and records as may be required by the Act and such other books and records as are required by Article 12.

(b) The shares of Alnylam and Isis are publicly traded in the United States. Consequently, the Company may be subject to financial reporting and legal requirements imposed upon publicly traded companies. Among these legal requirements are those imposed by Section 404 of the Sarbanes Oxley Act of 2002, as the same may be amended from time to time. Notwithstanding any differences in the internal control procedures of the Members, the Company will abide by the internal control procedures required by the Member consolidating the Company's financial books and records into such Member's books and records **("Consolidating Member")**.

7.4 Tax Status and Returns.

(a) Any provision hereof to the contrary notwithstanding, solely for United States federal income tax purposes, each of the Members hereby recognizes that the Company will be subject to all provisions of Subchapter K of Chapter 1 of Subtitle A of the Code.

(b) The Tax Matters Partner will prepare or cause to be prepared, at the Company's expense, all tax returns and statements, if any, that must be filed on behalf of the Company with any taxing authority, and will make timely filing thereof, including filings pursuant to extensions permitted under applicable federal and state tax regulations. To the extent allowed by applicable law, the Tax Matters Partner will take no position on any tax return which adversely affects one Member disproportionately, and will attempt to maximize, to the extent possible, the interests of all Members. On or before June 30 of each calendar year, the Tax Matters Partner will prepare or cause to be prepared and delivered to each Member a draft Internal Revenue Service Form 1065 and Schedule K-1 and a report setting forth in reasonable detail the information with respect to the Company during such calendar year reasonably required to enable each Member to prepare its federal, state and local income tax returns in accordance with applicable law then prevailing, including information required by such Member to allocate and apportion the Company's income for state income tax purposes. Each Member will have the right to object to any amount or information reported on the draft Form 1065 or Schedule K-1 on or before July 31 of such calendar year. If the Members cannot agree to the appropriate amounts or information to be included on Form 1065 or Schedule K-1, the President of the Company will resolve the dispute in a manner consistent with the guidance set forth in Financial Accounting Standards Board Interpretation No. 48, *Accounting for Uncertainty in Income Taxes*, specifically the concept that a tax position is more likely than not to be sustained on audit by the taxing authority based solely on the technical merits of the associated tax position.

7.5 754 Election.

In the event of a distribution of property to a Member or a transfer of any interest in the Company permitted under the Act or this Agreement, the Company will not file an election under section 754 of the Code and the Treasury Regulations thereunder to adjust the basis of the Company's assets under section 734(b) or 743(b) of the Code or corresponding election under the applicable provisions of state and local law, unless the Managing Board will have consented thereto. In the event the Company makes such an election, the Person making such request will pay all costs incurred by the Company in connection therewith, including reasonable attorneys' and accountants' fees.

7.6 Tax Information.

Each Member may request from the Company any information reasonably necessary for the Member to complete any of its tax returns or compute estimated tax payments and the Company will, within a reasonable period of time following the request, provide such information to the requesting Member.

7.7 Tax Matters Partner.

(a) Isis will be (and is hereby designated as) the Company's "Tax Matters Partner" in accordance with section 6231(a)(7) of the Code and will have all powers conferred on a "Tax Matters Partner" thereunder and all other powers necessary to perform thereunder, including the right to manage administrative tax proceedings conducted at the Company level by the Internal Revenue Service with respect to Company matters and the right to file for extensions for the Company's tax returns and statements pursuant to applicable federal and state tax regulations. The Tax Matters Partner will provide such information to the Members as is required by the Code and Treasury Regulations, which information will include informing each Member of administrative and judicial proceedings for the adjustment of Company items required to be taken into account by a Member for income tax purposes.

(b) *Notwithstanding anything in this Section 7.7 to the contrary*, the Tax Matters Partner will not enter into an agreement with the Internal Revenue Service or any other taxing authority to extend the period for assessment of any federal, state or local income, franchise or unincorporated business tax of any Member. The Tax Matters Partner will not settle with the Internal Revenue Service or any other taxing authority to disallow items of the Company's deductions or increase the Company's income unless the Managing Board will have agreed thereto. Each Member reserves all rights under applicable law, including the right to retain independent counsel of its choice at its expense (which counsel will receive the full cooperation of the Tax Matters Partner and will be entitled to prior review of all submissions by the Company in respect of any dispute with the relevant taxing authority).

(c) Reasonable expenses incurred by the Tax Matters Partner in connection with the performance of its duties as Tax Matters Partner, including third-party expenses of any such administrative proceeding described in this Section 7.7 and undertaken by the Tax Matters Partner will be paid out of (or reimbursed from) assets of the Company. The cost of participation

in any such proceeding by a Member and the cost of any audit or adjustment to a Member's tax return will be borne by the affected Member.

ARTICLE 8

Restrictions on Transfer

8.1 Transfer of Interests.

(a) No Member may directly or indirectly sell, assign, transfer, pledge, hypothecate, or otherwise deal with or encumber or dispose of in any way (each a "**Transfer**") such Member's Membership Interest, whether in whole or in part, voluntarily or involuntarily, by operation of law or otherwise, except in accordance with the terms and conditions set forth in this Article 8. Any attempt to Transfer in violation of this Article 8 will be deemed null and void and, for avoidance of doubt, any Person to whom Membership Interests are attempted to be transferred in violation of this Article 8 will not be entitled to vote on matters coming before the Members, act as an agent of the Company, designate Directors, receive distributions from the Company, or have any other rights in or with respect to such Membership Interests.

(b) Except as provided in this Article 8, each Member agrees that it may not and will not Transfer its Membership Interest without the prior written consent of the other Member. Any Member purporting to Transfer its Membership Interest, or any part thereof, in violation of this Article 8 will be liable to the Company and the other Member for all liabilities, obligations, damages, losses, costs and expenses (including reasonable attorneys' fees and

court costs) arising as a direct or consequential result of such non-complying transfer, attempted transfer or purported transfer, including any additional costs or taxes created thereby and any events of the types described in Section 8.2(a).

8.2 Exempt Transfers.

(a) Affiliates. The Transfer restrictions set forth in Section 8.1 will not apply to Transfers by a Member (the "**Transferring Member**") to an Affiliate of such Member; provided, however, that the Affiliate of the Transferring Member must have the resources, assets, experience, qualifications, permits and other rights necessary to perform under this Agreement and each of the Ancillary Agreements.

(b) Change in Control. The Transfer restrictions set forth in Section 8.1 will not apply to Transfers pursuant to a Change in Control of a Member. In the event of a Change in Control of a Member, the other Member may initiate a Buy-Out pursuant to Section 9.1.

(c) In the event of a Transfer pursuant to Section 8.2(a) or 8.2(b) the Transferring Member will indemnify and hold the Company, and, if applicable, any Member other than the Transferring Member, harmless for, and will pay to the Company and, if applicable, any such Member, the amount of all Losses arising from or related to such Transfer, including the following:

(i) expenses incurred by the Company in connection with the Transfer;

(ii) the violation of any securities laws or any other applicable Federal or state laws or the order of any court having jurisdiction over the Company or any of its assets;

(iii) the Transfer resulting in or creating a "prohibited transaction" as defined in section 4975(c) of the Code or resulting in or causing the Company or any Member, other than the Transferring Member, to be liable for excise tax under Chapter 42 of the Code or result in or cause the Company or the Company's assets to become the assets of an employee benefit plan (as defined in section 3(3) of ERISA);

(iv) the violation of or an event of default under, or result in acceleration of any indebtedness under, any note, mortgage, loan, or similar instrument or document to which the Company is a party;

(v) the imposition of a material obligation or liability under a material contract;

(vi) an adverse tax consequence to the Company or any of the Members, other than the Transferring Member, including any adverse tax consequence resulting, directly or indirectly, from the termination of the Company under section 708 of the Code; and

(vii) the Transfer causing the Company to be classified as an entity other than a partnership for purposes of the Code.

In addition to the foregoing, a Member may not Transfer less than all of its Membership Interest pursuant to Section 8.2(a) or 8.2(b) (a "**Partial Transfer**") unless such Partial Transfer is approved by the Managing Board, which approval will not be unreasonably withheld provided that (A) the Transferring Member agrees to any amendments to this Agreement and the Ancillary Agreements reasonably necessary to preserve the relative rights and obligations of the Transferring Member and its transferee, on the one hand, and those of the other Members, on the other, and (B) the Partial Transfer will not result in a material adverse effect on the Company.

(d) Obligations of Transferring Members. The Transfer of a Membership Interest will not release the Transferring Member from any liability or obligation that such Transferring Member or its transferee may have to the Company. For the avoidance of doubt, the Transferring Member will remain subject to the obligations of a Member under Section 6.1 and Section 12.4. In addition, unless otherwise agreed by the Managing Board, the Transferring Member will be directly liable for any non-performance or breach by the transferee under this Agreement.

(e) Transfer of Shares of Public Companies. The provisions of this Article 8 will not apply to any Transfer of interests in the Members that do not result in a Change of Control of such Member.

8.3 Substitution of Members.

Upon the Transfer of all or any part of a Membership Interest to a transferee in accordance with this Article 8, such transferee will have the right to become a Member only if (i) such Person becomes a party to this Agreement, and, if requested by the other Member, any

other Ancillary Agreement to which the transferor was a party immediately prior to the Transfer, by executing one or more instruments reasonably satisfactory in form and substance to the other Member and (ii) such Person pays any reasonable expenses in connection with such Person's admission as a new Member.

ARTICLE 9

Buy-Out

9.1 Right to Initiate Buy-Out.

(a) Within (a) the [***] day period immediately following the end of the Initial Commitment Period, (b) solely in the event of a Stalemate occurring after the end of the Initial Commitment Period, the [***] day period following such Stalemate, (c) at any time, whether before or after the end of the Initial Commitment Period, during the [***] day period following notice from a Member that it has entered into a binding agreement providing for a Change of Control of such Member (such [***] or [***] day period, a **"Buy-Out Notice Period"**), (d) as provided for in the Ancillary Agreements or (e) during the [***]

day period following the Managing Board's request for a Capital Contribution as provided in Section 6.1(d), either Member (in the case of (a) or (b)), the Member receiving the notice of a Change in Control (in the case of (c)), the Member or Members as specified in the Ancillary Agreements (in the case of (d)) or the Non-Defaulting Member (in the case of (e)) (in each case, the **"Initiating Member"**) has the right, exercisable upon written notice to the Company and the other Member (the **"Buy-Out Notice"**), to initiate the sale of the Company or the allocation of the Company's assets, including the Company Intellectual Property and Company's rights in Licensed IP (the **"Buy-Out"**).

(b) In the event a Buy-Out is initiated by a Member hereunder, the terms set forth in this Article 9 will apply (unless otherwise mutually agreed by the Parties).

9.2 Negotiated Resolution.

Following the Company's receipt of the Buy-Out Notice, the Members will mutually determine whether to attempt to sell the Company to a Third Party or a Member (whether through merger, acquisition of 100% of the Membership Interests or purchase of all or substantially all of the assets of the Company) (a "**Sale**"). In the event the Members determine to attempt such a Sale, the Company will retain a reputable investment bank chosen by mutual agreement of the Members to assist with the valuation and possible Sale of the Company; provided, however, that, *notwithstanding anything in this Section 9.2 to the contrary*, neither Member will be required to agree to enter into, or to approve the Company's entering into, such a Sale. Any such Sale will be subject to all other terms agreed upon by the Members and the Company, which will be documented in a separate written agreement among the parties (a **"Sale Agreement"**).

9.3 Non-Negotiated Resolution.

(a) If the Members do not determine pursuant to Section 9.2 to attempt a Sale of the Company, or have not within [***] days after the Company's receipt of the Buy-Out Notice, or such longer period as mutually agreed to by the Members (such period, the **"Buy-Out Negotiation Period"**), executed a Sale Agreement, the Company will, except as otherwise set forth in this Section 9.3, distribute and assign to the Members, or their designated Affiliate, jointly, in accordance with Percentage Interests, all of the Company's rights, interests and assets, other than any contracts and/or arrangements between the Company and Third Parties that the Managing Board determines cannot or should not be assigned ("**Third Party Contracts**") (provided that the Parties agree to use Commercially Reasonable Efforts to provide for the assignment of all Third Party Contracts), and the provisions of this Section 9.3 will apply.

(b) Distribution of Intellectual Property.

(i) Upon the distribution of the Company's assets pursuant to this Section 9.3, each Member or its designated Affiliate will receive, subject to Third Party Rights and Third Party Contracts, (1) a co-exclusive license under Company Intellectual Property Controlled by the Company at the end of the Buy-Out Negotiation Period, for any and all purposes, and (2) a co-exclusive license under Licensed IP licensed to the Company at the end of the Buy-Out Negotiation Period, for any and all purposes within the scope of the license granted to the Company (collectively, the **"Distributed IP"**); provided, however, that (y) to the extent that one Member has obtained a license in connection with an Opt-In Election or obtains a license pursuant to Section 9.3(d) or 9.3(e), the licenses to the Distributed IP under this Section 9.3(b) will not include the right to Develop, Manufacture or Commercialize the Program/Project Compounds or Program/Project Therapeutics subject to such Opt-In election or license pursuant to Section 9.3(d) or 9.3(e); and (z) to the extent that a Member has obtained a license in connection with Section 2.3 of the License Agreement, the licenses to the Distributed IP under this Section 9.3(b) will be subject to such license granted to such Member. For purposes of this Section 9.3(b)(i), "co-exclusive" means that such license is exercisable by each Member or its designated Affiliate, and that the Company retains no rights to exercise any such licensed Intellectual Property.

(ii) The rights granted to each Member in this Section 9.3(b) will be (1) royalty-bearing, as set forth in Section 9.3(b)(iii) below, and (2) sublicenseable solely (A) to such Member's Affiliates or (B) by such Member or its Affiliates to a Third Party pursuant to a Bona Fide Collaboration; provided that, (x) each such sublicense will be subject and subordinate to, and consistent with, the terms and conditions of the License Agreement and this Agreement, and will provide that any such sublicensee will not further sublicense except on terms consistent with this clause; (y) such Member will remain responsible for the performance of its sublicensees, and will ensure that all such sublicensees comply with the relevant provisions of the License Agreement and this Agreement and (z) in the event of a material default by any of its sublicensees under a sublicense agreement, such Member will inform the Company and the other Member and will take such action, after consultation with such other Parties, which, in such Member's reasonable business judgment, will address such default.

(iii) Each Member will, to the extent it, its Affiliates and/or Sublicensees develop a Royalty-Bearing Product under Intellectual Property distributed from the Company to the Member pursuant to this Section 9.3(b) that does not become subject to Section 9.3(d) or 9.3(e): (x) pay to the other Member (or its designated Affiliate) a royalty of [***]% on Net Sales of such Royalty-Bearing Products sold by the selling Member, its Affiliates and/or Sublicensees, on a Royalty-Bearing Product-by-Royalty-Bearing Product and a country-by-country basis, during the Royalty Term (provided, however, that, for the remainder of the relevant Royalty Term following the end of both the relevant Exclusivity Period, the royalty rate will be [***]%), and (y) be responsible for all milestones, royalties and other payments payable to Third Parties in respect of the exercise of such license by such selling Member, its Affiliates and/or Sublicensees, including without limitation any amounts payable by either Member or the Company to its Third Party licensors with respect to the license and sublicense granted to such Member pursuant to this Section 9.3(b). The royalty-paying Member will use Commercially Reasonable Efforts to benefit from offsets to the amounts payable to such Member's Third Party licensors.

(c) Retained Assets and Rights. Following the distribution of the Company's assets pursuant to this Section 9.3, the Company will not maintain any interest in or right to any assets of the Company, including Intellectual Property, except to the extent the Managing Board determines is necessary to maintain Third Party Contracts or its obligations to Opt-In Parties or Members pursuant to the Buy-Out. *Notwithstanding the foregoing*, the Parties will use their Commercially Reasonable Efforts to remove any restrictions on, and facilitate the distribution of, the Company's assets pursuant to this Section 9.3.

(d) Research Program Selection and Transfer.

(i) Within [***] Business Days following the distribution of the Company's assets in accordance with Section 9.3(a) and (b), the non-Initiating Member will submit a bid, consisting solely of a single up-front cash payment (**"First Selection Right Bid"**), to the Initiating Member to obtain the first right to select a Research Program from the most recent Program/Project List with respect to which such Member desires to acquire exclusive rights; provided, however, that in the event the non-Initiating Member does not submit such a bid with [***] Business Days, the Initiating Member may assume the rights of the non-Initiating Member set forth in this Section 9.3(d) with respect to the First Selection Right Bid. The Initiating Member will have [***] Business Days to notify the non-Initiating Member of its acceptance or rejection of such First Selection Right Bid.

(ii) If the Initiating Member accepts such First Selection Right Bid,

(1) The non-Initiating Member will have the right, upon payment to the Initiating Member of the amount set forth in the First Selection Right Bid (which amount will be due and payable within [***] Business Days after acceptance of such bid), to select one Research Program ("**Selected Program**"). Upon such selection, the non-Initiating Member will obtain the license set forth in clause (vi) below under Intellectual Property directed to such Selected Program; and

(2) Each of the Members, starting with the Initiating Member, will then take turns selecting (by written notice within [***] Business Days following the last selection by the other Member) a Research Program (other than the Selected Program), until all Research Programs on the Program/Project List have been selected by the Members (and each such selected Research Program is a "Selected Program" hereunder), and each Member will obtain the rights set forth in clause (vi) below under Intellectual Property directed to the Research Program selected by such Member.

(iii) If the Initiating Member rejects such First Selection Right Bid, such Member will submit to the non-Initiating Member, concurrently with such notice of rejection, a counterbid which is higher than such First Selection Right Bid by at least [***]% or $[***] (whichever is higher). The non-Initiating Member will have [***] Business Days to accept or reject such counterbid.

(iv) If the non-Initiating Member accepts such counterbid, the Initiating Member will have the right, upon payment to the non-Initiating Member of the amount set forth in such counterbid (which amount will be due and payable within [***] Business Days after acceptance of such counterbid), to select a Research Program (other than a Selected Program) and each such selected Research Program is a "Selected Program" hereunder. Upon completion of the Buy-Out, the Initiating Member will obtain from the non-Initiating Member the rights set forth in clause (vi) below with respect to the Research Program selected by such Member.

(v) If the non-Initiating Member rejects such counterbid, then such non-Initiating Member will submit, concurrently with such notice of rejection, its counterbid to the Initiating Member's counterbid, which counterbid must be higher than the Initiating Member's counterbid by at least [***]%, and the process will repeat itself until a bid is accepted or no counterbid exceeds the prior bid or counterbid by at least [***]%.

(vi) Each Member will grant to the other Member which purchased a Selected Program hereunder (the **"Buy-Out Party"**), subject to Third Party Rights, an exclusive (to the fullest extent possible) license under Distributed IP (which, with respect to Licensed IP therein, is within the scope of the license granted to the Member by the Company), to Develop, Manufacture and/or Commercialize the miRNA Compound(s) and miRNA Therapeutics included in such Selected Program in the Field.

(vii) Such licenses to Distributed IP will be (1) royalty-bearing as set forth in Section 9.3(d)(viii) below, and (2) sublicenseable; provided that, (x) each such sublicense will be subject and subordinate to, and consistent with, the terms and conditions of this Agreement, and will provide that any such Sublicensee will not further sublicense except on terms consistent with this clause; (y) such Member will remain responsible for the performance of its Sublicensees, and will ensure that all such Sublicensees comply with the relevant provisions of the License Agreement and this Agreement and (z) in the event of a material default by any of its Sublicensees under a sublicense agreement, such Member will inform the Company and the other Member and will take such action, after consultation with such other Parties, which, in such Member's reasonable business judgment, will address such default.

(viii) Each Member selecting a Selected Program will (1) pay to the other Member (or its designated Affiliate) a royalty of [***]% on Net Sales of any Royalty-Bearing Product with respect to such Selected Program, on a Royalty-Bearing Product-by-Royalty-Bearing Product and a country-by-country basis, during the Royalty Term (provided, however, that, for the remainder of the relevant Exclusivity Period, the royalty rate will be [***]%, and (2) be responsible for milestones, royalties and other payments payable to Third Parties in respect of the exercise of such license by such selling Member, its Affiliates and/or Sublicensees, including without limitation any amounts payable by either Member or the Company to its Third Party licensors with respect to the licenses granted to such Member pursuant to Section 9.3(a). The royalty-paying Member will use Commercially Reasonable Efforts to benefit from offsets to the amounts payable to such Member's Third Party licensors.

(ix) Each Member will assign or exclusively license to the other Member, to the fullest extent possible, all of its rights and obligations in assets, other than Intellectual Property, distributed by the Company to the Members pursuant to Section 9.3(a), to the extent such assets are solely related to any of the other Member's Selected Programs. In the event any such assets are related to Selected Programs of both Members, each Member will assign to or exclusively license the other, to the fullest extent possible, the rights to such assets as they relate to the other Member's Selected Programs.

(e) Development Project Selection and Transfer.

(i) Within [***] Business Days following the completion of the distribution of the Company's assets pursuant to Section 9.3(a), the non-Initiating Party (the **"Bidding Party"**) will have the right to submit to the other Member a bid, which need not be limited to a single up-front cash payment (**"Project Bid"**), with respect to one or more Development Projects included in the most recent Program/Project List; provided that, a separate Project Bid must be submitted for each and every Development Project for which the Party is bidding. *Notwithstanding the foregoing*, in the event the non-Initiating Party does not submit such a bid within [***] Business Days, the Initiating Party may assume the rights of the non-Initiating Party set forth in this

Section 9.3(e) with respect to a Project Bid. The non-Bidding Party will have [***] Business Days to notify the Bidding Party of its acceptance or rejection of a Project Bid made by the Bidding Party, on a Project Bid-by-Project Bid basis.

(ii) If the non-Bidding Party accepts a Project Bid or does not reject a Project Bid and provide a counterbid in accordance with clause (iii) below (in which case the Project Bid is deemed accepted) within such [***] Business Day period, the Bidding Party, subject to compliance with its payment obligations under the terms of such Project Bid (including, without limitation, payment of any upfront fees to the non-Bidding Party), will obtain the rights set forth in clause (vi) below with respect to the Development Project covered by such accepted Project Bid.

(iii) If the non-Bidding Party rejects a Project Bid, the non-Bidding Party (**"Counterbidding Party"**) will submit to the Bidding Party, concurrently with its notice of rejection, a counterbid with terms which are more favorable, when taken as a whole, to the Bidding Party than the terms set forth in the Project Bid, by at least the greater of (1) [***]% (as

measured by industry standards) or (2) $[***] (if the Project Bid is less than or equal to $[***]). The Bidding Party will have [***] Business Days to accept or reject such counterbid.

(iv) If the Bidding Party accepts such counterbid or does not reject such counterbid and provide a counterbid in accordance with clause (v) below (in which case the Counterbidding Party's counterbid is deemed accepted) within such [***] Business Day period, the Counterbidding Party, subject to compliance with its payment obligations under the terms of such counterbid (including, without limitation, payment of any upfront fees to the Bidding Party), will obtain the rights set forth in clause (vi) below with respect to the Development Project covered by such accepted counterbid.

(v) If the Bidding Party rejects such counterbid, such Bidding Party will submit, concurrently with its notice of rejection, its counterbid to the Counterbidding Party's counterbid, which counterbid must be higher than the Counterbidding Party's counterbid by at least [***]% (as measured by industry standards), and the process will repeat itself until a bid for a Development Project is accepted; provided, however, that, if a Member to which a counterbid is submitted determines in good faith that the terms of such counterbid are not more favorable to such Member, taken as a whole, than the terms offered in such Member's most-recent prior bid, by at least [***]% (as measured by industry standards), then at any time within the [***] day period during which such Member may accept or reject such counterbid, such Member (the **"Contesting Party"**) may notify the other Parties thereof and will have the right to submit such matter to a reputable investment bank (**"Qualified Third Party"**) chosen by mutual agreement of the Members. If the Members are unable to agree upon a Qualified Third Party within [***] Business Days after receipt of the Contesting Party's notice, the Company (through a vote of its Managing Board) will select a Qualified Third Party within [***] Business Days after the end of such initial [***] Business Day period and will promptly notify the Members of the Qualified Third Party selected. The Members will then submit the dispute to such Qualified Third Party and will instruct such Qualified Third Party to determine whether the counterbid most-recently proposed by the non-Contesting Party is more favorable, taken as a whole, than the terms proposed by the Contesting Party, by at least [***]% (as measured by industry standards) and to deliver a written report to both Members within [***] Business Days following submission of such dispute to such Qualified Third Party. Such Qualified Third Party's determination will be binding on the Members. If such Qualified Third Party determines that the counterbid proposed by the non-Contesting Party constitutes a sufficient counterbid, such counterbid will be deemed accepted by the Contesting Party. If such Qualified Third Party determines that the counterbid proposed by the non-Contesting Party does not constitute a sufficient counterbid, then the immediately preceding bid or counterbid terms proposed by the Contesting Party will be deemed accepted by the non-Contesting Party. The Member against whom the Qualified Third Party finds will bear the costs of such Qualified Third Party.

(vi) Each Member will grant to the other Member that purchased a Development Project hereunder (the Buy-Out Party), subject to Third Party Rights, an exclusive (to the fullest extent possible) sublicense under Distributed IP (which, with respect to Licensed IP therein, is within the scope of the license granted to the Member by the Company), to Develop, Manufacture and/or Commercialize miRNA Compounds and miRNA Therapeutics included in the Development Project in the Field.

(vii) Such license to such Development Project will be (1) royalty-bearing in accordance with the terms of the accepted bid covering such Development Project, and (2) sublicenseable; provided that, (1) each such sublicense will be subject and subordinate to, and consistent with, the terms and conditions of this Agreement, and will provide that any such Sublicensee will not further sublicense except on terms consistent with this clause; (2) such Member will remain responsible for the performance of its Sublicensees, and will ensure that all such Sublicensees comply with the relevant provisions of the License Agreement and this Agreement and (3) in the event of a material default by any of its Sublicensees under a sublicense agreement, such Member will inform the Company and the other Member and will take such action, after consultation with such other Parties, which, in such Member's reasonable business judgment, will address such default.

(viii) Each Member will assign or exclusively license to the other Member, to the fullest extent possible, all of its rights and obligations in assets, other than Intellectual Property, distributed by the Company to the Members pursuant to Section 9.3(a) to the extent such assets are solely related to any of the other Member's Selected Development Projects. In the event any such assets are related to Development Programs of both Members, each Member will assign to the other, to the fullest extent possible, the rights to such assets as they relate to the other Member's Development Programs.

(ix) The Parties will promptly negotiate in good faith and execute a written agreement substantially in accordance with the terms of the accepted bid covering each such Development Project.

(f) Company Following Buy-Out. In the event of a Buy-Out pursuant to this Section 9.3, the Company will not be dissolved if, in the discretion of the Managing Board, it should continue to exist for the purpose of maintaining Third Party Contracts and/or receiving payments from Third Parties that may become due to the Company following the completion of the Buy-Out, making tax and other distributions, filing tax and other required reports and conducting any activity necessary for the purpose of dissolving the Company pursuant to Section 10 (the **"Post Buy-Out Activities"**). In the event the Company is not dissolved following the completion of a Buy-Out pursuant to this Section 9.3, the Company will be prohibited from engaging in any activities other than the Post Buy-Out Activities, and any assets acquired by the Company after the completion of the Buy-Out will be distributed as determined by the Managing Board, unless otherwise distributable under then-existing agreements.

(g) Diligence. Each Member will use Commercially Reasonable Efforts to Develop and Commercialize the miRNA Compounds and miRNA Therapeutics covered by the Research Program or Development Project purchased by such Member under this Section 9.3, at such Member's own expense, in the Field, either by itself or with or through its Affiliates or Sublicensees.

(h) Non-Compete. With respect to any Research Program or Development Project, the non-Opt-In Party or non-Buy-Out Party will not, itself or through its Affiliates or with Third Parties, Discover, Develop, Manufacture or Commercialize the relevant Opt-In Products or Buy-Out Products during the period (i) prior to first commercial sale of an Opt-In Product or Buy-Out Product with respect to such Research Program or Development Project anywhere in the world,

as long as the relevant Opt-In Party or Buy-Out Party reasonably believes that the Opt-In Product or Buy-Out Product would be a Royalty-Bearing Product upon first commercial sale, and (ii) after first commercial sale of a Royalty-Bearing Product with respect to such Research Program or Development Project anywhere in the world, until the expiration of all Royalty Terms for all Royalty-Bearing Products for such Research Program or Development Project; provided, however, that each Party will be entitled to grant Permitted Licenses.

ARTICLE 10

Dissolution

10.1 Dissolution.

The Company will be dissolved and its affairs wound up upon the first to occur of the following:

(a) the written consent of the Members;

(b) the Bankruptcy or dissolution of a Member, unless the other Member votes to continue the business of the Company within ninety (90) days of receiving notice of such Bankruptcy; or

(c) Upon the occurrence of an event specified under non-waivable provisions of the Act or other applicable law as one effecting dissolution, except that where, under the terms of this Agreement or the Act, the Company is not to terminate, the Company will immediately be reconstituted and reformed on all the applicable terms, conditions, and provisions of this Agreement.

The Company will not be dissolved upon the death, insanity, retirement, resignation, expulsion, bankruptcy, dissolution or occurrence of any other event which terminates the membership of a Member.

10.2 Liquidation.

(a) Upon the occurrence of an event of dissolution as defined in Section 10.1 hereof, the Company will cease to engage in any further business, except to the extent necessary to perform existing obligations, and will wind up its affairs and liquidate its assets unless otherwise agreed by the Members. The Members will jointly appoint a liquidator (who may but need not be an Officer or Member) who will have sole authority and control (subject to this Agreement) over the winding up and liquidation of the Company's business and affairs. The liquidator will diligently pursue the winding up and liquidation of the Company.

(b) During the course of liquidation, the Members will continue to share profits and losses as provided in Section 7.1 of this Agreement, but there will be no cash distributions to the Members until the Distribution Date.

10.3 Liabilities.

Liquidation will continue until the Company's affairs are in such condition that there can be a final accounting, showing that all fixed or liquidated obligations and liabilities of the Company are satisfied or can be adequately provided for under this Agreement. The assumption or guarantee in good faith by one or more financially responsible Persons will be deemed to be an adequate means of providing for such obligations and liabilities. When the liquidator has determined that there can be a final accounting, the liquidator will establish a date (not to be later than the end of the taxable year of the liquidation, i.e., the time at which the Company ceases to be a going concern as provided in Treasury Regulations section 1.704-1(b)(2)(ii)(g), or, if later, ninety (90) days after the date of such liquidation) for the distribution of the proceeds of liquidation of the Company (the "**Distribution Date**"). The net proceeds of liquidation of the Company will be distributed to the Members as provided in Section 10.5 hereof not later than the Distribution Date.

10.4 Settling of Accounts.

Except as otherwise required by Section 18-804 of the Act, upon the dissolution and liquidation of the Company, the proceeds of liquidation will be applied in the following order: (i) to pay all expenses of the Company's liquidation and wind up costs, including the costs and expenses of the liquidator and any fees payable to the liquidator as agreed by the Members; (ii) to pay all debts, obligations and liabilities of the Company, in the order of priority as provided by law, other than debts owing to the Members or on account of Members' Capital Contributions; (iii) to pay all debts of the Company owing to a Member; and (iv) to establish reasonable reserves for any remaining contingent or unforeseen liabilities of the Company not otherwise provided for, which reserves will be maintained by the liquidator on behalf of the Company in a regular interest-bearing trust account for a reasonable period of time as determined by the liquidator. If any excess funds remain in such reserves at the end of such reasonable time, then such remaining funds will be distributed by the Company to the Members pursuant to Section 10.5 hereof.

10.5 Distribution of Proceeds.

Except as otherwise required by Section 18-804 of the Act, upon final liquidation of the Company but not later than the Distribution Date, the net proceeds of liquidation remaining following the settling of accounts in accordance with Section 10.4 hereof will be distributed to the Members in proportion to their respective positive Capital Accounts as those accounts are determined after all adjustments to such accounts for the taxable year of the Company during which the liquidation occurs as are required by this Agreement and Treasury Regulations Section 1.704-1(b), such adjustments to be made within the time specified in such Treasury Regulations.

10.6 Certificate of Cancellation.

Upon dissolution and liquidation of the Company, the liquidator will cause to be executed and filed with the Secretary of State of the State of Delaware, a certificate of cancellation in accordance with Section 18-203 of the Act.

10.7 Payment of Royalties.

Following the dissolution of the Company, any royalties, milestones and/or sublicense fees due to the Company by a Member in connection with an Opt-In Election under the License Agreement, will be reduced by [***] percent ([***]%) and this amount will instead be payable by the Member required to pay such fee directly to the other Member (the **"Receiving Member"**); provided, however, if the Receiving Member has pass-through obligations with respect to a royalty payment, milestone or sublicense fee, the payment to the Receiving Member will not be reduced to an amount less than the amount of the pass-through obligation.

10.8 Treatment of Certain Assets.

(a) Goodwill. The Company's name and goodwill will, as among the Members, be deemed to have no value and will belong to the Company, and no Member will have any right or claim individually to the use thereof. Upon liquidation of the Company, undivided interests on a pro rata basis in the proportion required by Section 10.5 in the right to use the name of the Company and any goodwill associated with the Company's name or business will be assigned to all Members that are Members who are not then in default of any of their material obligations hereunder.

(b) Distribution of In-Kind Assets. To the extent reasonably possible, the assets of the Company will be distributed in kind to the Members. Such assets distributed in kind will be distributed at their Fair Market Value as determined by the liquidator appointed pursuant to Section 10.2(a). Those of such assets that are indivisible (such as Intellectual Property, Intellectual Property rights and various contracts) will be distributed and licensed to the Members in accordance with Sections 10.8(c).

(c) Distribution of Indivisible Assets. Any assets of the Company that are indivisible (such as Intellectual Property and rights therein and various contracts) will be distributed in accordance with the following:

(i) Subject to the rights granted to and obligations assumed by either Member or a Third Party in connection with an Opt-In Election or Buy-Out and subject to any Third Party Rights, all of the Company's right, title and interest in Intellectual Property and other indivisible assets owned by the Company (including, without limitation, all Company Intellectual Property and other items of Intellectual Property owned in their entirety or in which the Company has a partial ownership interest or a transferable right or license) will be distributed and assigned to all those Members that are not then in default of any of their material obligations hereunder (each a **"Distributee Member"**), with each Distributee Member receiving an undivided ownership interest therein on a pro rata basis in the proportion required by Section 10.5, subject to Section 10.8(e), as follows:

(A) Co-exclusive in all respects, and "co-exclusive" means that such license is exercisable by each Member or its designated Affiliate, and that the Company retains no rights to exercise any such licensed Intellectual Property);

(B) Free of any obligation to make accounting or pay royalties or license fees or other amounts; and

(C) Perpetual and irrevocable.

(d) Maintenance and Enforcement of Intellectual Property. With respect to any issued patents, registered trademarks or registered copyrights and any applications to obtain or register the same that are distributed in accordance with Section 10.8(c)(i) (the **"Registered Intellectual Property"**), responsibility for the prosecution, registration, maintenance and protection thereof will be allocated to the Members with an ownership interest therein, subject to Third Party rights, as follows:

(i) in the case of Registered Intellectual Property licensed to a Member in connection with an Opt-In Election, in accordance with Section 9 of the License Agreement; and

(ii) in the case of Registered Intellectual Property licensed to a Member in connection with a Buy-Out, as determined by the Parties at the time of the Buy-Out, it being agreed that the Parties intend such allocation to be substantially similar to the provisions of Section 9 of the License Agreement as they apply to an Opt-In Product.

(e) Non-Transferable Licenses. As to any items of Intellectual Property and other indivisible assets that would have been distributed under Section 10.8(c)(i) but for the lack of a transferable right or license in the Company, the liquidator will use commercially reasonable efforts such that each Distributee Member thereunder has, from and after the time of dissolution, rights or licenses to use such Intellectual Property and other indivisible assets in the same manner and to the same extent as the Company.

(f) Binding on Transferees. In the event a Member transfers its interest in any Intellectual Property distributed or licensed to it under this Section 10.8, it will cause the transferee to agree in writing to be bound by the applicable obligations of this Section 10.8.

(g) Termination of Ancillary Agreements; Further Assurances.

(i) Upon consummation of a termination of this Agreement and the distribution or liquidation of the assets of the Company pursuant to this Article 10, the parties hereto will cause the termination of the Ancillary Agreements subject to the provisions of this Section 10.8 or unless otherwise agreed by the Members. At or any time after such distribution or liquidation, the Parties will execute and deliver such written agreements and instruments as may be requested by any Member or its Affiliate to confirm or document the licenses, rights and obligations of each Member, as described herein and in the License Agreement; provided, however:

(ii) The intent of the Parties is that all of such licenses, rights and obligations be self executing automatically, and without further act by any Person, upon the occurrence of the event that triggers the same;

(iii) Execution and delivery of any such written agreement or instrument is neither a condition precedent to nor a requirement or pre-requisite for the effectiveness of any of such licenses, rights and obligations; and

(iv) Neither a failure to make such request nor a failure to mutually agree on the text of and/or to execute or deliver any such written agreement or instrument will limit or constrain any of such licenses, rights and obligations.

(h) Survival of Provisions. The provisions of, and the licenses, rights and obligations set forth in, this Section 10.8 will survive any termination of this Agreement, any dissolution of the Company and any distribution of the assets of the Company pursuant to this Article 10 and will continue until fully performed.

ARTICLE 11

Exculpation and Indemnification

11.1 Duties of Directors.

Subject to the last sentence of this Section 11.1, each Director will owe such duty of loyalty and due care to the Company as is required of a director of a for profit corporation organized and existing under the Delaware General Corporation Law (the "**DGCL"**) to which the provisions of Subchapter XIV of the DGCL are not applicable, will discharge his or her duties in good faith with the care an ordinary prudent Person in like position would exercise under similar circumstances and in a manner such Director reasonably believes to be in the best interests of the Company, and in so acting will enjoy each and every protection afforded to the directors of a Delaware corporation under applicable Delaware law, including those afforded by the business judgment rule and the presumptions afforded thereby and the limitation on personal liability to the maximum extent permitted by Section 102(b) of the Delaware General Corporation Law as if the provisions thereof were set forth in this Agreement; provided, however, that any act of a Director relating to or affecting an acquisition or a potential acquisition of the Company will not be subject to a higher level of duty or greater scrutiny than is applied to any other act of a Director; provided, further, that the provisions of Section 3.6 hereof will, to the maximum extent necessary to give effect thereto, be construed as a "renunciation" of interest or expectancy in, or as being offered an opportunity to participate in, business opportunities presented to the Company or its Members, Directors or Officers as contemplated by Section 122(17) of the DGCL. *Notwithstanding the foregoing*, the Members understand that actions or refusals to act by a Director taken with respect to a matter requiring approval of Directors at the direction of the Member who designated such Director, if any, will not be a breach of such Director's fiduciary duty to the Company or the other Members.

11.2 Exculpation.

No Member or Affiliate, director or officer thereof, Director, Officer, or employee or agent of the Company (each an "**Indemnified Party**") will be liable, responsible or accountable for damages or otherwise to any other Member, their Affiliates or the Company for (i) any act performed or omission within the scope of the authority conferred on the Indemnified Party by this Agreement or otherwise by the Managing Board except for the gross negligence, fraud or willful misconduct (including any willful violation of the terms of this Agreement) of such Indemnified Party, (ii) the Indemnified Party's performance of, or failure to perform, any act on the reasonable reliance on advice of legal counsel to the Company or its accountants or other

experts retained by the Company, or (iii) the negligence, dishonesty or bad faith of any agent, consultant or broker of the Company selected, engaged or retained in good faith and with reasonable prudence. Each Member may (on its own behalf or on behalf of any Director designated by such Member, any Affiliates of such Member or their respective partners, shareholders, directors, officers, employees or agents) consult with counsel, accountants and other experts in respect of the Company's affairs and such Member will be fully protected and justified in any action or inaction which is taken in accordance with the advice or opinion of such counsel, accountants or other experts; provided, however, that such counsel, accountant or other experts will have been selected with reasonable care. *Notwithstanding any of the foregoing to the contrary*, the provisions of this Section 11.2 will not be construed so as to relieve (or attempt to relieve) an Indemnified Party of any liability, to the extent (but only to the extent) that such liability may not be waived, modified or limited under applicable law, but will be construed so as to effectuate the exculpation of the Member Indemnified Party to the fullest extent permitted by law.

11.3 Indemnification by the Company.

(a) In any threatened, pending or completed action, suit or proceeding, each Indemnified Party who is an Officer, Director or Member or Affiliate or director or officer thereof (the "**Member Indemnitees**") will, to the fullest extent permitted by law, be fully protected and indemnified and held harmless by the Company against all Losses incurred by virtue of his or her status as a Member Indemnitee or with respect to any action or omission taken or suffered in good faith, other than liabilities and losses resulting from the fraud, breach of fiduciary duty or willful misconduct (including any willful violation of the terms of this Agreement) of such Member Indemnitee. Any Indemnified Party who is not an Officer, Director or Member may, upon approval of the Managing Board, to the fullest extent permitted by law, be fully protected and indemnified and held harmless by the Company against all Losses incurred by virtue of his or her status as an Indemnified Party or with respect to any action or omission taken or suffered in good faith, other than liabilities and losses resulting from the fraud, breach of fiduciary duty or willful misconduct (including any willful violation of the terms of this Agreement) of such Indemnified

Party. The indemnification provided by this Section 11.3 will be recoverable only out of the assets of the Company, and no Member will have any personal liability on account thereof.

(b) To the extent that, at law or in equity, an Indemnified Party has duties (including fiduciary duties) and liabilities relating thereto to the Company, any Member or to any other Indemnified Party, an Indemnified Party acting under this Agreement will not be liable to the Company or to any Member or to any other Indemnified Party for its good faith reliance on the provisions of this Agreement. The provisions of this Agreement, to the extent that they restrict the duties and liabilities of an Indemnified Party otherwise existing at law or in equity, are agreed by the parties hereto to replace such other duties and liabilities of such Indemnified Party.

(c) As a condition precedent to the Member Indemnitee's right to be indemnified, the Member Indemnitee must notify the Company in writing as soon as practicable of any action, suit, proceeding or investigation involving him or her for which indemnity hereunder will or could be sought. With respect to any action, suit, proceeding or investigation of which the Company is so notified, the Company will be entitled to participate therein at its own expense

and/or to assume the defense thereof at its own expense, with legal counsel reasonably acceptable to the Member Indemnitee.

(d) In the event that the Company does not assume the defense of any action, suit, proceeding or investigation of which the Company receives notice under this Section 11.3, the Company will pay in advance of the final disposition of such matter any expenses (including attorneys' fees) incurred by a Member Indemnitee in defending a civil or criminal action, suit, proceeding or investigation or any appeal therefrom; provided, however, that the payment of such expenses incurred by a Member Indemnitee in advance of the final disposition of such matter will be made only upon receipt of an undertaking by or on behalf of the Member Indemnitee to repay all amounts so advanced in the event that it will ultimately be determined that the Member Indemnitee is not entitled to be indemnified by the Company as authorized in this Section 11.3, which undertaking will be accepted without reference to the financial ability of the Member Indemnitee to make such repayment; and further provided that the Member Indemnitee will repay the Company any such advancement of expenses in respect of a matter for which it is ultimately determined by a court of competent jurisdiction that (i) the Member Indemnitee did not act (A) in good faith and in a manner the Member Indemnitee reasonably believed to be in, or not opposed to, the best interests of the Company, or (B) in the good faith reliance on the provisions of this Agreement, or (ii) with respect to any criminal action or proceeding, the Member Indemnitee had reasonable cause to believe his conduct was unlawful.

(e) The Company will not indemnify a Member Indemnitee seeking indemnification in connection with a proceeding (or part thereof) initiated by such Member Indemnitee unless the initiation thereof was approved by both Members. In addition, the Company will not indemnify a Member Indemnitee to the extent such Member Indemnitee is reimbursed from the proceeds of insurance, and in the event the Company makes any indemnification payments to a Member Indemnitee and such Member Indemnitee is subsequently reimbursed from the proceeds of insurance, such Member Indemnitee will promptly refund such indemnification payments to the Company to the extent of such insurance reimbursement.

(f) All determinations hereunder as to the entitlement of a Member Indemnitee to indemnification or advancement of expenses will be made in each instance by (i) the Managing Board, (ii) independent legal counsel (who may, to the extent permitted by law, be regular legal counsel to the Company), or (iii) a court of competent jurisdiction.

(g) The indemnification rights provided in this Section 11.3 (i) will not be deemed exclusive of any other rights to which a Member Indemnitee may be entitled under any law, agreement or otherwise, and (ii) will inure to the benefit of the heirs, executors and administrators of the Member Indemnitees. The Company may, to the extent authorized from time to time by the Managing Board, grant indemnification rights to other employees or agents of the Company or other Persons serving the Company and such rights may be equivalent to, or greater or less than, those set forth in this Section 11.3. Any indemnification to be provided hereunder may be provided although the Person to be indemnified is no longer a Member, Director or Officer or an Affiliate, or a director or officer of a Member. *Notwithstanding the foregoing*, the indemnification rights provided in this Section 11.3 do not replace, amend or supersede the indemnity provisions set forth in the License Agreement.

11.4 Insurance.

The Company may purchase and maintain insurance on behalf of any Person who is or was a Member, Director, Officer, employee or agent of the Company, or is or was serving at the request of the Company as a manager, member, director, officer, employee or agent of another limited liability company, corporation, partnership, joint venture, trust or other enterprise, for any liability asserted against such Person and liability and expenses incurred by such Person in such Person's capacity as Member, Director, Officer, employee or agent, or arising out of such Person's status as such, whether or not the Company has the authority to indemnify such Person against such liability and expenses. *Notwithstanding the foregoing*, the Company will purchase or obtain directors' and officers' insurance at a level of coverage that is customary for an entity conducting a business of similar size, with a minimum level of coverage in the amount of $3.0 million.

11.5 Notice of Indemnification and Advancement.

Any indemnification of, or advancement of expenses to an Indemnified Party in accordance with this Article 11, if arising out of a proceeding by or on behalf of the Company, will be reported in writing to the Members.

11.6 Repeal or Modification.

Any repeal or modification of this Article 11 will not adversely affect any right of any indemnitee existing hereunder at the time of such repeal or modification.

11.7 Indemnification by Members.

(a) Subject to the terms and conditions of this Article 11, each Member hereby agrees to indemnify and hold harmless the Company and each other Member and such other Member's respective directors, officers, employees, members, managers, representatives or agents and stockholders (the "**Company Indemnitees**") from any liability for, or to the extent arising directly out of or based on (i) any Tax of such Member or any subsidiary of such Member (other than the Company and its subsidiaries for any period or portion thereof beginning after the Effective Date); and (ii) any Third Party claim arising out of (A) any actual or alleged death, personal bodily injury or damage to real or tangible personal property claimed to result, directly or indirectly, from the possession, use or consumption of, or treatment with, any miRNA Compound or miRNA Therapeutic Developed, Manufactured and/or Commercialized by such Member, its Affiliates or Sublicensees pursuant to a Buy-Out, regardless of the form in which any such claim is made, (B) any actual or alleged infringement or unauthorized use or misappropriation of any Patent Right or other intellectual property right of a Third Party with respect to the activities of such Member, its Affiliates or Sublicensees hereunder, (C) any breach by such Member of its warranties or covenants under this Agreement given to the other Party seeking indemnification hereunder, or (D) any grossly negligent act or omission, fraud or willful misconduct of such Member or its Affiliates, or any of their employees, contractors or agents, in performing its obligations or exercising its rights under this Agreement; provided, however, that the foregoing indemnity will not apply with respect to a Party and its directors, officers, employees, members, managers, representatives or agents to the extent that any such Losses are

(i) attributable to the gross negligence or willful misconduct of such Party or its officers or directors or (ii) otherwise subject to an obligation by such Party to indemnify the Member Indemnitees under Section 11.3(a).

(b) A Company Indemnitee will notify the indemnifying Member of any action, claim or proceeding ("**Claim**") for Losses in writing, and in reasonable detail, as promptly as reasonably possible after receipt by such Company Indemnitee of notice of such Claim; provided, however, that failure to give such notification on a timely basis will not affect the indemnification provided hereunder except to the extent that such indemnifying Member will have been actually prejudiced as a result of such failure. The indemnifying Member will assume the defense of such Claim, including the employment of counsel reasonably satisfactory to the Company Indemnitee and the payment of such counsel's fees and expenses. Thereafter, the Company Indemnitee will promptly deliver to the indemnifying Member copies of all notices and documents received by the Indemnitee relating to such Claim.

(c) The indemnifying Member will keep the Indemnitee advised as to all material developments in connection with any Claim, including promptly furnishing to the Indemnitee copies of all material documents filed or served in connection therewith. The indemnifying Member may not settle or compromise any Claim or consent to the entry of any judgment without the Company Indemnitee's consent (which consent may not unreasonably be withheld), unless such settlement, compromise or judgment involves only the payment of money damages by the indemnifying Member (which payment is made or adequately provided for at the time of such settlement, compromise or judgment) or provides for the unconditional release by the claimant or plaintiff of the Company Indemnitee and its Affiliates from all liability in respect of such Claim and does not impose injunctive relief against any of them. The Company Indemnitee will provide reasonable assistance to the indemnifying Member in the defense of the Claim.

(d) In the event that the indemnifying Member, within twenty (20) Business Days after receiving written notice of any such Claim, fails to assume the defense thereof, the Company Indemnitee will have the right to undertake the defense, compromise or settlement of such Claim at the expense of the indemnifying Member.

(e) If a Company Indemnitee receives a refund or credit of Taxes or insurance benefits for which it has been indemnified pursuant to this Section 11.7, such Company Indemnitee agrees to pay the indemnifying Member the amount of such refund, credit or benefits (including any interest received thereon) up to the amount paid by the indemnifying Member to indemnify the Company Indemnitee pursuant to this Section 11.7.

11.8 Limitation on Damages.

(a) Neither any Member nor the Company will be liable to the other for any indirect, special, incidental or consequential loss or damage or for loss of profits or loss of use suffered by a Member or the Company arising from or relating to a Member's performance, non-performance, breach of or default under a covenant, warranty, representation, term or condition hereof; and each Member and the Company, other than with respect to a claim arising from such other Member's willful misconduct or fraudulent actions, waives and relinquishes claims for indirect, special, incidental or consequential damages.

(b) The limitations on liability and damages set out in Section 11.8(a) apply to all causes of action that may be asserted under this Agreement, other than a cause of action resulting from another Member's willful misconduct or fraudulent actions, whether sounding in breach of contract, breach of warranty, tort, product liability, negligence or otherwise.

11.9 Contractual Limitation Period.

To be subject to indemnification hereunder, any Dispute arising from this Agreement and involving the Members or the Company must be commenced prior to the earlier of (i) the applicable statute of limitation and (ii) the third (3rd) anniversary of the occurrence of the cause of action giving rise to the Dispute; provided, however, that the foregoing shall not be applicable to any Dispute under Section 11.7(a)(ii)(A).

ARTICLE 12

Inspection of Records; Annual and Other Reports; Confidentiality

12.1 Records to be Kept.

The Company will keep at its registered office:

(a) A current list of the full name and last known business, residence or mailing address of each Member and each Director separately identifying the Members and Directors in alphabetical order;

(b) A copy of the filed Certificate and all amendments thereto, together with executed copies of any powers of attorney pursuant to which any document has been executed;

(c) Copies of this Agreement, and all amendments hereto, and copies of each Ancillary Agreement, and all amendments thereto;

(d) Copies of the Company's federal and state income tax returns and reports;

(e) Copies of any financial statements of the Company for the [***] most recent years; and

(f) The minutes of all meetings of the Managing Board and all meetings of the Members.

12.2 Inspection of Company Records.

The accounting books and records, the record of Members, and minutes of proceedings of the Members of the Company set forth in Section 12.1 and any other information a Member is entitled to inspect pursuant to Section 18-305 of the Act, will be open to inspection upon the reasonable request of any Member at any reasonable time during usual business hours, for a purpose reasonably related to such Member's interest as a Member. Such inspection by a Member may be made in person or by its agent or attorney, and the right of inspection includes the right to copy and make extracts at the inspecting Member's expense.

12.3 Reports.

(a) Commencing with respect to the period beginning on the Effective Date and ending December 31, 2007, and for each Fiscal Year during the term hereof after such interim period, the Company will deliver or mail to each Member the audited annual financial statements of the Company at least three (3) weeks prior to the earliest date by which either Member is required to file its annual report on Form 10-K for such Fiscal Year (or such earlier time as may be required by either Member to satisfy its reporting obligations under law, including without limitation, the rules and regulations of the SEC), which financial statements will have been prepared in accordance with U.S. generally accepted accounting principles and audited by the accounting firm approved by the Managing Board, which shall be the same accounting firm appointed by the Consolidating Member.

(b) Commencing with respect to the period beginning on the Effective Date and ending on September 30, 2007, for each fiscal quarter during the term hereof after such interim period (other than the fourth quarter), the Company will deliver or mail to each Member an unaudited balance sheet of the Company as at the end of such quarter and unaudited statements of income and cash flows of the Company for such quarter and for the current fiscal year to the end of such fiscal quarter within fourteen (14) days after the end of each fiscal quarter of the Company (or such earlier time as may be required by the Member to satisfy its reporting obligations under law, including without limitation, the rules and regulations of the SEC).

(c) Commencing with respect to the period beginning on the Effective Date and ending on September 30, 2007, the Company will deliver to each Member an unaudited balance sheet of the Company as at the end of such month and unaudited statements of income and of cash flows of the Company for such month and for the current fiscal year to the end of such month promptly following the Company's completion of the review of its financial statements for such month (other than the last month of any fiscal quarter) (or such earlier time as may be required by the Member to satisfy its reporting obligations under law, including without limitation, the rules and regulations of the SEC).

(d) The income statements and balance sheets referred to in this Section 12.3 will be accompanied by the report thereon, if any, of any independent accountants engaged by the Company or by the certificate of the President that such financial statements were prepared without audit from the books and records of the Company.

12.4 Confidentiality.

(a) Each Member and the Company will, and will cause each of its Affiliates, and its and their respective members, shareholders, directors, officers, employees, advisors and agents (collectively, "**Representatives**"), to keep secret and retain in strictest confidence, except as provided in subsection (c) hereof, any and all Confidential Information received by it ("**Recipient**") from another Member or the Company or their respective Affiliates or Representatives ("**Disclosing Party**") and will not distribute, disseminate or disclose a Disclosing Party's Confidential Information, and such Recipient will cause its Representatives not to distribute, disseminate or disclose such Confidential Information, except to (i) the Company, (ii) any lender to the Company, (iii) any Member or any of their respective Affiliates

or Representatives on a "need to know" basis in connection with the transactions leading up to and contemplated by this Agreement and the operation of the Business and the Company, which shall include disclosure to a Member's independent public accountants and tax and financial advisors, and who are bound by an obligation to maintain in confidence the Confidential Information of the Disclosing Party to the same extent as if they were parties hereto, (iv) any other Person that agrees in writing to keep in confidence such Confidential Information in accordance with the terms of this Section 12.4, or (v) as permitted under the Ancillary Agreements; provided, however, that the disclosure of financial statements of, or other information relating to, the Company will not be deemed to be the disclosure of Confidential Information (i) to the extent that any Member is required by law, including without limitation, the rules and regulations promulgated by the SEC, or GAAP to disclose such financial statements or other information; (ii) to the extent that in order to sustain a position taken for tax purposes, any Member deems it necessary and appropriate to disclose such financial statements or other information or (iii) if the disclosure of such information to a Member's Representatives is in the ordinary course of such Member's business. In addition, each Party may make Permitted Disclosures of another Party's Confidential Information. All Confidential Information disclosed in connection with the Company or pursuant to this Agreement will remain the property of the Person whose property it was prior to such disclosure.

(b) In the event that a Recipient or anyone to whom a Recipient transmits any Confidential Information becomes legally compelled (by oral questions, interrogatories, requests for information or documents, subpoena, investigative demand or similar process or by rules or regulations of any securities exchange or NASDAQ) to disclose any of the Confidential Information, such Recipient will use its Commercially Reasonable Efforts to provide the

Disclosing Party with prompt written notice prior to disclosure (not less than 24 hours) so that the Disclosing Party may seek a protective order or other appropriate remedy or waive compliance with the provisions of this Agreement. In the event that such protective order or other remedy is not obtained, or that the Disclosing Party waives compliance with the provisions of this Section 12.4, the Recipient who is compelled to disclose such Confidential Information will furnish only that portion of the Confidential Information which (based on the advice of counsel) it is legally required to disclose and will exercise its Commercially Reasonable Efforts (but without incurring significant expense) to obtain reliable assurance that protective treatment will be accorded the Confidential Information.

(c) No Party will have the right to make any public announcements with respect to this Agreement or the Ancillary Agreements, nor publicly disclose the terms of this Agreement or the Ancillary Agreements, without the prior written consent of the other Parties, except as follows:

(i) The Parties will issue a mutually agreed upon press release in the form attached as **Schedule 12.4**.

(ii) Each Party may make subsequent disclosures of information to the same extent that such information has been previously disclosed in accordance with this Agreement.

(iii) Each Member may publicly file this Agreement and/or the Ancillary Agreements with the SEC in a redacted form as mutually agreed in good faith and consistent

with custom in the industry (provided, however, that, if such agreement is not reached within a reasonable period of time after the Effective Date in order for such Member to comply with law, such Member may file this Agreement and/or the Ancillary Agreements in a redacted form reasonably determined by such Member), and will request, and use Commercially Reasonable Efforts to obtain, confidential treatment of all terms redacted from such redacted form of this Agreement and the Ancillary Agreements; provided that the redaction of such terms is permitted by the applicable rules and regulations of the SEC.

(iv) Each Party may disclose this Agreement and the Ancillary Agreements in whole or in part to (i) its then-current and potential Affiliate and Third Party licensors, collaborators and sublicensees, and (ii) its then-current and potential investors, lenders and acquirers (and their respective legal counsel); provided that such Persons are bound to maintain the confidentiality of this Agreement and the Ancillary Agreements to the same extent as if they were parties hereto.

(d) Each Member who ceases to be a Member will, and will cause its Affiliates and Representatives to, maintain the confidentiality required by this Section 12.4. *Notwithstanding the foregoing*, if a license is granted by the Company to the Member in connection with such Member's ceasing to be a Member, such Member's obligations under this Section 12.4(d) will be deemed modified to the extent necessary to give full effect to such license.

(e) To the fullest extent permitted by law, if a Recipient breaches, or threatens to commit a breach of, this Section 12.4, the other Members and, in the case of such breach, or threat to commit a breach, of this Section 12.4 by a Member or its Affiliate or Representative, the Company will have the right and remedy to have this Section 12.4 specifically enforced, it being acknowledged and agreed that money damages will not provide an adequate remedy to such other Members or the Company. Nothing in this Section 12.4 will be construed to limit the right of any Member or the Company to collect money damages in the event of breach of this Section 12.4.

ARTICLE 13

Miscellaneous

13.1 Governing Law.

This Agreement will in all respects be governed by and construed in accordance with the substantive laws of the State of Delaware, without regard to its choice of law rules.

13.2 Amendments.

Any amendment of the Certificate and this Agreement will be in writing and be duly executed by each Member (or by the Chairperson of the Managing Board solely with respect to conforming amendments to Schedule 3.1) and, in the case of an amendment to the Certificate, will be executed and filed in accordance with Section 18-202 of the Act.

13.3 Nature of Membership Interest; Agreement Is Binding upon Successors.

The successors, assigns and legal representatives of each Member will be bound by the provisions of this Agreement, including Article 8, Article 11 and Section 12.4.

13.4 Seal.

The President may adopt a seal of the Company in such form as the President will decide.

13.5 Entire Agreement.

This Agreement, together with the Ancillary Agreements, including the exhibits and schedules hereto and thereto, constitutes the entire agreement among the Members and the Company with respect to the specific subject matter hereof, and supersedes all prior and contemporaneous agreements, representations, and understandings of the parties with respect to such specific subject matter. No party hereto will be liable or bound to the other in any manner by any warranties, representations or covenants with respect to the subject matter hereof except as specifically set forth herein. *Notwithstanding the*

foregoing and except as provided herein or in any Ancillary Agreement, neither the dissolution of the Company nor the termination of any Ancillary Agreement will have any affect on any other agreement or contract between the Members, and the termination or cancellation of any such other agreement or contract will have no effect on this Agreement or any Ancillary Agreement.

13.6 Further Actions.

Each Member will execute and deliver such other certificates, agreements and documents, and take such other actions, as may reasonably be requested by the Company in connection with the formation of the Company and the achievement of its purposes, including (a) any documents that the Company deems necessary or appropriate to form, qualify or continue the Company as a limited liability company in all jurisdictions in which the Company conducts or plans to conduct the Business and (b) all such agreements, certificates, tax statements and other documents as may be required to be filed in respect of the Company.

13.7 Power of Attorney.

Each Member hereby constitutes and appoints the President with full power of substitution, the true and lawful attorney-in-fact and agent of such Member, to execute, acknowledge, verify, swear to, deliver, record and file, in its or its assignee's name, place and stead, all in accordance with the terms of this Agreement, all instruments, documents and certificates which may from time to time be required by the laws of the United States of America, the State of Delaware, any other jurisdiction in which the Company conducts or plans to conduct its affairs, or any political subdivision or agency thereof to effectuate, implement and continue the valid existence and affairs of the Company, including the power and authority to verify, swear to, acknowledge, deliver, record and file:

(a) all certificates and other instruments, including any amendments to this Agreement or to the Certificate, which the Managing Board deems appropriate to form, qualify

or continue the Company as a limited liability company in the State of Delaware and all other jurisdictions in which the Company conducts or plans to conduct its affairs; and

(b) certificates of assumed name and such other certificates and instruments as may be necessary under the fictitious or assumed name statutes from time to time in effect in the State of Delaware and all other jurisdictions in which the Company conducts or plans to conduct its affairs.

Such attorneys-in-fact and agents will not, however, have the right, power or authority to amend or modify this Agreement when acting in such capacities, except to the extent authorized herein. The power of attorney granted herein will be deemed to be coupled with an interest, will survive and not be affected by the dissolution, bankruptcy or legal disability of the Member and will extend to its successors and assigns; and may be exercisable by such attorney-in-fact and agent for all Members (or any of them) by listing all (or any) of such Members required to execute any such instrument, and executing such instrument acting as attorney-in-fact. Any Person dealing with the Company may conclusively presume and rely upon the fact that any instrument referred to above, executed by such attorney-in-fact and agent, is authorized, regular and binding, without further inquiry. If required, each Member will execute and deliver to the Company within five (5) days after the receipt of a request therefor, such further designations, powers of attorney or other instruments as the Company will reasonably deem necessary for the purposes described in this Section 13.7.

13.8 No Third Party Beneficiary.

Nothing in this Agreement, express or implied, is intended to confer upon any Person, other than the parties hereto, and their respective successors and permitted assigns, the Indemnified Parties, the Member Indemnitees and Company Indemnitees any rights, remedies, obligations or liabilities under or by reason of this Agreement, except as expressly provided herein.

13.9 Notice.

Except where otherwise specifically provided in this Agreement, all notices, requests, consents, approvals and statements will be in writing and will be deemed to have been properly given by (i) personal delivery, (ii) electronic facsimile transmission, (iii) electronic mail, or by (iv) nationally recognized overnight courier service, addressed in each case, to the intended recipient as set forth below:

To the Company:	Regulus Therapeutics LLC 1896 Rutherford Road Carlsbad, California 92008 Attention: President
With a copy to:	Alnylam and/or Isis at the addresses below

To Alnylam:	Alnylam Pharmaceuticals, Inc. 300 Third Street, 3rd Floor Cambridge, MA 02142 Attention: Vice President, Legal
With a copy to:	WilmerHale 60 State Street Boston, MA 02109 Attention: Steven D. Singer, Esq.

To Isis:	Isis Pharmaceuticals, Inc. 1896 Rutherford Road Carlsbad, California 92008 Attention: Chief Financial Officer
With a copy to:	Isis Pharmaceuticals, Inc. 1896 Rutherford Road Carlsbad, California 92008 Attn: General Counsel(fax) 760-268-4922

Such notice, request, demand, claim or other communication will be deemed to have been duly given on (a) the date of personal delivery, (b) the date actually received if by facsimile or electronic mail; or (c) on the third Business Day after delivery to a nationally recognized overnight courier service, as the case may be. Any Party may change the address to which notices, requests, demands, claims, and other communications hereunder are to be delivered by giving the other Parties notice in the manner herein set forth.

13.10 Limited Liability Company.

The Members agree to form a limited liability company and do not intend to form a partnership or other relationship in which a Member has or has had any interest in the business or affairs or assets of the other Members or their Affiliates under the laws of the State of Delaware or any other laws; provided, however, that, to the extent permitted by law, the Company will be treated as a partnership for federal, state and local income tax purposes. No Member is the agent of the other and no Member is authorized to take any action on behalf of the other, except as set forth herein or in an Ancillary Agreement.

13.11 Fees and Expenses.

Each party will pay all costs and expenses that it incurs with respect to the negotiation, execution, delivery and performance of this Agreement and each Ancillary Agreement. If any action at law or in equity is necessary to enforce or interpret the terms of any of this Agreement or any of the Ancillary Agreements, the prevailing party will be entitled to reasonable attorneys'

fees, costs and necessary disbursements in addition to any other relief to which such party may be entitled. For purposes of this Section 13.11, "prevailing party" means the net winner of a Dispute, taking into account the claims pursued, the claims on which the pursuing party was successful, the amount of money sought, the amount of money awarded, and offsets or counterclaims pursued (successfully or unsuccessfully) by the other Party. If a written settlement offer is rejected and the judgment or award finally obtained is equal to or more favorable to the offeror than an offer made in writing to settle, the offeror is deemed to be the prevailing party from the date of the offer forward.

13.12 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, and will become effective when there exist copies hereof which, when taken together, bear the authorized signatures of each of the parties hereto. Only one such counterpart signed by the party against whom enforceability is sought needs to be produced to evidence the existence of this Agreement.

13.13 Precedence.

The provisions of this Agreement will prevail over any inconsistencies or conflicting provisions of any of the Ancillary Agreements.

13.14 Titles and Subtitles; Form of Pronouns; Construction and Definitions.

The titles of the Sections and paragraphs of this Agreement are for convenience only and are not to be considered in construing this Agreement. All pronouns used in this Agreement will be deemed to include masculine, feminine and neuter forms, the singular number includes the plural and the plural number includes the singular and will not be interpreted to preclude the application of any provision of this Agreement to any individual or entity. Unless the context otherwise requires, (i) each reference in this Agreement to a designated "Section," "Schedule," "Exhibit," or "Appendix" is to the corresponding Section, Schedule, Exhibit, or Appendix of or to this Agreement; (ii) the word "or" will not be applied in its exclusive sense; (iii) "including" will mean "including, without limitation"; (iv) references to "$" or "dollars" will mean the lawful currency of the United States; and (v) "herein," "hereof," "hereunder" and other words of similar import refer to this Agreement as a whole and not to any particular Section or other subdivision. References in this Agreement to particular sections of the Code, the Act or to any other provisions of Delaware law will be deemed to refer to such sections or provisions as they may be amended or succeeded after the date of this Agreement.

13.15 Severability.

If one or more provisions of this Agreement are held by a proper court or arbitral tribunal to be unenforceable under applicable law, the unenforceable portions of such provisions, or such provisions in their entirety, to the extent necessary and permitted by law, will be severed herefrom, and the balance of this Agreement will be enforceable in accordance with its terms.

13.16 Survival of Certain Provisions.

The obligations of each Member pursuant to Section 11 will survive until 30 days after the expiration of all statutes of limitation applicable to the matters referred to therein and the obligations of the Members pursuant to Section 12.4 will survive for a period of [***] years following the termination of this Agreement and the winding-up, liquidation and dissolution of the Company.

13.17 Survival of Warranties.

The warranties, representations and covenants of the Company contained in or made pursuant to this Agreement will survive the execution and delivery of this Agreement and will in no way be affected by any investigation of the subject matter thereof made by or on behalf of a Member or the Company.

13.18 Waiver of Partition.

Except as may otherwise be required by law in connection with the winding-up, liquidation and dissolution of the Company in accordance with Article 10 or the Act, each Member hereby irrevocably waives any and all rights that it may have to maintain an action for partition of any of the Company's property.

13.19 Delaware Limited Liability Company Act Prevails.

Unless the context otherwise requires, the general provisions, rules of construction and definitions contained in the Act and the DGCL will govern the construction of this Agreement; provided, however, that in the event of any inconsistency between such laws, the provisions of the Act will prevail.

13.20 Specific Performance.

The failure of any party to this Agreement to perform its agreements and covenants hereunder may cause irreparable injury to the other parties to this Agreement for which monetary damages, even if available, will not be an adequate remedy. Accordingly, each of the parties hereto hereby consents to the granting of equitable relief (including specific performance and injunctive relief) by any court of competent jurisdiction to enforce any Member's obligations hereunder. The parties further agree to waive any requirement for the securing or posting of any bond in connection with the obtaining of any such equitable relief and that this Section 13.20 is without prejudice to any other rights that the Members and the Company hereto may have for any failure to perform this Agreement.

[*Remainder of page intentionally left blank*]

IN WITNESS WHEREOF, the Company and its Members hereby execute this Limited Liability Company Agreement as of the date first written above.

REGULUS THERAPEUTICS LLC,
a Delaware limited liability company

By: /s/ Philip T. Chase

Name: Philip T. Chase

Title: Authorized Person

ALNYLAM PHARMACEUTICALS, INC.,
a Delaware corporation

By: /s/ Barry Greene

Name: Barry Greene

Title: Chief Operating Officer

ISIS PHARMACEUTICALS, INC.,
a Delaware corporation

By: /s/ B. Lynne Parshall

Name: B. Lynne Parshall

Title: EVP & CFO

SCHEDULE 1

DEFINITIONS

"**Act**" has the meaning provided in the recitals of this Agreement.

"Additional Capital Contribution" has the meaning provided in Section 6.1(c).

"Additional Requested Capital Contribution" has the meaning provided in Section 6.1(d).

"**Affected Member**" has the meaning provided in the definition of "**Change in Control**."

"**Affiliate**" means, with respect to any Person, another Person that directly or indirectly, through one or more intermediaries, controls, is controlled by, or is under common control with such first Person. For purpose 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 a Person, whether through the ownership of voting securities or by contract relating to voting rights or corporate governance. For purposes of this Agreement, including the other definitions set forth in this **Schedule 1**, (i) the Company will not be deemed to be an Affiliate of any Member and (ii) a Member and its Affiliates will not be considered an Affiliate of the Company.

"**Agreement**" means this Limited Liability Company Agreement, as amended from time to time.

"Alnylam" has the meaning provided in the preamble of this Agreement.

"Alnylam Director" has the meaning provided in Section 4.1.

"Alnylam Initial IP Contribution" has the meaning provided in Section 6.1(a).

"**Ancillary Agreements**" means the License Agreement, the Services Agreement, the Director Consulting Agreements and the SAB Consulting Agreements, each as amended from time to time.

"**Approved Operating Plan**" has the meaning provided in Section 5.2(c).

"Bankruptcy" will mean, with respect to a Person,

(a) an adjudication that it is bankrupt or insolvent, or the entry of an order for relief under applicable bankruptcy or any similar law;

(b) the making by it of a general assignment for the benefit of creditors;

(c) the commencement by it of a voluntary case or other proceeding seeking liquidation, reorganization or other relief with respect to itself or its debts under any bankruptcy, insolvency or other similar law now or hereafter in effect (other than a liquidation for tax

---

restructuring purposes that results in a Member's Membership Interest being distributed to a permitted assignee under this Agreement), or seeking the appointment of a trustee, receiver, liquidator, custodian or other similar official over it or any substantial part of its property, or consent to any such relief or to the appointment of or taking of possession by any such official in an involuntary case or other proceeding commenced against it; or

(d) the commencement against it of an involuntary case or other proceeding seeking liquidation, reorganization or other relief with respect to it or its debts under any bankruptcy, insolvency or other similar law now or hereafter in effect or seeking the appointment of a trustee, receiver, liquidator, custodian or other similar official over it or any substantial part of its property, such involuntary case or other proceeding remaining undismissed or unstayed for a period of sixty (60) days.

"Bidding Party" has the meaning provided in Section 9.3(e)(i).

"Bona Fide Collaboration" means a collaboration (pursuant to a written agreement) between the relevant Member or one of its Affiliates, on the one hand, and a Third Party, on the other hand, involving the Development of miRNA Compounds or miRNA Therapeutics in which such Member or such Affiliate plays an integral, though not necessarily dominant or co-equal, role in the decision-making, relating to the Development of miRNA Compounds or miRNA Therapeutics, and which may, thereafter, involve the Commercialization of any such miRNA Compounds and miRNA Therapeutics.

"**Book Value**" means the value of the Company's assets less the Company's liabilities, all as determined in accordance with United States Generally Accepted Accounting Principles.

"**Business**" has the meaning provided in Section 2.5.

"**Business Day**" means any day that is not a Saturday, Sunday or other day on which commercial banks are required or authorized by law to be closed in San Diego, California.

"**Buy-Out**" has the meaning provided in Section 9.1(a).

"Buy-Out Negotiation Period" has the meaning provided in Section 9.3(a).

"**Buy-Out Notice**" has the meaning provided in Section 9.1(a).

"Buy-Out Notice Period" has the meaning provided in Section 9.1(a).

"Buy-Out Party" has the meaning provided in Sections 9.3(d)(vi) and 9.3(e)(vi).

"**Buy-Out Product**" means any miRNA Therapeutic that is Developed, Manufactured or Commercialized pursuant a Research Program or Development Project obtained by a Member pursuant to Section 9.3(d) or 9.3(e).

"**Capital Account**" has the meaning provided in Section 6.4(a).

"**Capital Contribution**" means a contribution made to the Company by a Member pursuant to Section 6.1 hereof and, in the case of all of the Members, the aggregate of all of such Capital Contributions.

"**Capital Contribution Schedule**" has the meaning provided in the definition of "**Operating Plan**."

"Certificate" has the meaning provided in the recitals of this Agreement.

"**Chairperson**" has the meaning provided in Section 4.1(b).

"Change of Control" means, with respect to a Member (the "**Affected Member**"), the earlier of (x) the public announcement of and (y) the closing of: (a) a merger, reorganization or consolidation involving the Affected Member in which its shareholders immediately prior to such transaction would hold less than 50% of the securities or other ownership or voting interests representing the equity of the surviving entity immediately after such merger, reorganization or consolidation, or (b) a sale to a Third Party of all or substantially all of the Affected Member's assets or business relating to this Agreement. Any Member will notify each other Member within two (2) Business Days of entering into an agreement which, if consummated, would result in a Change of Control.

"**Claim**" has the meaning provided in Section 11.7(b).

"**Code**" means the United States Internal Revenue Code of 1986, as amended, or any corresponding provision or provisions of any succeeding law.

"Collaboration Working Group" has the meaning provided in the License Agreement.

"Commercialization" or **"Commercialize"** means any and all activities directed to marketing, promoting, detailing, distributing, importing, having imported, exporting, having exported, selling or offering to sell a miRNA Therapeutic following receipt of Regulatory Approval for such miRNA Therapeutic.

"Commercializing Party" means the Party Manufacturing, Developing or Commercializing a miRNA Therapeutic pursuant to a license granted under this Agreement or under Sections 2.2 or 5.6 of the License Agreement.

"Commercially Reasonable Efforts" means, reasonable, diligent, good faith efforts to accomplish an objective as such Party would normally use to accomplish a similar objective, under similar circumstances exercising reasonable business judgment. With respect to the Development, Manufacturing or Commercialization of a miRNA Therapeutic, such efforts will be substantially equivalent to the efforts used by such Party for other products at similar stages in their development or product life and of similar market potential, taking into account the profile of the miRNA Therapeutic, the competitive landscape and other relevant factors commonly considered in similar circumstances. For all Parties the level of effort will be at least that of a typical medium sized biopharmaceutical company.

"**Company**" has the meaning provided in the preamble of this Agreement.

"Company Indemnitees" has the meaning provided in Section 11.7(a).

"Company Intellectual Property" means all Company Know-How and Company Patent Rights.

"Company Know-How" means all Know-How conceived and/or developed by or on behalf of the Company (including by employees of a Member or its Affiliates in performance of the Services Agreement), or over which the Company otherwise acquires Control, including but not limited to any Know-How assigned to the Company by a Member, but specifically excluding Licensed IP.

"Company Patent Rights" means any Patent Right claiming an invention conceived and/or developed by or on behalf of the Company (including by employees of a Member or its Affiliates in performance of the Services Agreement), or over which the Company otherwise acquires Control, including but not limited to any Patent Right assigned to Company by a Member, but specifically excluding Licensed IP.

"**Company Work Product**" means all (i) Work Product conceived or developed solely by the Company (or by the employees, consultants or representatives) and (ii) any Intellectual Property conceived, authored or developed under or pursuant to an Ancillary Agreement and owned or made the property of Company by such Ancillary Agreement, in each case to the extent of Company's interest therein.

"**Confidential Information**" means, with respect to a Party, information which is (i) of a confidential and proprietary nature; and (ii) not readily available to that Party's competitors and which, if known by a competitor of that Party, might lessen any competitive advantage of that Party or give such competitor a competitive advantage. Once a Member obtains an exclusive license, pursuant to Company Know-How, such Company Know-How will be considered Confidential Information (to the extent such Know-How otherwise is considered confidential herein) of such Member, rather than of the Company. The terms of this Agreement and each Ancillary Agreement will be Confidential Information of each Party.

Notwithstanding the foregoing, information of a Party will not be deemed Confidential Information to the extent that the receiving Party can show by competent proof that such information:

(a) was already known to the receiving Party, prior to the time of disclosure to such receiving Party pursuant to this Agreement;

(b) is generally available in the public domain through no fault of the receiving Party or its Affiliates, or is known to Persons reasonably skilled in the field to which such information pertains;

(c) was disclosed to such receiving Party by a Third Party lawfully in possession thereof; or

(d) was independently discovered or developed 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.

"Consolidating Member" has the meaning provided in Section 7.3(b).

"Contesting Party" has the meaning provided in Section 9.3(e)(i).

"Control" means, with respect to any Intellectual Property right, the possession of the right (whether by ownership, license or otherwise) to assign, or grant a license, sublicense or other right to or under, such Intellectual Property right as provided for herein without violating the terms of any agreement or other arrangement with any Third Party; provided, however, that neither Member will be deemed to Control Company Intellectual Property and no Party other than the relevant Member shall be deemed to Control such Member's Licensed IP.

"Counterbidding Party" has the meaning provided in Section 9.3(e)(ii).

"Covered" means, (a) with respect to a patent, that, in the absence of a license granted to a Person under a Valid Claim included in such patent, the practice by such Person of an invention claimed in such patent would infringe such Valid Claim, or (b) with respect to a patent application, that, in the absence of a license granted to a Person under a Valid Claim included in such patent application, the practice by such Person of an invention claimed in such patent application would infringe such Valid Claim if it were to issue as a patent.

"**Defaulting Party**" has the meaning provided in Section 6.1(e).

"Develop" or **"Development"** means, with respect to a miRNA Compound or miRNA Therapeutic, any discovery, characterization, preclinical or clinical activity with respect to such miRNA Compound or miRNA Therapeutic, including human clinical trials conducted after Regulatory Approval of such miRNA Therapeutic to seek Regulatory Approval for additional Indications for such miRNA Therapeutic.

"**Development Plan**" has the meaning provided in the definition of "**Operating Plan**."

"Development Project" means a Research Program for which the Company's Officers and Managing Board agree there exists a sufficient portfolio of data to support the initiation of [***] on a miRNA Compound drug candidate targeting such miRNA.

"DGCL" means the Delaware General Corporation Law, 8 Del. Code Sec. 101 et seq.

"**Director**" has the meaning provided in Section 4.1(a).

"Director Consulting Agreement" has the meaning provided in Section 4.5(c).

"**Disclosing Party**" has the meaning provided in Section 12.4(a).

"**Dispute**" means any dispute, controversy or claim concerning the validity, interpretation, scope, performance or enforceability of one or more provisions of this Agreement

or any Ancillary Agreement; provided, however, that a difference of opinion concerning a choice among one or more business alternatives, including a matter subject to a vote by the Members or the Managing Board (but not concerning the legal consequences under this Agreement or any Ancillary Agreement of such choice or vote once made), in the operation or management of any aspect of the Company or its business that does not involve the interpretation of any provision of this Agreement or any Ancillary Agreement but involves only a disagreement between optimal and suboptimal decisions will not be a "Dispute."

"Distributee Member" has the meaning provided in Section 10.8(c)(i).

"Distributed IP" has the meaning provided in Section 9.3(b).

"**Distribution Date**" has the meaning provided in Section 10.3.

"**Effective Date**" means the date set forth in the preamble of this Agreement.

"Exclusivity Period" means, with respect to a Royalty-Bearing Product in a country, that period of time beginning with the first commercial sale of such Royalty-Bearing Product in such country and ending on the later to expire of (1) the time during which the applicable Regulatory Authority in such country is not permitted to grant Regulatory Approval for a generic equivalent of such Royalty-Bearing Product and (2) the last Valid Claim of the Patent Rights under the Licensed IP and/or Regulus IP licensed to the relevant Commercializing Party pursuant to the License Agreement or this Agreement Covering (i) the Manufacture of such Royalty-Bearing Product in such country, or (ii) the use, sale or other Commercialization of such Royalty-Bearing Product in such country.

"**Fair Market Value**" means, with respect to any property, as of the date of determination, the cash price at which a willing buyer would buy and a willing seller would sell, each being apprised of all relevant facts and neither acting under compulsion, such property in an arm's length, negotiated transaction with an unaffiliated third party without time constraints, determined according to the procedure set forth below. The Members will mutually select an independent expert who will provide a written determination of the requested valuation and such valuation will be binding upon the parties. If the Members fail to agree on an independent expert within [***] days of the delivery of the request for valuation, each of the Members will select an independent expert by written notice to the other Members. The independent experts so selected will meet and confer and attempt to agree on a valuation. If they reach such agreement, their written determination will be binding on the Members. If the independent experts are unable to agree upon a valuation within [***] days of their appointment, and the highest valuation is less than [***] percent ([***]%) of the lowest valuation, the valuation will be deemed to be the average of the valuations and such valuation will be binding on the Members. If the independent experts are unable to agree within [***] days of their appointment, and the highest valuation is greater than [***] percent ([***]%) of the lowest valuation, the independent experts will, within [***] days following expiration of such [***]-day period, select an additional independent expert. If the first independent experts cannot agree on an additional independent expert within such [***] day period, the additional independent expert will be designated by the independent certified public accountants of the Company. The additional independent expert will meet and confer with the first independent experts, but the decision of the independent expert whose

valuation was the median amount will be binding on the Members. Such decision will be delivered in writing and state the reasons supporting it.

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

"Field" means treatment and/or prophylaxis of any or all Indications.

"**Fiscal Year**" means the annual accounting period of the Company, which is the twelve (12) months ended on December 31.

"First Selection Right Bid" has the meaning provided in Section 9.3(d).

"Future Operating Plan Contributions" has the meaning provided in Section 6.1(c).

"GLP" means the then-current good laboratory practice standards promulgated or endorsed by the FDA as defined in 21 C.F.R., Part 58, and comparable foreign regulatory standards.

"[***]" means a [***].

"**Indemnified Party**" has the meaning provided in Section 11.2.

"Independent Director" means a Director who is not an (i) Affiliate, director or officer of, or an immediate family member of, any director or officer of the Member designating such Director, or (ii) an Officer or employee of, or immediate family member of any Officer or employee of, the Company.

"Indication" means any disease or condition, or sign or symptom of a disease or condition, or symptom associated with a disease or syndrome.

"Initial Approved Operating Plan" means the operating plan attached hereto as Exhibit A.

"Initial Capital Contributions Schedule" means the schedule of capital contributions included in the Initial Approved Operating Plan, attached as Exhibit A.

"Initial Commitment Period" has the meaning provided in Section 5.2.

"Initial Operating Plan" has the meaning provided in Section 5.2.

"Initial Operating Plan Contributions" has the meaning provided in Section 6.1(c).

"Initiating Member" has the meaning provided in Section 9.1(a).

"**Intellectual Property**" means all patents and patent rights, copyrights and copyright rights (including moral rights and rights in music, audio, visual and audiovisual works), trademarks and trademark rights (and related intellectual property such as service marks and trade dress and rights therein), trade secrets and trade secret rights, mask works and other designs

and design rights, proprietary rights, confidentiality rights and any and all other intellectual property and intellectual property rights recognized by the law of the applicable jurisdiction.

"Isis" has the meaning provided in the preamble of this Agreement.

"Isis Director" has the meaning provided in Section 4.1.

"Isis Initial IP Contribution" has the meaning provided in Section 6.1(b).

"Joint Venture" has the meaning provided in the recitals of this Agreement.

"Know-How" means any information, inventions, trade secrets or technology (excluding Patent Rights), whether or not proprietary or patentable and whether stored or transmitted in oral, documentary, electronic or other form. Know-How includes ideas, concepts, formulas, methods, procedures, designs, compositions, plans, documents, data, discoveries, developments, techniques, protocols, specifications, works of authorship, biological materials, and any information relating to research and development plans, experiments, results, compounds, therapeutic leads, candidates and products, clinical and preclinical data, clinical trial results, and Manufacturing information and plans.

"License Agreement" means that certain License and Collaboration Agreement by and among the Company, Alnylam and Isis dated the Effective Date, as amended from time to time.

"Licensed IP" means, with respect to a Licensor, such Licensor's Licensed Know-How and Licensed Patent Rights.

"Licensed Know-How" means, with respect to a Member, all Know-How Controlled by such Member on the Effective Date or during the term of the License Agreement (except as otherwise expressly provided therein) that relates to (a) miRNA Compounds or miRNA Therapeutics in general, (b) specific miRNA Compounds or miRNA Therapeutics, (c) chemistry or delivery of miRNA Compounds or miRNA Therapeutics, (d) mechanism(s) of action by which a miRNA Antagonist directly prevents the production of a specific miRNA or (e) methods of treating an Indication by modulating one or more miRNAs; provided, however that in each case, (i) for any such Know-How that include financial or other obligations to a Third Party, the provisions of Section 2.4 of the License Agreement will govern whether such Know-How will be included as Licensed Know-How and (ii) Licensed Know-How does not include manufacturing technology (including but not limited to analytical methods).

"Licensed Patent Rights" means, with respect to a Member, (A) all Patent Rights Controlled by such Member on the Effective Date and listed on **Schedule 2.2(A)** to the License Agreement and (B) all Patent Rights Controlled by such Member during the term of the License Agreement (except as otherwise expressly provided therein) that claim (a) miRNA Compounds or miRNA Therapeutics in general, (b) specific miRNA Compounds or miRNA Therapeutics, (c) chemistry or delivery of miRNA Compounds or miRNA Therapeutics, (d) mechanism(s) of action by which a miRNA Antagonist directly prevents the production of the specific miRNA, or (e) methods of treating an Indication by modulating one or more miRNAs; provided, however, that in each case, (i) for any such Patent Rights that include financial or other obligations to a Third Party, the provisions of Section 2.4 of the License Agreement will govern whether such

Patent Right will be included as a Licensed Patent Right and (ii) Licensed Patent Rights do not include manufacturing technology (including but not limited to analytical methods).

"**Losses**" means all liabilities, obligations, losses, damages, penalties, actions, judgments, taxes, suits, proceedings, charges, costs, expenses and disbursements of any kind or nature whatsoever (including reasonable attorneys' fees, costs of investigation, fines, judgments, awards and amounts paid in settlement, actually incurred in connection with such an action, suit or proceeding).

"Major Decisions" has the meaning provided in Section 4.3.

"**Managing Board**" has the meaning provided in Section 4.1.

"Manufacture" or **"Manufacturing"** means any activity involved in or relating to the manufacturing, quality control testing (including in-process, release and stability testing), releasing or packaging, for pre-clinical, clinical or commercial purposes, of a miRNA Compound or a miRNA Therapeutic.

"**Member**" will mean, as of the Effective Date, each of Alnylam or Isis, and will include thereafter their respective successors and permitted assigns, and any other members admitted in accordance with Section 8.3.

"Member Indemnitee" has the meaning provided in Section 11.3(a).

"**Membership Interest**" means the ownership interest of a Member in the Company, including a Member's right to share in Company items of income, gain, loss, deduction, credits and similar items, and the right to receive distributions from the Company, as well as a Member's right to vote and otherwise participate in the operation or affairs of the Company, all as provided herein and under the Act and the Certificate.

"miRNA" means a structurally defined functional RNA molecule usually between 21 and 25 nucleotides in length, which is derived from genetically-encoded non-coding RNA which is predicted to be processed into a hairpin RNA structure that is a substrate for the double-stranded RNA-specific ribonuclease Drosha and subsequently is predicted to serve as a substrate for the enzyme Dicer, a member of the RNase III enzyme family; including, without limitation, those miRNAs exemplified in miRBase (http://microrna.sanger.ac.uk/). To the extent that [***] for purposes of this Agreement; provided, however, that nothing contained herein shall require any Party hereto to [***].

"miRNA Antagonist" means a single-stranded oligonucleotide (or single-stranded analogs thereof) that is designed to interfere with or inhibit a particular miRNA. For purposes of clarity, the definition of "miRNA Antagonist" is not intended to include oligonucleotides that function predominantly through the RNAi mechanism of action or the RNase H mechanism of action.

"miRNA Compound" means a compound consisting of (a) a miRNA Antagonist, (b) to the extent listed in Schedule 1.58 of the License Agreement or otherwise agreed upon by the Company and the relevant Member(s) pursuant to Section 2.2(b) of the License Agreement, a

miRNA Precursor Antagonist (an **"Approved Precursor Antagonist"**), or (c) to the extent agreed upon by Regulus and the relevant Licensor(s) pursuant to Section 2.2(b) of the License Agreement, a miRNA Mimic (an **"Approved Mimic"**).

"miRNA Mimic" means a double-stranded or single-stranded oligonucleotide or analog thereof with a substantially similar base composition as a particular miRNA and which is designed to mimic the activity of such miRNA.

"miRNA Precursor" means a transcript that originates from a genomic DNA and that contains, but not necessarily exclusively, a non-coding, structured RNA comprising one or more mature miRNA sequences, including, without limitation, (a) polycistronic transcripts comprising more than one miRNA sequence, (b) miRNA clusters comprising more than one miRNA sequence, (c) pri-miRNAs, and/or (d) pre-miRNAs.

"miRNA Precursor Antagonist" means a single-stranded oligonucleotide (or single-stranded analogs thereof) that is designed to bind to a miRNA Precursor to prevent the production of one or more miRNAs. For purposes of clarity, the definition of "miRNA Precursor Antagonist" is not intended to include oligonucleotides that function predominantly through the RNAi mechanism of action or the RNase H mechanism of action.

"miRNA Therapeutic" means a therapeutic product having one or more miRNA Compounds as an active ingredient(s).

"NDA" means a New Drug Application or similar application or submission for approval to market and sell a new pharmaceutical product filed with or submitted to a Regulatory Authority.

"Net Sales" means, with respect to a Royalty-Bearing Product, the gross invoice price of all units of such Royalty-Bearing Products sold by the relevant Commercializing Party, its Affiliates and/or their direct Sublicensees to any Third Party, less the following items: (a) trade discounts, credits or allowances, (b) credits or allowances additionally granted upon returns, rejections or recalls, (c) freight, shipping and insurance charges, (d) taxes, duties or other governmental tariffs (other than income taxes), (e) government-mandated rebates, and (f) a reasonable reserve for bad debts. "Net Sales" under the following circumstances will mean the fair market value of such Royalty-Bearing Product: (i) Royalty-Bearing Products which are used by such Commercializing Party, its Affiliates or direct Sublicensees for any commercial purpose without charge or provision of invoice, (ii) Royalty-Bearing Products which are sold or disposed of in whole or in part for non cash consideration, or (iii) Royalty-Bearing Products which are provided to a Third Party by such Commercializing Party, its Affiliates or direct Sublicensees without charge or provision of invoice and used by such Third Party except in the cases of Royalty-Bearing Products used to conduct clinical trials, reasonable amounts of Royalty-Bearing Products used as marketing samples and Royalty-Bearing Product provided without charge for compassionate or similar uses.

Net Sales will not include any transfer between or among a Party and any of its Affiliates or direct Sublicensees for resale.

In the event a Royalty-Bearing Product is sold as part of a Combination Product (as defined below), the Net Sales from the Combination Product, for the purposes of determining royalty payments, will be determined by multiplying the Net Sales (as determined without reference to this paragraph) of the Combination Product, by the fraction, A/A+B, where A is the average sale price of the Royalty-Bearing Product when sold separately in finished form and B is the average sale price of the other therapeutically active pharmaceutical compound(s) included in the Combination Product when sold separately in finished form, each during the applicable royalty period or, if sales of all compounds did not occur in such period, then in the most recent royalty reporting period in which sales of all occurred. In the event that such average sale price cannot be determined for both the Royalty-Bearing Product and all other therapeutically active pharmaceutical compounds included in the Combination Product, Net Sales for the purposes of determining royalty payments will be calculated as above, but the average sales price in the above equation will be replaced by a good faith estimate of the fair market value of the compound(s) for which no such price exists. As used above, the term **"Combination Product"** means any pharmaceutical product which consists of a Royalty-Bearing Product and other therapeutically active pharmaceutical compound(s).

"**Non-Defaulting Party**" has the meaning provided in Section 6.1(h).

"**Observer Rights**" has the meaning provided in Section 4.1(c).

"**Officer**" has the meaning provided in Section 5.1(b).

"**Operating Budget**" has the meaning provided in the definition of "**Operating Plan**."

"**Operating Plan**" means the comprehensive "Joint Venture Business Plan" developed in support of the creation of the Company. The Operating Plan will include a Development Plan, an Operating Budget and a Capital Contribution Schedule, all as described below:

(a) The Development Plan (the "**Development Plan**") will reflect the research and development activities to be carried out by the Company for the applicable period set forth in the Operating Plan.

(b) The Operating Budget (the "**Operating Budget**") will include monthly income statements, balance sheets and capital budgets and cash flow statements which will show in reasonable detail the receipts (including the anticipated distributions and disbursements to the Members) projected for the Company for such period and the amount of any corresponding cash deficiency or surplus, if any. The Operating Budget will be the basis for the creation and subsequent revisions of the Capital Contribution Schedule.

(c) The Capital Contribution Schedule (the "**Capital Contribution Schedule**") will forecast the cash surplus or deficit of the Company as determined by the Operating Budget, and forecast the cash requirements of the Company, all on a monthly basis for a one year period (except with respect to the initial Capital Contribution Schedule, as to which the period will be from the Effective Date through [***]).

"Operating Plan Contributions" has the meaning provided in Section 6.1(c).

"Opt-In Election" means the election by at least one Member, pursuant to the License Agreement, to continue to pursue the Development and Commercialization of a Development Project that the Company has determined not to pursue.

"Opt-In Party" means the single Member which, pursuant to an Opt-In Election, is granted the right, pursuant to the License Agreement to continue to pursue the Development and Commercialization of a Development Project that the Company has determined not to pursue.

"Opt-In Product" means any miRNA Therapeutic that is Developed, Manufactured or Commercialized pursuant to a Development Project for which one and only one Member has exercised an Opt-In Election and which the relevant Opt-In Party subsequently licensed.

"Option Value" means the value of the relevant stock options, as determined based on the method and assumptions then used by the relevant Member to value stock options for financial reporting purposes.

"**Partial Transfer**" has the meaning provided in Section 8.2(c).

"Parties" means Alnylam, Isis and the Company, or any combination thereof.

"Party" means Alnylam, Isis or the Company.

"Patent Rights" means (a) patent applications (including provisional applications and for certificates of invention); (b) any patents issuing from such patent applications (including certificates of invention); (c) all patents and patent applications based on, corresponding to, or claiming the priority date(s) of any of the foregoing; and (d) any substitutions, extensions (including supplemental protection certificates), registrations, confirmations, reissues, divisionals, continuations, continuations-in-part, re-examinations, renewals and foreign counterparts thereof.

"**Percentage Interest**" means the respective Percentage Interests of the Members as indicated on **Schedule 3.1** hereto.

"Permitted Disclosures". The following are Permitted Disclosures:

(a) To the extent that a Recipient has been granted the right to sublicense under the terms of this Agreement, such Party will have the right to provide a Disclosing Party's Confidential Information to the employees, consultants and advisors of such Recipient's Affiliate and Third Party sublicensees and potential sublicensees who have a need to know the Confidential Information for purposes of exercising such sublicense and are bound by an obligation to maintain in confidence the Confidential Information of the Disclosing Party; provided, that such Persons are bound to maintain the confidentiality of such information to the same extent as if they were parties hereto.

(b) Each Recipient will have the right to provide a Disclosing Party's Confidential Information:

(i) to governmental or other regulatory agencies in order to seek or obtain patents, to seek or obtain approval to conduct clinical trials, or to gain Regulatory Approval, as contemplated by this Agreement; provided that such disclosure may be made only to the extent reasonably necessary to seek or obtain such patents or approvals; and

(ii) as necessary, if embodied in products, to develop and commercialize such products as contemplated by this Agreement.

"Permitted License" means a license granted by a Licensor to a Third Party to enable such Third Party to broadly manufacture or formulate oligonucleotides, where such Third Party is primarily engaged in [***] and is not engaged in [***]; provided, however, that any such license will not grant rights to research, manufacture or formulate miRNA Compounds or miRNA Therapeutics for which the other Licensor has obtained or later obtains a license pursuant to Section 5 of the License Agreement or pursuant to a Buy-Out.

"**Person**" means a natural person, company, corporation, partnership, trust or other organization or legal entity of any type, whether or not formally organized.

"Post Buy-Out Activities" has the meaning provided in Section 9.3(f).

"**Prevailing Party**" has the meaning provided in Section 12.11.

"Program/Project Compound" means, with respect to a Research Program or Development Project, any miRNA Compound directed to the miRNA(s) which is the focus of such Research Program or Development Project.

"Program/Project List" means the list, which the Company is required to maintain pursuant to the License Agreement, specifying the Company's Research Programs and Development Projects.

"Project Bid" has the meaning provided in Section 9.3(e)(i).

"**Proposed Capital Contribution Schedule**" has the meaning provided in Section 5.2(b).

"**Proposed Development Plan**" has the meaning provided in Section 5.2(b).

"**Proposed Operating Budget**" has the meaning provided in Section 5.2(b).

"**Proposed Business Plan**" has the meaning provided in Section 5.2(b).

"Qualified Third Party" has the meaning provided in Section 9.3(e)(v).

"Receiving Member" has the meaning provided in Section 10.7.

"**Recipient**" has the meaning provided in Section 12.4(a).

"Registered Intellectual Property" has the meaning provided in Section 10.8(d).

"Regulatory Approval" means the act of a Regulatory Authority necessary for the marketing and sale (including, if required for marketing and sales, pricing) of such product in a country or regulatory jurisdiction, including, without limitation, the approval of an NDA by the FDA.

"Regulatory Authority" means any applicable government regulatory authority involved in granting approvals for the marketing and/or pricing of a product in a country or regulatory jurisdiction including, without limitation, the FDA.

"Representatives" has the meaning provided in Section 12.4(a).

"Required Additional Capital Contribution" has the meaning provided in Section 6.1(e).

"Research Program" means a program for which discovery or characterization activities focused on one or more specific miRNA(s) have commenced after preliminary validation of the biological function of such miRNA(s) have been identified (i.e., compound discovery, not target validation) and will include all activities with respect to the Development, Manufacturing and Commercialization of miRNA Compounds and miRNA Therapeutics directed to such miRNA(s).

"**Reserves**" means the reserves established and maintained from time to time by the Managing Board to pay taxes, fees, insurance or other costs and expenses incident to the Company's business.

"Royalty-Bearing Product" means (a) an Opt-In Product or (b) a Buy-Out Product that, on a country-by-country basis, is, or the relevant Buy-Out Party reasonably believes will be, at the time of first commercial sale of such Buy-Out Product, Covered in such country by a Valid Claim of a Patent Right or covered by Know-How, which Patent Right or Know-How is licensed to the applicable Buy-Out hereunder.

"Royalty Term" means, with respect to each Royalty-Bearing Product in a country, the period commencing upon first commercial sale of such Royalty-Bearing Product in such country and ending upon the later of (a) the expiration of the Exclusivity Period, or (b) 10 years following first commercial sale of such Royalty-Bearing Product.

"SAB" has the meaning provided in Section 5.3.

"SAB Consulting Agreement" has the meaning provided in Section 5.3(b).

"Sale" has the meaning provided in Section 9.2.

"Sale Agreement" has the meaning provided in Section 9.2.

"SEC" means the United States Securities and Exchange Commission.

"Selected Program" has the meaning provided in Section 9.3(d)(ii).

"Services Agreement" means that certain Services Agreement by and between the Company, Alnylam and Isis dated the Effective Date, as amended from time to time.

"Stalemate" has the meaning provided in Section 5.2.

"Sublicensee" means a Third Party to whom a Party or its Affiliates or Sublicensees, has granted a sublicense in accordance with the terms of the License Agreement or this Agreement.

"**Tax**" and "**Taxes**" means any and all national, local and foreign taxes, assessment and other governmental charges, duties, impositions and liabilities including taxes based upon or measured by gross receipts, income, profits, sales, use or occupation, and value added, ad valorem, transfer, franchise, withholding, payroll, recapture, employment, excise and property taxes, together with all interest, penalties and additions imposed with respect to such amounts.

"**Tax Distribution**" has the meaning provided in Section 7.2(a)(i).

"**Tax Distribution Date**" has the meaning provided in Section 7.2(a)(iii).

"Tax Matters Partner" has the meaning provided in Section 7.7.

"**Terminated Director**" has the meaning provided in Section 4.7(b).

"Third Party" means any Person other than the Members or any of their Affiliates.

"Third Party Contracts" has the meaning provided in Section 9.3(a).

"Third Party Rights" has the meaning ascribed to it in the License Agreement.

"**Transfer**" has the meaning provided in Section 8.1(a).

"**Transfer Taxes**" has the meaning provided in Section 6.1(i).

"**Transferring Member**" has the meaning provided in Section 8.2(a).

"Valid Claim" means a claim (a) of any issued, unexpired patent that has not been revoked or held unenforceable or invalid by a decision of a court or governmental agency of competent jurisdiction from which no appeal can be taken, or with respect to which an appeal is not taken within the time allowed for appeal, and that has not been disclaimed or admitted to be invalid or unenforceable through reissue, disclaimer or otherwise; or (b) of any patent application that has not been cancelled, withdrawn or abandoned, or been pending for more than [***] years.

SCHEDULE 2

REPRESENTATIONS AND WARRANTIES OF EACH MEMBER TO THE OTHER MEMBER AND THE COMPANY

1. Such Member is a corporation duly organized, validly existing and in good standing under the laws of the jurisdiction of its incorporation, and has all corporate powers and all material licenses, authorizations, consents and approvals required to enter into and perform this Agreement, each of the Ancillary Agreements to which it is a party, and the transactions contemplated hereby and thereby.

2. The execution, delivery and performance by such Member of this Agreement and each of the Ancillary Agreements to which it is a party, and the consummation by such Member of the transactions contemplated hereby and thereby, are within such Member's corporate powers and have been duly authorized by all necessary corporate action on the part of such Member. This Agreement and each of the Ancillary Agreements to which it is a party have been duly executed and delivered by, and constitute the legal, valid and binding agreement of such Member, enforceable against such Member in accordance with their respective terms, subject to bankruptcy, insolvency, reorganization, moratorium or similar laws affecting the rights of creditors generally and to equitable principles.

3. The execution, delivery and performance by such Member of this Agreement and the Ancillary Agreements to which it is a party do not require any notice to, action or consent by, or in respect of, or filing with, any governmental authority.

4. The execution, delivery and performance by such Member of this Agreement and each of the Ancillary Agreements to which it is a party do not (i) contravene or conflict with the organizational or constitutional documents of such Member; (ii) contravene or conflict with or constitute a violation of any provision of any law, rule or regulation binding upon or applicable to such Member; (iii) contravene or conflict with or constitute a violation of any judgment, injunction, order or decree binding upon or applicable to such Member; (iv) constitute a default under or give rise to any right of termination, cancellation or acceleration of any right or obligation of such Member; or (v) require the consent or permission of any Person.

5. There is no action, suit, investigation or proceeding pending or, to the knowledge of such Member, threatened before any governmental authority to which such Member is a party that would materially and adversely affect such Member's ability to perform its obligations under this Agreement and each of the Ancillary Agreements to which it is a party.

SCHEDULE 3.1

SCHEDULE OF MEMBERS

Names and Addresses, Initial Percentage Interests and Capital Account Balances

Name and Address of Member	Percentage Interest	Capital Account Balance
Alnylam Pharmaceuticals, Inc. 300 Third Street, 3rd Floor Cambridge, MA 02142	[***]%	$[***]
Isis Pharmaceuticals, Inc. 1896 Rutherford Road Carlsbad, California 92008	[***]%	$[***]

SCHEDULE 4.5

FORM OF CONSULTING AGREEMENT

This Consulting Agreement (together with its attachments, this "Agreement") made as of [DATE] (the "Effective Date") is between Alnylam Pharmaceuticals, Inc. ("Alnylam"), Isis Pharmaceuticals Inc. ("Isis"), Regulus Therapeutics, LLC ("Regulus") and [NAME] ("Consultant"). Alnylam, Isis, Regulus, and Consultant may each be referred to herein as a "Party" and collectively as the "Parties".

WHEREAS, Alnylam and Isis have combined to form Regulus, and are the sole stockholders of Regulus; and

WHERAS, Consultant has agreed to serve on the Scientific Advisory Board of Regulus; and

WHEREAS, Alnylam, Isis and Regulus each desire that Consultant advise them independently with respect to microRNA technology and the business and strategy of developing microRNA products, and Consultant desires to so advise Alnylam, Isis and Regulus; and

NOW, THEREFORE, in furtherance of the foregoing and in exchange for good and valuable consideration, the sufficiency of which is hereby acknowledged, the Parties hereby agree as follows:

1. Advisory Services. Alnylam, Isis and Regulus (collectively, the "Engaging Parties") each independently hereby retains Consultant and Consultant agrees to provide consulting and advisory services to each Engaging Party (the "Advisory Services") as it may from time to time reasonably request; provided, however, that Consultant shall provide only advisory and educational services for Alnylam and Isis, and that any work performed by Consultant that could reasonably be expected to lead to the creation of intellectual property pursuant hereto shall only be performed by Consultant on behalf of Regulus and not on behalf of Alnylam or Isis. Any changes to the Advisory Services (and any related compensation adjustments) must be agreed upon in writing between Consultant and the Engaging Parties prior to commencement of the changes.

1.1 Performance. Consultant agrees to render the Advisory Services to each Engaging Party, (a) at such reasonably convenient times and places as such Engaging Party may direct, (b) under the general supervision of such Engaging Party, and (c) on a best efforts basis; provided, however, that in the event of logistical conflict between the Engaging Parties, the Engaging Parties shall be responsible for coordinating among themselves without liability to Consultant. Consultant will comply with all rules, procedures and standards promulgated from time to time by an Engaging Party with regard to Consultant's access to and use of such Engaging Party's property, information, equipment and facilities. Consultant agrees to furnish each Engaging Party with written reports with respect to the Advisory Services if and when requested by such Engaging Party.

1.2 Third Party Confidential Information. Consultant agrees not to use any trade secrets or other confidential information of any other person, firm, corporation, institution or other entity in connection with any of the Advisory Services.

1.3 No Conflicts. Consultant is under no contractual or other obligation or restriction which is inconsistent with Consultant's execution of this Agreement or the performance of the Advisory Services. Consultant will not enter into any agreement, either written or oral, in conflict with Consultant's obligations under this Agreement. Consultant will arrange to provide the Advisory Services in such manner and at such times that the Advisory Services will not conflict with Consultant's responsibilities under any other agreement, arrangement or understanding or pursuant to any employment relationship Consultant has at any time with any third party.

1.4 Compliance with Policies. If Consultant is a faculty member at or employee of a university or hospital ("Institution") or of another company, Consultant represents and warrants that (i) Consultant has a good faith belief that such Institution will not oppose this arrangements set forth in this Agreement and (ii) Consultant shall comply with such Institution's policies and procedures. If Institution's approval of this Agreement is required by Institution policies, Consultant will obtain and deliver to each Engaging Party, Institution's consent on the form attached to this Agreement.

1.5 Absence of Debarment. Consultant represents that Consultant has not been debarred, and to the best of Consultant's knowledge, is not under consideration to be debarred, by the U.S. Food and Drug Administration from working in or providing Advisory Services to any pharmaceutical or biotechnology company under the Generic Drug Enforcement Act of 1992.

2. Compensation. In consideration for the Advisory Services rendered by Consultant to each Engaging Party, each Engaging Party agrees to compensate Consultant as set forth in the **Business Terms Exhibit** attached hereto. Unless otherwise specified in the **Business Terms Exhibit**, undisputed payments will be made by each Engaging Party within thirty (30) days from such Engaging Party's receipt of Consultant's invoice. Invoices will contain such detail as each Engaging Party may reasonably require and will be payable in U.S. Dollars. Each Engaging Party will reimburse Consultant for reasonable business expenses incurred by Consultant in the performance of the Advisory Services as specified in the **Business Terms Exhibit**.

3. Inventions.

3.1 Definition. Consultant will promptly disclose in confidence to each Engaging Party all inventions, discoveries, improvements, ideas, designs, processes, products, computer programs, works of authorship, databases, mask works, trade secrets, know-how, research and creations (whether or not patentable or subject to copyright or trade secret protection) that Consultant makes, conceives or reduces to practice, either alone or jointly with others, and that (a) result from the performance of the Advisory Services with any Engaging Party pursuant hereto,

and/or (b) result from use of facilities, equipment, supplies, or Confidential Information (defined below) of any Engaging Party ("Inventions").

3.2 Ownership. All Inventions arising solely under Advisory Services will be the property of Regulus. For purposes of the copyright laws of the United States, all Inventions will constitute "works made for hire", except to the extent such Inventions cannot by law be "works made for hire". To the extent Inventions have not been previously assigned to Regulus, Consultant hereby assigns and, to the extent any such assignment cannot be made at present, hereby agrees to assign to Regulus, without further compensation, all right, title and interest in and to all Inventions and any and all related patents, patent applications, copyrights, copyright applications, trademarks, trade names, trade secrets and other proprietary rights in the United States and throughout the world. For purposes of clarity, it is the intention of the Parties that any invention made by Consultant pursuant hereto shall be owned exclusively by Regulus.

3.3 **Records.** Consultant shall make and maintain adequate and current written records of all Inventions, which records shall be available to and remain the property of each Engaging Party at all times.

3.4 **Agreement with Institution.** This Agreement is made subject to the understanding that Consultant, if affiliated with an Institution, may be required to fulfill certain obligations, including teaching, directing laboratory operations, conducting research, and publishing work. It is further understood that Consultant may have signed an agreement concerning inventions with Institution, under which Consultant may be obligated to assign to Institution certain inventions which arise out of or otherwise relate to Consultant's work at or for Institution or from Consultant's use of certain of its facilities or intellectual property. In performing the Advisory Services, Consultant agrees not to utilize Institution facilities or intellectual property if the result of such use is that any Inventions will not be assignable solely to the Engaging Parties. Consultant agrees to confirm with Institution that use of Institution's telephone, fax machines or computers for communication purposes, does not constitute use of Institution's facilities under this Agreement.

3.5 **Work at Third Party Facilities.** Consultant agrees not to make any use of any funds, space, personnel, facilities, equipment or other resources of a third party in performing the Advisory Services nor take any other action that would result in a third party owning or having a right in any Inventions, unless agreed upon in writing in advance by each Engaging Party.

4. Confidential Information.

4.1 **Definition.** "Confidential Information" means all trade secrets and confidential or proprietary information owned, possessed or used by an Engaging Party, learned of by Consultant or developed by Consultant in connection with the Advisory Services, whether or not labeled "Confidential", including but not

limited to (a) Inventions, scientific data and sequence information, (b) marketing plans, business strategies, financial information, forecasts, personnel information and customer lists of an Engaging Party, (c) all information of third parties that an Engaging Party has an obligation to keep confidential, and (d) the terms and conditions of this Agreement (including the compensation paid to Consultant pursuant to Section 2). Confidential Information does not include information which (i) is in the public domain or which becomes part of the public domain through no wrongful act on Consultant's part but only after it becomes so publicly known, (ii) is already in Consultant's possession at the time of disclosure by an Engaging Party, other than by previous disclosure by an Engaging Party, as evidenced by written or electronic records, or (iii) that becomes known to Consultant through disclosure by a third party having the right to disclose the information, as evidenced by written or electronic records.

4.2 **Obligations of Confidentiality.** During the Term and for a period of five (5) years thereafter, Consultant will not directly or indirectly publish, disseminate or otherwise disclose, use for Consultant's own benefit or for the benefit of a third party, deliver or make available to any third party, any Confidential Information, other than in furtherance of the purposes of this Agreement, and only then with the prior written consent of each Engaging Party. If required, Consultant may disclose the Confidential Information to a governmental authority or by order of a court of competent jurisdiction, provided that such disclosure is subject to all applicable governmental or judicial protection available for like material and reasonable advance notice is given to each Engaging Party. Consultant will exercise all reasonable precautions to physically protect the integrity and confidentiality of the Confidential Information and will not remove any Confidential Information or copies thereof from an Engaging Party's premises except to the extent necessary to fulfill the Advisory Services, and then only with each Engaging Party's prior consent. Each Engaging Party will be entitled to seek injunctive relief as a remedy for any breach of the terms of this Section 4.

5. **Non-Competition.** During the Term, Consultant shall not provide (whether for or without compensation) Advisory Services to any business or entity developing a product which is a microRNA therapeutic other than an Engaging Party. It shall not be considered a competitive activity within the meaning of this Section for Consultant to be a member of the faculty or staff of a university, college or other educational or non-profit research institution.

6. **Publication.** Consultant agrees to submit to each Engaging Party a copy of any proposed manuscript or other materials to be published or otherwise publicly disclosed which may contain Confidential Information in sufficient time to enable each Engaging Party to determine if patentable Inventions or any Confidential Information of an Engaging Party would be disclosed. Consultant will cooperate with each Engaging Party in this respect and will delete from the manuscript or other disclosure any Confidential Information if requested by an Engaging Party, and if Inventions arose solely through Advisory Services, then Consultant will assist the Engaging Parties in filing for patent protection for any patentable Inventions prior to publication or other disclosure.

7. Term and Termination.

7.1 **Term.** This Agreement will commence on the Effective Date and continue until terminated by the Consultant, on the one hand, or the Engaging Parties acting collectively, on the other hand, on not less than thirty (30) days notice (the "Term"); provided, however, that Alnylam or Isis, respectively, may terminate this Agreement with respect to such company's involvement in this Agreement in which case the Agreement shall remain in place for the remaining Parties.

7.2 **Effect of Expiration/Termination.** Upon expiration or termination, neither any Engaging Party nor Consultant will have any further obligations under this Agreement, except (a) the liabilities accrued through the date of termination, and (b) the obligations under, sections 3, 4, 5, 6, 7 and 8 will survive. Upon expiration or termination, and in any case upon an Engaging Party's request, Consultant will return immediately to each Engaging Party all tangible Confidential Information, including all copies and reproductions thereof, except for one (1) copy which may be retained solely for archival purposes.

8. Miscellaneous.

8.1 **Independent Contractor.** All Advisory Services will be rendered by Consultant as an independent contractor and this Agreement does not create an employer-employee relationship between any Engaging Party and Consultant. Consultant will have no rights to receive any employee benefits, such as health and accident insurance, sick leave or vacation which are accorded to regular employees of any Engaging Party. Consultant will not in any way represent himself to be an employee, partner, joint venturer, or agent of any Engaging Party.

8.2 **Taxes.** Consultant will pay all required taxes on Consultant's income from any Engaging Party under this Agreement. Consultant will provide each Engaging Party with Consultant's taxpayer identification number or social security number, as applicable.

8.3 **Use of Name.** Consultant consents to the use by each Engaging Party of Consultant's name and likeness in written materials and oral presentations to current or prospective customers, partners, investors or others, provided that such materials or presentations accurately describe the nature of Consultant's relationship with or contribution to such Engaging Party.

8.4 **Assignability and Binding Effect.** The Advisory Services to be rendered by Consultant are personal in nature. Consultant may not assign or transfer this Agreement or any of Consultant's rights or obligations hereunder except to a corporation of which Consultant is the sole stockholder. In no event will Consultant assign or delegate responsibility for actual performance of the Advisory Services to any other natural person. This Agreement will be binding upon and inure to the benefit of the parties and their respective legal representatives, heirs, successors and permitted assigns.

8.5 **Headings.** The section headings are included solely for convenience of reference and will not control or affect the meaning or interpretation of any of the provisions of this Agreement.

8.6 **Notices.** Any notices or other communications from one party to the other will be in writing and will be given by addressing the same to each other Party at the address or facsimile number set forth below:

If to Alnylam: Alnylam Pharmaceuticals, Inc.
300 Third Street
Cambridge, MA 02142
Attn: Philip Chase, VP, Legal
pchase@alnylam.com
617-551-8200

If to Isis: Isis Pharmaceuticals, Inc
1896 Rutherford Ave.
Carlsbad CA 92008-7208
760-931-9200

Notice will be deemed to have been duly given when (a) deposited in the United States mail with proper postage for first class Registered or Certified Mail prepaid, return receipt requested, (b) sent by any reputable commercial courier, delivery confirmation requested, (c) delivered personally, or (d) if promptly confirmed by mail or commercial courier as provided above, when dispatched by facsimile.

8.7 **No Modification.** This Agreement may be changed only by a writing signed by authorized representatives of each Party; provided, however that Alnylam or Isis may terminate its participation in this Agreement pursuant to Section 7.1 without a further agreement in writing between the Parties.

8.8 **Severability.** In the event that any one or more of the provisions contained in this Agreement will, for any reason, be held to be invalid, illegal or unenforceable in any respect, such invalidity, illegality or unenforceability will not affect any other provisions of this Agreement, and all other provisions will remain in full force and effect. If any provision of this Agreement is held to be excessively broad, it will be reformed and construed by limiting and reducing it so as to be enforceable to the maximum extent permitted by law.

8.9 **Entire Agreement.** This Agreement constitutes the entire agreement of the parties with regard to its subject matter, and supersedes all previous written or oral representations, agreements and understandings between the parties.

8.10 **Governing Law.** This Agreement will be governed by, and construed and enforced in accordance with, the laws of the Commonwealth of Massachusetts

applicable to contracts made and to be performed therein, without giving effect to the principles thereof relating to the conflict of laws.

8.11 **Counterparts.** This Agreement may be executed in any number of counterparts, each of which will be deemed an original, but all of which together will constitute one and the same instrument.

IN WITNESS WHEREOF, the parties hereto have duly executed this Agreement under seal as of the Effective Date.

ALNYLAM PHARMACEUTICALS, INC.

By: _____

Name: _____

Title: _____
duly authorized

ISIS PHARMACEUTICALS INC.

By: _____

Name: _____

Title: _____
duly authorized

CONSULTANT:

_____

Name: _____

Title: _____
duly authorized

Address: _____

_____

Telephone: _____

Facsimile: _____

SS or Tax ID No.: _____
(required for payment)

INSTITUTION ACKNOWLEDGEMENT AND CONSENT FORM

Alnylam Pharmaceuticals, Inc. ("Alnylam"), Isis Pharmaceuticals Inc. ("Isis"), Regulus Therapeutics, LLC ("Regulus") are prepared to enter into the foregoing Agreement with the consultant named on the preceding signature page ("Consultant"). Alnylam, Isis, and Regulus recognize that as a member of the institution named below ("Institution"), Consultant is responsible for ensuring that any consulting agreement Consultant enters into with a for-profit entity is not in conflict with the patent, consulting or other policies of Institution. The proposed Agreement requires Consultant, if required by Institution policies, to disclose the proposed Agreement to Institution and/or to obtain Institution's consent to enter into the proposed Agreement.

Institution hereby acknowledges and consents to Consultant entering into the foregoing Agreement.

INSTITUTION:

By: _____

Print Name _____

Title: _____
duly authorized

Date _____

BUSINESS TERMS EXHIBIT

1. Compensation:

a. **Compensation for SAB membership.** Regulus will pay Consultant quarterly cash compensation of $[ ] at the end of each calendar quarter as compensation for serving on the Scientific Advisory Board. Such quarterly retainer will be prorated with respect to the first calendar quarter of service hereunder.

b. **Expenses.** Each Engaging Party will reimburse Consultant for all reasonable travel and other business expenses incurred by Consultant in rendering the Advisory Services for such Engaging Party, provided that such expenses are agreed upon in writing in advance, and are confirmed by appropriate written expense statements and other supporting documentation.

On the last day of each calendar month, Consultant will invoice each Engaging Party for expenses incurred during the preceding month. Invoices should reference this Agreement and should be submitted to the following address:

If to Alnylam:
Alnylam Pharmaceuticals, Inc.
Attn: Accounts Payable Dept.
300 Third Street, 3rd Floor
Cambridge, MA 02142

If to Isis:
Isis Pharmaceuticals, Inc
Attn: Accounts Payable
1896 Rutherford Ave.
Carlsbad CA 92008-7208
760-931-9200

c. **Initial Option Grant.** As additional compensation for the Advisory Services, Consultant will receive options to purchase [ ] shares of Alnylam's common stock (the "Alnylam Options") and [ ] shares of Isis' common stock (the "Isis Options", and together with the Alnylam Options, the "Options"), each at a purchase price equal to the fair market value of the shares at the close of the market in the United States for such shares on the day of issuance. The vesting of the Options and other terms will be detailed in the standard form of Stock Option Agreement of Alnylam and Isis, respectively, which Consultant must execute as a condition of receiving the Options. To the extent not previously approved by the Board of Directors of Alnylam or Isis, as the case may be, the grant herein of Alnylam Options or Isis Options, as the case may be, remains subject to such approval.

d. **Annual Option Grant.** Consultant will receive an annual grant of [ ] options to purchase Alnylam stock and [ ] options to purchase Isis stock, subject in both cases to the terms of the respective stock plans and policies of Alnylam and Isis, as applicable, as compensation for Consultant's continued advisory role.

SCHEDULE 4.6

INITIAL MANAGING BOARD MEMBERS

Name	Title
TBD	President, Regulus Therapeutics LLC
David Baltimore, Ph.D.	Independent Director nominated by Alnylam
TBD	Independent Director nominated by Isis
John M. Maraganore, Ph.D.	Alnylam Director
Barry E. Greene	Alnylam Director
Stanley T. Crooke, M.D., Ph.D.	Isis Director
B. Lynne Parshall, J.D.	Isis Director

SCHEDULE 5.3

INITIAL SAB MEMBERS AND CHAIRPERSON

Name	Title
David Baltimore, Ph.D.	Member and Chairperson
Scott Hammond, Ph.D.	Member
Markus Stoffel, M.D., Ph.D.	Member

Thomas Tuschl, Ph.D.	Member
Philip Zamore, Ph.D.	Member

SCHEDULE 12.4

PRESS RELEASE

Isis and Alnylam Launch Regulus Therapeutics, a Joint Venture to Discover, Develop, and Commercialize microRNA Therapeutics

- By Targeting Gene Pathways, microRNA Therapeutics Represent a New Approach for the Treatment of a Broad Range of Human Disease - - David Baltimore to Join Regulus Board of Directors and Chair Scientific Advisory Board Comprised of Key Pioneers in microRNA Research - - Companies to Host Conference Call Webcast to Discuss Regulus Therapeutics at 8:30 a.m. ET Friday -

CAMBRIDGE, Mass. & CARLSBAD, Calif., Sep 07, 2007 (BUSINESS WIRE) —

Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY) and Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today the launch of Regulus Therapeutics LLC, a joint venture focused on the discovery, development, and commercialization of microRNA (miRNA) therapeutics. Because miRNAs regulate whole networks of genes that can be involved in discrete disease processes, miRNA therapeutics represent a new approach to target the pathways of human disease. Regulus will combine the strengths and assets of Isis' and Alnylam's technologies, know-how, and intellectual property (IP) with strong leadership from a focused management team and Scientific Advisory Board to be chaired by Nobel laureate David Baltimore and include key pioneers in the miRNA field.

Both Isis and Alnylam will grant Regulus exclusive licenses to their IP for miRNA therapeutic applications, as well as certain early fundamental patents in the miRNA field including the "Tuschl III" patent. Alnylam will make an initial investment of $10 million to balance venture ownership; thereafter Isis and Alnylam will share funding of Regulus. Regulus will be operated as an independent company with an independent Board of Directors and management team. Alnylam and Isis will retain rights to develop and commercialize on pre-negotiated terms miRNA therapeutic products that Regulus decides not to develop either itself or with a partner.

"The emerging biology of microRNAs points to a completely new understanding of cellular mechanisms for regulation of gene expression," said David Baltimore, Ph.D., of California Institute of Technology. "I believe that microRNAs represent previously unexplored disease targets where pharmacological approaches could lead to the emergence of novel therapies for many human disorders. Accordingly, I'm very excited to join in the formation of Regulus and to help build the leading microRNA therapeutics company."

"The opportunity to antagonize microRNAs could create a new frontier for pharmaceutical research where an entire disease pathway is targeted for intervention, not just a single disease target. Indeed, due to their mechanism of action, we believe

microRNA therapeutics could have profound implications for the treatment of a broad range of diseases including cancer, viral infection, and metabolic disorders," said John Maraganore, Ph.D., President and Chief Executive Officer of Alnylam. "Isis' and Alnylam's intellectual property and technologies open the door to these new opportunities and, when combined to form Regulus, create an unmatched effort to establish the leading microRNA therapeutics company."

"We are excited to embark on this venture, which represents an opportunity to invest in a focused expansion of our ongoing microRNA research efforts through Regulus' application of our antisense technology platform to create microRNA therapeutics. Indeed, it is timely to extend our know-how and clinical advances with antisense drugs to the field of microRNAs, an area that stands at the forefront of modern biology," said Stanley Crooke, M.D., Ph.D., Chairman and Chief Executive Officer of Isis. "Regulus will be fully enabled with intellectual property, technology, and funding from Isis and Alnylam to create a bold and successful new venture."

Regulus' newly formed Scientific Advisory Board will be chaired by David Baltimore, Ph.D., who will also serve as the first Regulus independent Director, and, subject to relevant institutional approvals, initially will comprise the following members:

— David Baltimore, Ph.D., Professor of Biology at California Institute of Technology and the recipient of the 1975 Nobel Prize in Physiology or Medicine;

— David Bartel, Ph.D., Professor of Biology at MIT and a member of the Whitehead Institute for Biomedical Research;

— Scott Hammond, Ph.D., Assistant Professor of Cell and Developmental Biology at the University of North Carolina School of Medicine;

— Markus Stoffel, M.D., Ph.D., Professor for Metabolic Diseases at the Institute of Molecular Systems Biology, Swiss Federal Institute of Technology (ETH);

— Thomas Tuschl, Ph.D., Associate Professor at the Rockefeller University; and

— Phillip D. Zamore, Ph.D., Gretchen Stone Cook Professor of Biomedical Sciences at the University of Massachusetts Medical School.

Conference Call Information

Alnylam and Isis will host a conference call on September 7, 2007 at 8:30 a.m. ET to discuss the formation and launch of Regulus Therapeutics. The call may be accessed by dialing 800-901-5231 (domestic) or 617-786-2961 (international) five minutes prior to the start time, and providing the passcode 44818346. A

replay of the call will be available from 10:30 a.m. ET September 7, 2007 until September 13, 2007. To access the replay, please dial 888-286-8010 (domestic) or 617-801-6888 (international), and provide the passcode 11989900. A live audio webcast of the call will be available on Isis' website at www.isispharm.com and on the "Investors" section of the Alnylam's website, www.alnylam.com, and on Regulus' website at www.regulusrx.com. An archive of the

webcast will be available on the both companies' websites approximately two hours after the event.

About microRNA

microRNAs (miRNAs) are a recently discovered class of genetically encoded small RNAs, approximately 20 nucleotides in length, and are believed to regulate the expression of a large number of human genes. miRNA therapeutics represent a new approach for the treatment of a broad range of human disease When inappropriately encoded, miRNAs represent potential disease targets whose selective antagonism can result in the correction of an entire disease pathway in a manner unachievable by today's medicines. In fact, the inappropriate absence or presence of specific miRNA molecules in various cells has been shown to be associated with specific human diseases including cancer, viral infection, and metabolic disorders.

About Regulus

Regulus Therapeutics LLC is a biopharmaceutical company formed to discover, develop and commercialize miRNA therapeutics. The company was created as a joint venture between Alnylam Pharmaceuticals, a leader in RNAi therapeutics, and Isis Pharmaceuticals, a leader in antisense technologies and therapeutics. Isis and Alnylam scientists and collaborators were the first to discover miRNA antagonist strategies that work in vivo in animal studies (Krutzfeldt et al. (2005) Nature 438, 685-689; Esau et al. (2006) Cell Metab., 3, 87-98). Isis and Alnylam have also created and consolidated key IP believed by the companies to be required for development and commercialization of miRNA therapeutics. The company, founded in 2007, maintains facilities in Carlsbad, California. For more information, visit www.regulusrx.com.

About Alnylam Pharmaceuticals

Alnylam is a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. The company is applying its therapeutic expertise in RNAi to address significant medical needs, many of which cannot effectively be addressed with small molecules or antibodies, the current major classes of drugs. Alnylam is leading the translation of RNAi as a new class of innovative medicines with peer-reviewed research efforts published in the world's top scientific journals including Nature, Nature Medicine, and Cell. The company is leveraging these capabilities to build a broad pipeline of RNAi therapeutics; its most advanced program is in Phase II human clinical trials for the treatment of respiratory syncytial virus (RSV) infection. In addition, the company is developing RNAi therapeutics for the treatment of influenza, hypercholesterolemia, and liver cancers, amongst other diseases. The company's leadership position in fundamental patents, technology, and know-how relating to RNAi has enabled it to form major alliances with leading companies including Merck, Medtronic, Novartis, Biogen Idec, and Roche. The company, founded in 2002, maintains headquarters in Cambridge, Massachusetts. For more information, visit www.alnylam.com.

About Isis Pharmaceuticals

Isis is exploiting its expertise in RNA to discover and develop novel drugs for its product pipeline and for its partners. The Company has successfully commercialized the world's first antisense drug and has 17 drugs in development. Isis' drug development programs are focused on treating cardiovascular and metabolic diseases. Isis' partners are developing drugs for cancer, and inflammatory and other diseases. Ibis Biosciences, Inc., Isis' wholly owned subsidiary, is developing and commercializing the Ibis T5000(TM) Biosensor System, a revolutionary system to identify infectious organisms. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of over 1,500 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

Alnylam Forward-Looking Statements

Various statements in this release concerning Alnylam's future expectations, plans and prospects, including statements concerning the potential of miRNA therapeutics and the importance of Alnylam's IP, know-how, and other technology in the discovery, development and commercialization of miRNA therapeutics, constitute forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by these forward-looking statements as a result of various important factors, including risks related to: Alnylam's approach to discover and develop novel drugs, which is unproven and may never lead to marketable products; Alnylam's ability to attract and retain highly qualified employees; obtaining, maintaining and protecting intellectual property utilized by Alnylam's products; Alnylam's ability to enforce its patents against infringers and to defend its patent portfolio against challenges from third parties; Alnylam's ability to obtain additional funding to support its business activities; Alnylam's dependence on third parties for development, manufacture, marketing, sales and distribution of products; the successful development of Alnylam's product candidates, all of which are in early stages of development; obtaining regulatory approval for products; competition from others using technology similar to Alnylam's and others developing products for similar uses; Alnylam's dependence on collaborators; and Alnylam's short operating history; as well as those risks more fully discussed in the "Risk Factors" section of its most recent quarterly report on Form 10-Q on file with the Securities and Exchange Commission. In addition, any forward-looking statements represent Alnylam's views only as of today and should not be relied upon as representing its views as of any subsequent date. Alnylam does not assume any obligation to update any forward-looking statements.

Isis Forward Looking Statements

This press release includes forward-looking statements regarding the future therapeutic and commercial potential of Isis' technologies and intellectual property related to microRNA therapeutics being discovered and developed by Regulus. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' goals. 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, and in the endeavor of building a business around such products. Isis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2006, and its quarterly report on Form 10-Q for the quarter ended June 30, 2007, which are on file with the SEC. Copies of this and other documents are available from the Company.

EXHIBIT A

INITIAL APPROVED OPERATING PLAN
[***]

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: November 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: November 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 September 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: November 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.