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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended March 31, 2009

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 has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes o No o

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See definition of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer x	Accelerated filer o
Non-accelerated filer o (Do not check if a smaller reporting company)	Smaller reporting company o

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

The number of shares of voting common stock outstanding as of May 4, 2009 was 98,130,347.

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ISIS PHARMACEUTICALS, INC.
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TRADEMARKS

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

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

	March 31, 2009 (Unaudited)	December 31, 2008 (1)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 254,057	$ 217,918
Short-term investments	398,179	273,080
Contracts receivable	2,351	4,121
Inventories	2,591	2,718
Other current assets	6,514	5,085
Assets from discontinued operations (including cash and cash equivalents of $6.1 million as of December 31, 2008)	—	15,462
Total current assets	663,692	518,384

Property, plant and equipment, net	24,183	17,371
Licenses, net	16,276	16,861
Patents, net	16,616	16,260
Deposits and other assets	3,739	3,900
Total assets	$ 724,506	$ 572,776
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 7,445	$ 5,710
Accrued compensation	3,181	6,835
Income taxes payable	29,627	—
Accrued liabilities	7,750	9,557
Current portion of long-term obligations	2,876	2,065
Current portion of deferred contract revenue	85,581	92,662
Liabilities from discontinued operations	—	7,870
Total current liabilities	136,460	124,699
2 5/8% convertible subordinated notes	119,713	117,993
Long-term obligations, less current portion	11,370	9,938
Long-term deferred contract revenue	154,293	172,766
Total liabilities	421,836	425,396
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 97,965,475 and 97,172,380 shares issued and outstanding at March 31, 2009 and December 31, 2008, respectively	98	97
Additional paid-in capital	967,648	960,361
Accumulated other comprehensive income	473	982
Accumulated deficit	(679,373)	(851,216)
Total Isis Pharmaceuticals, Inc. stockholders' equity	288,846	110,224
Noncontrolling interest in Regulus Therapeutics Inc.	13,824	4,737
Noncontrolling interest in Ibis Biosciences, Inc. — discontinued operations	—	32,419
Total stockholders' equity	302,670	147,380
Total liabilities and stockholders' equity	$ 724,506	$ 572,776

(1) The Condensed Consolidated Balance Sheet at December 31, 2008 has been derived from the audited financial statements as adjusted for the required retroactive adoption of FSP 14-1 and SFAS 160.

See accompanying notes

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

	Three Months Ended March 31,	
	2009	2008 (1)
Revenue:		
Research and development revenue under collaborative agreements	$ 29,685	$ 17,707
Licensing and royalty revenue	1,891	668
Total revenue	31,576	18,375
Expenses:		
Research and development	28,541	21,785
General and administrative	3,677	2,831
Total operating expenses	32,218	24,616
Loss from operations	(642)	(6,241)
Other income (expense):		
Investment income	2,192	3,035
Interest expense	(3,081)	(2,899)
Loss from continuing operations, before income tax benefit	(1,531)	(6,105)
Income tax benefit	717	—
Net loss from continuing operations, net of income tax benefit	(814)	(6,105)
Discontinued operations:		

Loss from discontinued operations	(29)	(564)
Gain on sale of Ibis Biosciences, Inc., net of tax	171,773	—
Net income (loss) from discontinued operations, net of tax	171,744	(564)
Net income (loss)	170,930	(6,669)
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	913	883
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ 171,843	$ (5,786)
Basic net income (loss) per share:		
Net income (loss) from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ —	$ (0.06)
Net income (loss) from discontinued operations	1.76	—
Basic net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ 1.76	$ (0.06)
Shares used in computing basic net income (loss) per share	97,521	90,799
Diluted net income (loss) per share:		
Net income (loss) from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ 0.03	$ (0.06)
Net income (loss) from discontinued operations	1.54	—
Diluted net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ 1.57	$ (0.06)
Shares used in computing diluted net income (loss) per share	111,274	90,799

(1) Adjusted for the required retroactive adoption of FSP 14-1 and SFAS 160.

See accompanying notes.

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

	Three Months Ended March 31,	
	2009	2008
Net cash (used in) provided by operating activities	$ (34,346)	$ 75,114
Investing activities:		
Purchases of short-term investments	(224,186)	(73,921)
Proceeds from the sale of short-term investments	98,973	62,635
Purchases of property, plant and equipment	(3,141)	(1,373)
Acquisition of licenses and other assets	(210)	(84)
Purchases of strategic investments	(349)	—
Net cash used in investing activities	(128,913)	(12,743)
Financing activities:		
Net proceeds from issuance of equity	6,143	2,727
Proceeds from equipment financing arrangement	2,705	—
Principal payments on debt and capital lease obligations	(517)	(1,738)
Proceeds from stock purchase by Genzyme Corporation, net of fees	—	49,962
Proceeds from sale of Ibis Biosciences, Inc. to Abbott Molecular Inc.	175,000	20,000
Proceeds from Alnylam's capital contribution to Regulus Therapeutics Inc.	10,000	—
Net cash provided by financing activities	193,331	70,951
Net increase in cash and cash equivalents	30,072	133,322
Cash and cash equivalents at beginning of period	223,985	138,614
Cash and cash equivalents at end of period	$ 254,057	$ 271,936
Supplemental disclosures of cash flow information:		
Interest paid	$ 2,250	$ 2,244
Income taxes paid	$ 350	$ —
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 5,016	$ 1,372

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
March 31, 2009
(Unaudited)

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three month periods ended March 31, 2009 and 2008 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2008. The financial statements include all normal recurring adjustments, which we consider necessary for a fair presentation of the financial position at such dates and the operating results and cash flows for those periods. The condensed consolidated financial statements have been adjusted for the required retroactive adoption of Staff Position No. APB 14-1, *Accounting for Convertible Debt Instruments That May be Settled in Cash upon Conversion (Including Partial Cash Settlement)*, ("FSP 14-1") and Statement of Financial Accounting Standards ("SFAS") 160, *Noncontrolling Interests in Consolidated Financial Statements, an amendment to ARB No. 51*. See Note 5, *Long-Term Obligations* for additional information about FSP 14-1. 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, 2008 included in our 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. ("we", "us" or "our"), our wholly owned subsidiaries, Isis USA Ltd. and Symphony GenIsis, Inc. In addition to our wholly owned subsidiaries, our condensed consolidated financial statements include one variable interest entity, Regulus Therapeutics Inc., for which we are 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*. As a result of completing the sale of Ibis Biosciences, Inc. to Abbott Molecular Inc., or AMI, in January 2009, we have presented Ibis' financial position and results of operations separately as discontinued operations in our condensed consolidated financial statements in accordance with SFAS 144, *Accounting for the Impairment or Disposal of Long-Lived Assets.* We have reclassified amounts in the prior period financial statements to conform to the current period presentation. Prior to the sale of Ibis, we identified Ibis as a variable interest entity that we consolidated. All significant intercompany balances and transactions have been eliminated.

2. Significant Accounting Policies

Revenue recognition

We follow 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*."

We generally recognize revenue when we have satisfied all contractual obligations and 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 received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on the consolidated balance sheet.

Research and development revenue under collaborative agreements

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. The revenue we recognize could be materially different if different estimates prevail. To date, we have not had to make material adjustments to our estimates. We have made estimates of our continuing obligations on several agreements. Our collaborative agreements typically include a research and/or development project plan that includes the activities the agreement requires each party to perform during 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, according to the underlying agreements. We generally recognize revenue related to milestone payments upon completion of the milestone's substantive performance requirement, as long as we are reasonably assured of collecting the resulting receivable and we have no future performance obligations related to the achievement of the milestone.

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 we had met the provisions in SAB 104 before we recognized the related revenue.

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 fair 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.

As part of our Genzyme strategic alliance, in February 2008 Genzyme Corporation made a $150 million equity investment in us by purchasing 5 million shares of our common stock at $30 per share. The price Genzyme paid for our common stock represented a significant premium over the fair value of our stock. Using a Black-Scholes option valuation model, we determined that the value of the premium was $100 million, which represents value Genzyme gave to us to help fund the companies' research collaboration, which began in January 2008. We accounted for this premium as deferred revenue and are

amortizing it along with the $175 million licensing fee that we received in June 2008 ratably into revenue until June 2012, which represents the end of our performance obligation based on the research and development plan included in the agreement.

Licensing and royalty 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 significant performance obligations and are reasonably assured of collecting the resulting receivable.

Short-term investments

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 except Regulus, our majority owned subsidiary, which we consolidate with our financial results. In determining if and when a decrease in market value below our cost in our equity positions is temporary or 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. We record unrealized gains and losses related to temporary declines in the publicly-held companies as a separate component of stockholders' equity and account for securities in the privately-held companies under the cost method of accounting according to Accounting Principles Board ("APB") 18, *The Equity Method of Accounting for Investments in Common Stock*. 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. We determined that there were no other-than-temporary declines in value of our investments during the three months ended March 31, 2009 and 2008.

Inventory valuation

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. We can use each of our raw materials in multiple products and, as a result, each raw material has future economic value independent of the development status of any single drug. For example, if one of our drugs failed, we could use the raw materials allocated for that drug to manufacture our other drugs. We expense these costs when we deliver the drugs to our partners, or as we provide these drugs for our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf life of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. We did not record any inventory write-offs during the first three months of 2009 and 2008. Total inventory, which consisted of raw materials, was $2.6 million and $2.7 million as of March 31, 2009 and December 31, 2008, respectively.

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Patents

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents. We review our capitalized patent costs regularly to ensure that they include costs for patent applications that have future value. We evaluate costs related to patents that we are not actively pursuing and write off any of these costs, if appropriate. We amortize patent costs over their estimated useful lives of ten years, beginning with the date the United States Patent and Trademark Office issues the patent. For the first quarter of 2009 and 2008, we recorded a non-cash charge of $186,000 and $96,000, respectively, which we included in research and development expenses, related to the assignment of patents to certain of our partners and the write-down of our patent costs to their estimated net realizable values.

Long-lived assets

We assess the value of our long-lived assets, which include property, plant and equipment, patent costs, and licenses acquired from third parties, under the provisions set forth by SFAS 144 and we evaluate our long-lived assets for impairment on at least a quarterly basis.

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, our estimates have been accurate as we have not experienced any material differences between our estimates and our actual results.

Basic and diluted net income (loss) per share

We follow the provisions of SFAS 128, *Earnings per Share*. We compute basic net income (loss) per share by dividing the net income (loss) by the weighted-average number of common shares outstanding during the period. Diluted net income (loss) per share reflects the potential dilution that could occur from the following items:

- $2^5/_8$% convertible subordinated notes;
- GSK convertible promissory note;
- Dilutive stock options; and
- Warrants issued to Symphony GenIsis Holdings LLC

Computations for basic and diluted net income (loss) per share are as follows: (in thousands, except per share amounts)

	Numerator: Net Income (Loss)	Denominator: Shares	Amount
For the three months ended March 31, 2009			

Basic net income per share:			
Net income from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ 99		
Net income from discontinued operations, net of taxes	171,744		
Total basic net income	$ 171,843	97,521	$ 1.76
Diluted net income per share:			
Dilutive stock options	—	2,286	
2⅝% convertible subordinated notes, net of tax	2,379	11,111	
GSK convertible promissory note, net of tax	12	185	
Warrants issued to Symphony GenIsis Holdings LLC	—	171	
Net income from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders plus assumed conversions	2,490		
Net income from discontinued operations, net of taxes	171,744		
Total diluted net income	$ 174,234	111,274	$ 1.57

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Potentially dilutive securities not included above since they are anti-dilutive:		
Anti-dilutive stock options	4,159	

As we incurred a loss for the three months ended March 31, 2008, we did not include diluted common equivalent shares in the computation of diluted net loss per share because the effect would be anti-dilutive.

	Numerator: Net Income (Loss)	Denominator: Shares	Amount
For the three months ended March 31, 2008			
Basic and diluted net loss per share:			
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (5,222)		
Net loss from discontinued operations	(564)		
Total basic and diluted net loss	$ (5,786)	90,799	$ (0.06)

Consolidation of variable interest entities

We have implemented the provisions of FIN 46R, which addresses consolidation by business enterprises of variable interest entities either: (1) that do not have sufficient equity investment at risk to permit the entity to finance its activities without additional subordinated financial support, or (2) in which the equity investors lack an essential characteristic of a controlling financial interest. As of March 31, 2009, we had collaborative arrangements with eight entities that we consider to be variable interest entities under FIN 46R. For the three months ended March 31, 2009, our condensed consolidated financial statements include one variable interest entity, Regulus, for which we were the primary beneficiary. For the three months ended March 31, 2008, our condensed consolidated financial statements include two variable interest entities, Ibis and Regulus, for which we were the primary beneficiary. Prior to completing the sale of Ibis to AMI in January 2009, we identified Ibis as a variable interest entity that we consolidated.

Noncontrolling Interests

On January 1, 2009, we adopted SFAS 160. This statement recharacterizes the accounting and reporting for minority interests as noncontrolling interests and classifies them as a component of stockholders' equity. Although the adoption of SFAS 160 did not impact our results of operations and financial position, SFAS 160 required us to reclassify noncontrolling interests as stockholders' equity, include the net loss attributable to noncontrolling interests as part of our consolidated net income (loss) and provide additional disclosures as part of our financial statements. As required by SFAS 160, we implemented the presentation and disclosure requirements of this new standard retrospectively to all periods presented.

The following table presents the statement of changes in stockholders' equity in conformity with the requirements of SFAS 160 for the quarter ended March 31, 2009 (in thousands):

	Isis Pharmaceuticals, Inc. Stockholders' Equity					Noncontrolling Interests		
	Common stock		Additional paid in capital	Accumulated other comprehensive income	Accumulated deficit	Ibis	Regulus	Total stockholders' equity
Description	Shares	Amount						
Balance at December 31, 2008	97,172	$ 97	$ 960,361	$ 982	$ (851,216)	$ 32,419	$ 4,737	$ 147,380
Comprehensive income:								
Net income (loss)	—	—	—	—	171,843	—	(913)	170,930
Change in unrealized losses	—	—	—	(509)	—	—	—	(509)
Comprehensive income	—	—	—	—	—	—	—	170,421
Options exercised and employee stock purchase plan issuances	793	1	6,142	—	—	—	—	6,143
Share-based compensation expense	—	—	1,145	—	—	—	—	1,145
Sale of Ibis to AMI	—	—	—	—	—	(32,419)	—	(32,419)
Alnylam's capital contribution to noncontrolling interest	—	—	—	—	—	—	10,000	10,000
Balance at March 31, 2009	97,965	$ 98	$ 967,648	$ 473	$ (679,373)	$ —	$ 13,824	$ 302,670

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The following table presents the statement of changes in stockholders' equity in conformity with the requirements of SFAS 160 for the quarter ended March 31, 2008 (in thousands):

Description	Isis Pharmaceuticals, Inc. Stockholders' Equity					Noncontrolling Interests		
	Common stock		Additional paid in capital	Accumulated other comprehensive income	Accumulated deficit	Ibis	Regulus	Total stockholders' equity
	Shares	Amount						
Balance at December 31, 2007	87,239	$ 87	$ 882,633	$ 538	$ (833,044)	$ —	$ 9,371	$ 59,585
Comprehensive loss:								
Net loss	—	—	—	—	(5,786)	(105)	(883)	(6,774)
Change in unrealized gains	—	—	—	1,585	—	—	—	1,585
Comprehensive loss	—	—	—	—	—	—	—	(5,189)
Options exercised and employee stock purchase plan issuances	349	—	2,727	—	—	—	—	2,727
Warrants exercised	407	1	—	—	—	—	—	1
Share-based compensation expense	—	—	3,759	—	—	—	—	3,759
Issuance of common stock to Genzyme	5,000	5	49,956	—	—	—	—	49,961
AMI's capital contribution to noncontrolling interest	—	—	—	—	—	14,471	—	14,471
Balance at March 31, 2008	92,995	$ 93	$ 939,075	$ 2,123	$ (838,830)	$ 14,366	$ 8,488	$ 125,315

Convertible debt

On January 1, 2009, we adopted FSP 14-1. This standard requires us to account for convertible debt instruments that may be settled in cash upon conversion (including partial cash settlement) by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate when we recognize interest cost in subsequent periods. Using the provisions of FSP 14-1, we assigned a value to the debt component of our 2 5/8% convertible notes equal to the estimated fair value of a similar debt instrument without the conversion feature, which resulted in us recording the debt at a discount. We are amortizing the resulting debt discount over the life of the debt as additional non-cash interest expense. As required by FSP 14-1, we implemented this standard retrospectively to all periods presented. For additional information about FSP 14-1, see Note 5, *Long-Term Obligations*.

Stock-based compensation expense

We account for our stock-based compensation expense related to employee stock options and employee stock purchases under SFAS 123R, *Share-Based Payment*. We estimate 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. We estimated the expected term of options granted based on historical exercise patterns.

For the quarter ended March 31, 2009 and 2008, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Three Months Ended March 31,	
	2009	2008
Risk-free interest rate	1.8%	3.1%
Dividend yield	0.0%	0.0%
Volatility	57.0%	55.0%
Expected Life	4.9 years	4.6 years

ESPP:

	Three Months Ended March 31,	
	2009	2008
Risk-free interest rate	0.3%	3.3%
Dividend yield	0.0%	0.0%
Volatility	70.4%	56.7%
Expected Life	6 months	6 months

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We record stock options granted to non-employees, which consist primarily of options granted to Regulus' Scientific Advisory Board, at their fair value in accordance with the requirements of SFAS 123R, 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 the expense over the service period.

Stock-based compensation expense for the three months ended March 31, 2009 and 2008 (in thousands, except per share data) was allocated as follows:

	Three Months Ended March 31,	
	2009	2008
Research and development	$ 2,260	$ 2,716
General and administrative	443	567
Non-cash compensation expense related to stock options included in continuing operations	2,703	3,283
Non-cash compensation expense (benefit) related to stock options included in discontinued operations	(1,558)	476
Total	$ 1,145	$ 3,759
Basic stock-based compensation expense, per share:		
Net loss per share included in continuing operations	$ (0.03)	$ (0.04)

Net income per share included in discontinued operations	0.02	—
Total	$ (0.01)	$ (0.04)
Diluted stock-based compensation expense, per share:		
Net loss per share included in continuing operations	$ (0.02)	$ (0.04)
Net income per share included in discontinued operations	0.01	—
Total	$ (0.01)	$ (0.04)

As part of our Regulus joint venture, both we and Alnylam Pharmaceuticals, Inc. issued our own company's stock options to members of Regulus' Board of Directors and Scientific Advisory Board. In addition, we and Alnylam issued our own company's stock options to those employees of each company who were seconded to Regulus under the three companies' limited liability agreement. These employees became Regulus employees in January 2009 as part of Regulus' conversion to a C-Corporation. As part of the conversion, both we and Alnylam modified our own company's stock options issued to Regulus' employees, members of Regulus' Board of Directors and Scientific Advisory Board to stop vesting in these stock awards before the awards were fully vested. Additionally, in February 2009, Regulus issued options to purchase its own common stock to Regulus' employees, members of Regulus' Board of Directors and members of Regulus' Scientific Advisory Board. Consistent with our accounting policies discussed above, Regulus accounts for these options using SFAS 123R for employees and members of Regulus' Board of Directors and EITF 96-18 for members of Regulus' Scientific Advisory Board. Regulus records the expenses associated with these options on its books.

As of March 31, 2009, total unrecognized compensation cost related to non-vested stock-based compensation plans was $18.5 million. We will adjust total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize this cost over a weighted average period of 1.5 years.

Impact of recently issued accounting standards

On April 9, 2009, the Financial Accounting Standards Board ("FASB") issued three FSPs intended to provide additional application guidance and enhanced disclosures regarding fair value measurements and other-than-temporary impairments of securities.

- FSP FAS 157-4, *Determining Fair Value When the Volume and Level of Activity for the Asset or Liability Have Significantly Decreased and Identifying Transactions That Are Not Orderly,* provides guidelines for making fair value measurements more consistent with the principles presented in SFAS 157, *Fair Value Measurements.* FSP FAS 157-4 must be applied prospectively.

- FSP FAS 115-2 and FAS 124-2, *Recognition and Presentation of Other-Than-Temporary Impairments,* provides additional guidance designed to create greater clarity and consistency in accounting for and presenting impairment losses on debt securities. FSP FAS 115-2 and FAS 124-2 must be applied retrospectively.

- FSP FAS 107-1 and APB 28-1, *Interim Disclosures about Fair Value of Financial Instruments,* enhances consistency in financial reporting by increasing the frequency of fair value disclosures. FSP FAS 107-1 and APB 28-1 must be applied prospectively.

These FSPs are effective for interim and annual periods ending after June 15, 2009, which will be effective for our quarter ending June 30, 2009. We are currently evaluating what the impact of adopting these FSPs will have on our condensed consolidated financial statements.

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3. Discontinued Operations

In 2008, AMI purchased approximately 18.6% of the issued and outstanding common stock of Ibis for a total purchase price of $40 million. In December 2008, we, Ibis and AMI executed a stock purchase agreement (the "Stock Purchase Agreement"). Under the Stock Purchase Agreement, AMI purchased the remaining equity in Ibis from us for $175 million. We, Ibis and AMI completed the acquisition on January 6, 2009.

We reflect Ibis as a discontinued operation because Ibis meets the criteria for a component of an entity under SFAS 144. Accordingly, we have presented the operating results of Ibis in our Condensed Consolidated Statements of Operations as discontinued operations and we have reclassified all prior periods. Net income from discontinued operations in the first quarter of 2009 primarily consists of the $202.5 million gain related to the sale of Ibis to AMI less $30.7 million of income tax expense. The components of discontinued operations for the periods presented are as follows (in thousands):

	Quarter Ended March 31,	
	2009	2008
Revenue	$ —	$ 2,979
Total operating expenses	35	5,569
Loss from operations	(35)	(2,590)
Other income, net	—	1,921
Loss attributed to noncontrolling interest in Ibis Biosciences, Inc.	6	105
Loss from discontinued operations	(29)	(564)
Gain on sale of Ibis Biosciences, Inc., net of tax	171,773	—
Net income (loss) from discontinued operations, net of tax	$ 171,744	$ (564)

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At December 31, 2008, we had the following assets and liabilities as assets and liabilities from discontinued operations in our accompanying Condensed Consolidated Balance Sheets (in thousands):

Cash and cash equivalents	$	6,067
Contracts receivable		818
Inventories		1,422
Property, plant and equipment, net		2,792
Patents, net		2,001
Other assets		2,362
Assets from discontinued operations	$	15,462
Accounts payable		2,632
Accrued compensation		371
Accrued liabilities		1,982
Notes payable		585
Deferred contract revenue		2,300
Liabilities from discontinued operations	$	7,870
Noncontrolling interest in Ibis Biosciences, Inc. — discontinued operations	$	32,419

As permitted by SFAS 95, *Statement of Cash Flows*, we have not separately classified cash flows from discontinued operations in our Condensed Consolidated Statement of Cash Flows.

4. Fair Value Measurements

In September 2006, the FASB issued SFAS 157, *Fair Value Measurements*. SFAS 157 defines fair value, establishes a framework for measuring fair value in accordance with accounting principles generally accepted in the United States, and expands disclosures about fair value measurements. We adopted the provisions of SFAS 157 on January 1, 2008. Although the adoption of SFAS 157 did not impact our financial condition, results of operations, or cash flow, SFAS 157 requires us to provide additional disclosures as part of our financial statements.

SFAS 157 establishes a three-tier fair value hierarchy, which prioritizes the inputs used in measuring fair value. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets, which includes our money market funds and treasury securities classified as available-for-sale securities and equity securities in publicly-held biotechnology companies; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring an entity to develop its own assumptions.

We measure our assets and liabilities that SFAS 157 requires us to measure at fair value on a recurring basis using the following inputs in accordance with SFAS 157 at March 31, 2009 (in thousands):

	Total	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents and short-term investments (1)	$ 622,735	$ 314,332	$ 308,403	$ —
Equity securities (2)	1,816	1,816	—	—
Total	$ 624,551	$ 316,148	$ 308,403	$ —

(1) Included in cash and cash equivalents and short-term investments on our Condensed Consolidated Balance Sheet.

(2) Included in other current assets on our Condensed Consolidated Balance Sheet.

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5. Long-Term Obligations

Convertible Subordinated Notes

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. We included the issuance costs in our balance sheet and are amortizing these costs to interest expense over the life of the debt. The $162.5 million convertible subordinated notes mature in 2027 and bear interest at 2⅝%, which is payable semi-annually. The 2⅝% notes are convertible, at the option of the note holders, into approximately 11.1 million shares of our common stock at a conversion price of $14.63 per share. At December 31, 2008, the principal and accrued interest outstanding on the notes was $162.5 million and $1.6 million, respectively. In the first quarter of 2009, we included 11.1 million shares of our common stock in the computation of diluted net loss per share for the conversion of the 2⅝% Notes. We did not include any shares in the first quarter of 2008 because the effect would have been anti-dilutive.

We will be able to redeem the 2⅝% notes at a redemption price equal to 100.75% of the principal amount between February 15, 2012 and February 14, 2013; 100.375% of the principal amount between February 15, 2013 and February 14, 2014; and 100% of the principal amount thereafter. Holders of the 2⅝% notes also are able to require us to repurchase these notes on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100% of the principal amount of the 2⅝% notes being repurchased plus accrued and unpaid interest.

In 2009, we began accounting for the 2⅝% Notes using the guidance contained in FSP 14-1. This standard requires us to assign a value to our convertible debt equal to the estimated fair value of a similar debt instrument without the conversion feature, which results in us recording our convertible debt at a discount. FSP 14-1 then requires us to amortize the resulting debt discount over the expected life of the debt as additional non-cash interest expense. FSP 14-1 requires retrospective application to all periods presented. Using a combination of the present value of the debt's cash flows and a Black-Scholes valuation model, we determined that our nonconvertible debt borrowing rate for the notes was 9.3%. As a result, we retrospectively adjusted the carrying

value of the notes. Below is a table summarizing the changes to our balance sheet as of December 31, 2008 as a result of adopting this new accounting standard (in thousands):

	As Originally Reported	As Adjusted	Effect of Change
Debt issuance costs (included in deposits and other assets)	$ 3,943	$ 2,569	$ (1,374)
2⅝% convertible subordinated notes	$ 162,500	$ 117,993	$ (44,507)
Additional paid-in capital	$ 905,721	$ 960,361	$ 54,640
Accumulated deficit	$ (839,708)	$ (851,216)	$ (11,508)

Additionally, we adjusted interest expense for the first quarter of 2008 to reflect our nonconvertible debt borrowing rate as follows (in thousands):

	As Originally Reported	As Adjusted	Effect of Change	Effect of Change per share (Basic and Diluted)
Interest expense:				
First quarter 2008	$ 1,398	$ 2,899	$ 1,501	$ 0.02

As a result of adopting FSP 14-1, interest expense for the first quarter 2009 includes $1.7 million, or $0.02 and $0.01 for basic and diluted per share, respectively, of non-cash interest expense related to the amortization of the debt discount.

Equipment Financing Arrangement

In October 2008, we entered into a loan agreement related to an equipment financing. Under the loan agreement, we may borrow up to approximately $10 million in principal to finance the purchase of equipment. The $10 million includes the $600,000 Ibis borrowed in October 2008 that was fully repaid in the first quarter of 2009. Each loan under the loan agreement will have a term of approximately three years, with principal and interest payable monthly. We calculate interest on amounts we borrow under the loan agreement based upon the three year interest rate swap at the time we make each draw down plus 4%. We are using the equipment purchased under the loan agreement as collateral. In October 2008, we drew down $6.6 million in principal under the loan agreement at an interest rate of 7.22%. In March 2009, we drew down an additional $2.7 million in principal under this loan agreement at an interest rate of 6.28%. We have now drawn down the full amount available under the loan. The carrying balance under this loan agreement at March 31, 2009 and December 31, 2008 was $8.7 million and $6.5 million, respectively.

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6. Income Taxes

Primarily as a result of the significant upfront funding that we received from our strategic alliance with Genzyme in 2008 and the gain we recognized on the sale of Ibis to AMI earlier this year, we will have a substantial amount of taxable income in 2009. To reduce our tax liability, we will offset a portion of the taxable income with our projected 2009 loss from continuing operations. We will also use some of our net operating loss carryforwards (NOL's) to reduce our federal income taxes in 2009. The tax law changes that were enacted with the 2008/2009 California Budget have suspended our ability to use NOL's to offset our California tax expense for 2009. However, we will offset our California income tax liability to the full extent allowed under the tax regulations with our research and development tax credit carryforwards, which California tax regulations limit to 50% of our California liability. After using all of our allowable losses and tax credits to reduce our tax liability, we estimate that our annual tax expense will be approximately $20 to 25 million for the entire year of 2009.

SFAS 109, *Income Taxes*, requires us to allocate our 2009 tax expense between discontinued operations and continuing operations in our Consolidated Statement of Operations. Since the sale of Ibis to AMI was a discrete event that occurred in the first quarter of 2009, SFAS 109 requires us to record the total amount of our estimated income tax expense for discontinued operations in the first quarter of this year. Further, the allocation rules of SFAS 109 require us to gross up this amount by the projected annual tax benefit we expect to record as part of our loss from continuing operations in 2009, which we describe below. This means that in addition to the tax expense for the gain on the sale of Ibis, discontinued operations also includes the tax expense for other timing differences, which principally consists of the timing difference associated with the upfront funding we received from Genzyme. Accordingly, we have recorded tax expense of $30.7 million in discontinued operations in the first quarter of 2009.

SFAS 109 requires us to include an income tax benefit in continuing operations because we will be using the tax benefits generated from our current year loss from continuing operations to offset a portion of our taxable income. We calculated this benefit by applying our estimated effective tax rate to our loss from continuing operations for the quarter. As a result, in the first quarter of 2009, we recorded an income tax benefit of $717,000.

At March 31, 2009, our balance sheet includes an income tax payable of $29.6 million. For each quarter in which we incur a loss from continuing operations during the rest of this year, we will record an income tax benefit using the calculation above. The income tax benefit we record each quarter will reduce our overall tax expense and income tax payable until we reach our estimated annual amount of $20 to 25 million at the end of 2009.

Pursuant to Internal Revenue Code Sections 382 and 383, annual usage of our NOL's and credit carryforwards to offset future taxable income may be limited due to changes in ownership of more than 50%. We recently completed a Section 382 analysis and determined that we have not experienced a change in ownership that limits our ability to use our NOL's and credit carryforwards that we had accumulated through December 31, 2008. At December 31, 2008, we had federal, California and foreign tax net operating loss carryforwards of approximately $591.1 million, $180.6 million and $1.1 million, respectively. The Federal and California tax loss carryforwards will continue to expire in 2010 and 2013, respectively, unless previously utilized. We also had federal and California research and development tax credit carryforwards of approximately $31.3 million and $22.2 million, respectively. The Federal research and development tax credit carryforwards began expiring in 2004 and will continue to expire unless utilized. The California research and development tax credit carryforwards are available indefinitely. The difference between the tax loss carryforwards for federal and California purposes is attributable to the capitalization of research and development expenses for California tax purposes and a required 50% to 60% limitation on the utilization of prior years' California loss carryforwards. The foreign tax losses may be carried forward indefinitely and used to offset future taxable profits, provided there is no substantial change in ownership.

7. Collaborative Arrangements and Licensing Agreements

The information discussed below represents material changes to partnerships entered into prior to 2009. There are no other material changes from the information provided in Note 7—Collaborative Arrangements and Licensing Agreements of the Consolidated Financial Statements section, included in our Annual Report on Form 10-K for the year ended December 31, 2008.

Regulus Collaboration

In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development, and commercialization of microRNA-based therapeutics. We and Alnylam each granted Regulus exclusive rights to our respective intellectual property for microRNA therapeutic applications, including a portfolio of over 900 patents and patent applications (including over 600 issued patents) owned by us and Alnylam pertaining to chemical modifications as well as certain early fundamental patents in the microRNA field, including the "Tuschl III", "Sarnow" and "Esau" patent series. Alnylam made an initial investment of $10 million in Regulus to balance venture ownership. Thereafter, we and Alnylam share funding of Regulus. We own 51% of Regulus and Alnylam owns the remaining 49%. Regulus operates as an independent company with a separate board of directors, scientific advisory board and management team. We and Alnylam 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.

We and Alnylam provide Regulus research and development and general and administrative services under the terms of a services agreement.

In January 2009, Regulus completed a legal reorganization from an LLC to a C-Corporation. In March 2009, Regulus raised $20 million in a Series A preferred equity financing. We and Alnylam were the sole and equal investors in the financing. Since we are consolidating the financial results of Regulus, our cash and cash equivalents balance only increased by the $10 million Alnylam contributed.

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8. Segment Information and Concentration of Business Risk

Segment information

Prior to AMI's acquisition of our Ibis business, we reported our financial results in three segments. We currently report our financial results in two reportable segments, Drug Discovery and Development and Regulus. Segment loss from operations includes revenue less research and development expenses and general and administrative expenses attributable to each segment. See the Business Segments discussion within the "Management's Discussion and Analysis of Financial Condition and Results of Operations" in Item 2 below for additional information on the segments.

Our Drug Discovery and Development segment generates revenue from collaborations with corporate partners and from licensing proprietary patent rights. Revenue from collaborations with corporate partners may consist of upfront payments, funding for research and development activities, milestone payments and royalties or profit sharing payments. This segment's proprietary technology to discover and characterize novel antisense inhibitors has enabled our scientists to modify the properties of our antisense drugs for optimal use with particular targets and thus, to produce a broad proprietary portfolio of drugs applicable to many disease targets.

Our Regulus segment generates revenue from research grants and collaborations with corporate partners such as its strategic alliance with GSK.

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

Three Months Ended March 31, 2009	Drug Discovery and Development	Regulus	Total
Revenue:			
Research and development	$ 29,047	$ 638	$ 29,685
Licensing and royalty	1,891	—	1,891
Total segment revenue	$ 30,938	$ 638	$ 31,576
Income (loss) from operations	$ 1,223	$ (1,865)	$ (642)
Total assets as of March 31, 2009	$ 695,335	$ 29,171	$ 724,506

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Three Months Ended March 31, 2008	Drug Discovery and Development	Regulus	Total
Revenue:			
Research and development	$ 17,615	$ 92	$ 17,707
Licensing and royalty	668	—	668
Total segment revenue	$ 18,283	$ 92	$ 18,375
Loss from operations	$ (4,806)	$ (1,435)	$ (6,241)
Total assets as of December 31, 2008 (1)	$ 533,637	$ 23,677	$ 557,314

(1) Total assets do not include $15.5 million of assets from discontinued operations as of December 31, 2008.

Concentrations of business risk

We have historically funded our operations from collaborations with corporate partners and a relatively small number of partners have accounted for a significant percentage of our revenue. Revenue from significant partners, which is defined as 10% or more of our total revenue, was as follows:

	Three Months Ended March 31,	
	2009	2008
Partner A	53%	34%
Partner B	22%	44%
Partner C	8%	12%

Contract receivables from three significant partners comprised approximately 30%, 30% and 20% of contract receivables at March 31, 2009. Contract receivables from three significant partners comprised approximately 25%, 18% and 14% of contract receivables at December 31, 2008.

9. Subsequent Event

In April 2009, we and Alnylam formed a new collaboration focused on the development of single-stranded RNAi (ssRNAi) technology. As part of the collaboration, we have co-exclusively licensed our ssRNAi technology to Alnylam in exchange for upfront payments, research and development milestone payments, and royalties. The alliance provides Alnylam with access to our intellectual property and expertise regarding the development of ssRNAi antisense drugs, while both companies will have the opportunity to discover and develop drugs employing the new technology. In addition to the new collaboration, we and Alnylam also extended our broad cross-licensing arrangement regarding double-stranded RNAi that was established in 2004.

Under the terms of the licensing and collaboration agreement, Alnylam paid us an upfront license fee of $11 million and will potentially pay us up to $20 million in additional license fees payable in three tranches that include $10 million in 18 months or earlier if in vivo efficacy in rodents is demonstrated sooner, $5 million upon achievement of in vivo efficacy in non-human primates, and $5 million upon initiation of the first clinical trial with an ssRNAi drug. Alnylam will fund research activities at a minimum of $3 million each year for three years with research development activities conducted both at Isis and Alnylam. If Alnylam develops and commercializes drugs utilizing ssRNAi technology on its own or with a partner, we will receive milestones and royalties. Also, initially we are eligible to receive up to 50 percent of any sublicense payments due to Alnylam based on Alnylam partnering of ssRNAi products, which will decline over time as Alnylam's investment in the technology and drugs increases. In turn, Alnylam is eligible to receive up to 5 percent of any sublicense payments due to us based on our partnering of ssRNAi products. Both we and Alnylam are eligible to receive royalties from each other on any ssRNAi products developed by the other company.

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

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

Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, this Report includes forward-looking statements regarding our business, the therapeutic and commercial potential of our technologies and products in development, and the financial position of Isis Pharmaceuticals, Inc. and Regulus Therapeutics, our majority-owned subsidiary. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. 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. 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, 2008, which is on file with the U.S. Securities and Exchange Commission, and those identified within this Item entitled "Risk Factors" beginning on page 28 of this Report.

Overview

We are the leading company in antisense technology, exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Antisense technology is a direct route from genomics to drugs. Our highly efficient and prolific drug discovery platform enables us to expand our drug pipeline and our partners' pipelines with antisense drugs that address significant unmet medical needs. Our business strategy is to do what we do best—to discover unique antisense drugs and develop these drugs to key value inflection points. In this way, our organization remains small and focused. We discover new drugs, outlicense our drugs to partners and build a broad base of license fees, milestone payments and royalty income. We maximize the value of the drugs we discover by putting them in the hands of quality partners with late-stage development and commercialization expertise. For example, we partner our drugs with leading pharmaceutical companies with mature development, commercialization and marketing expertise, such as BMS, Genzyme, Lilly and OMJP. Additionally, we created a consortium of smaller companies that can broadly exploit the technology with their expertise in specific disease areas. We call these smaller companies our satellite companies. In addition to our cutting edge antisense programs, we maintain technology leadership beyond our core areas of focus through collaborations with Alnylam and Regulus, our jointly owned company focused on microRNA therapeutics. We also exploit our inventions with other therapeutic opportunities through collaborations with Achaogen and Archemix. Beyond human therapeutics, we benefit from the commercialization of products of our inventions by other companies that are better positioned to maximize the commercial potential of these inventions, such as our Ibis Biosciences subsidiary, which we sold to AMI in the first quarter of 2009. All of these aspects fit into our unique business model and create continued shareholder value.

We protect our proprietary RNA-based technologies and products through our substantial patent estate. We remain one of the most prolific patent holders in the United States, ranked as having one of the highest ratios of issued patents per employee with more than 1,600 issued patents. With our ongoing research and development, our patent portfolio continues to grow. The patents not only protect our key assets—our technology and our drugs—they also form

the basis for attractive licensing and partnering arrangements. To date, we have generated more than $357 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

The clinical success of mipomersen, the lead drug in our cardiovascular franchise, is a clear example of the power of our RNA-based technology because it demonstrates that antisense drugs can work in man. With mipomersen we have additional evidence, as we have shown with other antisense drugs, that we can predict the activity of our drugs in man from the preclinical successes we observe in animals. We believe mipomersen's success has validated our technology platform, increased the value of our drugs, and created renewed interest from potential partners in antisense technology.

The clinical successes of the drugs in our pipeline continue to result in new partnering opportunities. Over the past two years, we have established a number of notable pharmaceutical partnerships, which include Genzyme, BMS and OMJP, to develop and commercialize certain of our key cardiovascular and diabetes drugs. Since 2007, we have also added more than $750 million in cash from our partnerships. If our current partnerships continue to be successful, we have the opportunity to earn additional milestone payments. We also will share in the future commercial success of our inventions and drugs resulting from these partnerships through earn out, profit sharing, and/or royalty arrangements. Our strong financial position is a result of the persistent execution of our business strategy and our inventive and focused research and development capabilities.

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Business Segments

Prior to AMI's acquisition of our Ibis Biosciences business, we focused on three segments. We currently focus our business on two principal segments:

Drug Discovery and Development Within our primary business segment, we are exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs for us and our partners. Our proprietary drug discovery platform enables us to rapidly identify drugs, providing a wealth of potential targets to treat a broad range of diseases. We focus our efforts in therapeutic areas where our drugs will work best, efficiently screening many targets in parallel and carefully selecting the best drugs. This efficiency combined with our rational approach to selecting disease targets enables us to build a large and diverse portfolio of drugs designed to treat a variety of health conditions including cardiovascular, metabolic, inflammatory, ocular and neurodegenerative diseases, and cancer. We currently have 19 drugs in development. Our partners are licensed to develop, with our support, 15 of these 19 drugs, which substantially reduces our development costs.

Regulus Therapeutics Inc. In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development and commercialization of microRNA therapeutics. Regulus is addressing therapeutic opportunities that arise from alterations in microRNA expression. Since microRNAs may act as master regulators, affecting the expression of multiple genes in a disease pathway, microRNA therapeutics define a new platform for drug discovery and development and microRNAs may also prove to be an attractive new diagnostic tool for disease characterization.

Ibis Biosciences, Inc. In January 2009, we sold our Ibis Biosciences subsidiary to AMI for a total purchase price of $215 million. In 2008, AMI invested $40 million in Ibis, which provided the capital for Ibis to make significant progress in expanding commercial product offerings and building the foundation for Ibis to enter regulated markets, such as clinical diagnostics. Early in 2009, AMI completed the acquisition of Ibis and we received an additional $175 million. We are also eligible to receive an earn out on future sales of Ibis products that will enable us and our shareholders to continue to benefit from Ibis' successes. The earn out payments from AMI are equal to a percentage of Ibis' revenue related to sales of Ibis systems, including instruments, assay kits and successor products, through the end of 2025. The earn out payments will be 5% of net sales over $140 million through net sales of $2.1 billion and 3% of net sales over $2.1 billion, with the percentages subject to reduction in certain circumstances.

As a result of selling Ibis to AMI, Ibis' financial results are considered discontinued operations. Accordingly, we have presented the operating results of Ibis for all prior periods in our financial statements separately as discontinued operations and therefore Ibis is no longer included in our segment reporting. Net income from discontinued operations in the first quarter of 2009 primarily consists of a $202.5 million gain related to the sale of Ibis to AMI less $30.7 million of income taxes.

Recent Events

Drug Development Highlights

Mipomersen, the most advanced drug in our cardiovascular pipeline, is being evaluated in a broad Phase 3 program in patients who cannot adequately control their cholesterol levels with current therapies and who need new treatment options.

- We and Genzyme initiated a Phase 3 study evaluating mipomersen in severe hypercholesterolemia patients. This latest mipomersen study is the fourth new clinical study initiated by us and Genzyme since the formation of the collaboration in early 2008.
- The regulatory strategy for European approval of mipomersen continues to evolve. Genzyme is planning an initial European submission for homozygous Familial Hypercholesterolemia, or FH, with timing expected to be similar to that of the United States homozygous FH submission anticipated in the second half of 2010. Data from the severe hypercholesterolemia trial should be available at the time of this submission and may be basis for a broader indication. A potential second filing in Europe for patients with heterozygous FH could take place as early as late 2012. Genzyme will await data from an outcomes study prior to making additional submissions to potentially expand mipomersen's indication.

Our internal and partnered pipeline continues to mature as drugs in the pipeline advance in clinical development.

- We initiated a Phase 1 clinical study of ISIS-SGLT2$_{Rx}$ for the treatment of type 2 diabetes, in healthy volunteers.
- Investigators participating in a Phase 1 study of iCo-007 presented data from an interim analysis of the study that showed iCo-007 appears to be well tolerated and demonstrates promising signs of activity in patients with diffuse diabetic macular edema.
- OncoGenex reached an agreement with the FDA on the design of a second Phase 3 registration trial of OGX-011 that features durable pain palliation as the primary endpoint in patients with castrate resistant prostate cancer, via the Special Protocol Assessment process.

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We broadened our pipeline with the addition of new drugs that our partners are developing including,

- A novel aminoglycoside drug, ACHN-490, which Achaogen is developing to treat bacterial infections.

We continue to expand our research and development activities including the evaluation of new and novel targets to treat diseases.

- We presented research at the American Association for Cancer Research (AACR) annual meeting demonstrating the potential of new RNA targets, including a class of non-coding RNAs, to treat cancer.
- We and our collaborators highlighted new antisense therapeutic programs and targets to treat cardiovascular disease and thrombosis at the Arteriosclerosis, Thrombosis and Vascular Biology (ATVB) annual conference, including data from a post-hoc analysis of a recently completed clinical study of mipomersen in which treatment with mipomersen resulted in a decrease in apoC-III.
- One of our scientist was awarded the 2008 Ebert Prize for published research that provided the first proof-of-concept for the oral administration of antisense drugs in man.

Corporate Highlights

We continue to execute our business strategy by monetizing key assets with partners to continue the development and commercialization of the assets with attractive terms in upfront payments, milestone payments and participation in the commercial success of each asset.

- We sold our Ibis subsidiary to AMI for a total purchase price of $215 million, plus an earn out on sales of assay kits and services.

We benefit financially as our partners advance drugs in development while also receiving upfront and royalty payments. This strategy provides us with cash while the drugs in our pipeline mature in clinical development.

- We received a $1 million milestone payment from Achaogen for the filing of an IND for Achaogen's aminoglycoside drug, ACHN-490.

We also benefit from our partnerships focused on developing and advancing certain RNA-based therapeutic technologies. These partnerships take advantage of our dominant intellectual property estate, expertise, and ongoing innovation and allow us to participate in newly emerging approaches to RNA-based therapeutics and augment our active programs in these areas.

- We received $1 million from Alnylam related to Alnylam's alliance with Cubist Pharmaceuticals, Inc.
- We also earned a milestone payment from Alnylam related to Alnylam's clinical development of ALN-VSP in patients with advanced liver cancers.
- We co-exclusively licensed our single-strand RNA interference (ssRNAi) technology to Alnylam as part of a new strategic initiative to continue to develop the ssRNAi platform.

Regulus Therapeutics, our and Alnylam's jointly owned company, continues to make significant progress in all areas of its business. We continue to support Regulus as it translates one of the most important new discoveries in biology into a novel approach for treating disease.

- Regulus raised $20 million in a Series A financing in which we and Alnylam were the sole and equal investors in the financing.

Critical Accounting Policies

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States of America. As such, we are required to make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. Each quarter, our senior management discusses the development, selection and disclosure of such estimates with our audit committee of our board of directors. There are specific risks associated with these critical accounting policies and we caution that future events rarely develop exactly as expected, and that best estimates routinely require adjustment.

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;

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- 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.

Except as set forth below, there have been no material changes to our critical accounting policies and estimates from the information provided in Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations", included in our Annual Report on Form 10-K for the year ended December 31, 2008.

Convertible debt

On January 1, 2009, we adopted FSP 14-1. This standard requires us to account for convertible debt instruments that may be settled in cash upon conversion (including partial cash settlement) by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate when we recognize interest cost in subsequent periods. Using the provisions of FSP 14-1, we assigned a value to the debt

component of our 2 5/8% convertible notes equal to the estimated fair value of a similar debt instrument without the conversion feature, which resulted in us recording the debt at a discount. We are amortizing the resulting debt discount over the life of the debt as additional non-cash interest expense. As required by FSP 14-1, we implemented this standard retrospectively to all periods presented. For additional information about FSP 14-1, see Note 5, *Long-Term Obligations*.

Determining the fair value of the debt component requires the use of accounting estimates and assumptions. These estimates and assumptions are judgmental in nature and could have a significant impact on the determination of the debt component and in effect, the associated non-cash interest expense. According to FSP 14-1, the carrying amount of the liability component is determined by measuring the fair value of a similar debt instrument that does not have the conversion feature. If no similar debt instrument exists, estimates of fair value are primarily determined using assumptions that market participants would use in pricing a debt instrument, including market interest rates, credit standing, yield curves and volatilities.

Results of Operations

Revenue

Total revenue for the three months ended March 31, 2009 was $31.6 million compared to $18.4 million for the same period in 2008. This increase in revenue is primarily due to an increase in revenue from our collaboration with Genzyme. As part of our strategic relationship with Genzyme, in the first quarter of 2008 Genzyme purchased $150 million of our common stock at $30 per share and in the second quarter paid us a license fee of $175 million. We are amortizing the premium on the stock, $100 million calculated using a Black-Scholes option valuation model, and the license fee ratably into revenue through June 2012, which represents the end of our performance obligation based on the research and development plan included in the agreement. Revenue from Genzyme was higher in 2009 because the first quarter of 2008 only included revenue from amortization of the stock premium. Also contributing to the increase was the revenue Regulus earned from its strategic alliance with GSK which began in April 2008. Although not a material factor in the quarter to quarter change in revenue, we also earned revenue from the research and development we performed for our partners and from ongoing licensing agreements. Our satellite companies also continued to contribute to our revenue from sublicensing fees, milestone payments and contract manufacturing. Although less predictable than the previously mentioned revenue sources, revenue from these sources contributes meaningfully to our total revenue. Beginning in the second quarter, we will recognize revenue related to our recent license agreement with Alnylam, which will consist of the amortization of the $11 million upfront fee and the research funding we will earn as part of the collaboration, as well as the milestone payment we earned when Alnylam initiated clinical trials on ALN-VSP.

Collaborations with Genzyme, OMJP, BMS and Regulus' strategic alliance with GSK include ongoing research and development activities. Therefore, we will continue to recognize significant amounts of revenue from these collaborations in the future from the amortization of the upfront fees we received and from research and development funding.

Period to period fluctuations in our revenue are common because the nature and timing of payments under agreements with our partners, including license fees and milestone payments, significantly affects our revenue. For example, in the first quarter of 2009, we also earned $1 million of sublicensing revenue from Alnylam, and a $1 million milestone payment as a result of Achaogen's IND filing for its aminoglycoside drug, ACHN-490. Half of Achaogen's payment consisted of Achaogen securities; therefore we only recorded $500,000 of revenue because we do not recognize revenue when we receive equity in private companies. We also earned $1.4 million in the first quarter of 2009 when we sold ATL/TV-1102 drug substance to Teva Pharmaceuticals Industries Ltd. for use in its clinical trials.

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

	Three Months Ended March 31,	
	2009	2008
Drug Discovery and Development:		
Research and development revenue	$ 29,047	$ 17,615
Licensing and royalty revenue	1,891	668
	$ 30,938	$ 18,283

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Regulus Therapeutics:		
Research and development revenue	$ 638	$ 92
	$ 638	$ 92
Total revenue:		
Research and development revenue	$ 29,685	$ 17,707
Licensing and royalty revenue	1,891	668
	$ 31,576	$ 18,375

Drug Discovery & Development

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the three months ended March 31, 2009 was $29.0 million, compared to $17.6 million for the same period in 2008. The significant increase was primarily due to the increase in revenue from our collaboration with Genzyme described above.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the three months ended March 31, 2009 was $1.9 million, compared to $668,000 for the same period in 2008. The increase primarily relates to the $1 million sublicensing revenue received in the first quarter of 2009 from Alnylam when Alnylam entered into a transaction with Cubist that included technology we had licensed to Alnylam.

Regulus Therapeutics

Regulus' revenue for the first quarter ended March 31, 2009 was $638,000, compared to $92,000 for the same period in 2008. The increase was primarily due to revenue from its collaboration with GSK. As part of Regulus' strategic alliance with GSK, Regulus received a $15 million upfront fee, which Regulus began amortizing into revenue in the second quarter of 2008 and will continue to amortize over Regulus' six year period of performance under the agreement.

Operating Expenses

Operating expenses for the quarter ended March 31, 2009 were $32.2 million compared to $24.6 million for the same period of 2008. The higher expenses in 2009 compared to 2008 were primarily due to the expansion of our clinical development programs, including additional expenses associated with the development of mipomersen, and expenses for Regulus.

The increase was partly offset by the decrease in non-cash compensation expense related to stock options. Non-cash compensation expense related to stock options was $2.7 million for the first quarter of 2009 compared to $3.3 million for the same period in 2008. See *Note 2, Significant Accounting Policies*, in the Notes to the Condensed Consolidated Financial Statements for additional information.

Our operating expenses by segment were as follows (in thousands):

	Three Months Ended March 31,	
	2009	2008
Drug Discovery and Development	$ 29,715	$ 23,089
Regulus Therapeutics	2,503	1,527
Total operating expenses	$ 32,218	$ 24,616

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 expense related to stock options. We believe non-cash compensation expense is not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding it.

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Research and Development Expenses

Our research and development ("R&D") expenses consist of costs for antisense drug discovery, antisense drug development, manufacturing and operations and R&D support costs. In addition, our research and development expenses include costs associated with the research activities Regulus is conducting to advance its microRNA technology.

The following table sets forth information on research and development costs (in thousands):

	Three Months Ended March 31,	
	2009	2008
Research and development expenses	$ 26,281	$ 19,069
Non-cash compensation expense related to stock options	2,260	2,716
Total research and development expenses	$ 28,541	$ 21,785

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

	Three Months Ended March 31,	
	2009	2008
Drug Discovery and Development	$ 26,697	$ 20,473
Regulus Therapeutics	1,844	1,312
Total research and development expenses	$ 28,541	$ 21,785

For the three months ended March 31, 2009, we incurred total research and development expenses of $26.3 million compared to $19.1 million for the same period in 2008, both amounts excluding non-cash compensation expense related to stock options. We attribute the increase in expenses to the expansion of our clinical development programs and expenses for Regulus. We discuss expenses related to Regulus in a separate section below. During the remainder of 2009, our research and development expenses will increase modestly as we continue the development of mipomersen, as Regulus continues to build its core team, and as we expand our research and development efforts in different disease areas.

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 continue to advance our antisense technology, we are investing in our antisense drug discovery programs to expand our and our partners' drug pipeline. 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.

Our antisense drug discovery expenses were as follows (in thousands):

	Three Months Ended March 31,	
	2009	2008
Antisense drug discovery	$ 5,389	$ 4,206
Non-cash compensation expense related to stock options	698	589
Total antisense drug discovery	$ 6,087	$ 4,795

Antisense drug discovery costs for the three months ended March 31, 2009 were $5.4 million compared to $4.2 million for the same period in 2008, both amounts excluding non-cash compensation expense related to stock options. The higher expenses in the first quarter of 2009 compared to the first quarter of 2008 were primarily due to increased activity levels related to our planned investment to fill our pipeline and additional spending to support collaborative research efforts for which we earn revenue, which required an increase in personnel and laboratory supplies.

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Antisense Drug Development

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

	Three Months Ended March 31,	
	2009	2008
Mipomersen	$ 4,758	$ 3,512
Other antisense development products	4,464	2,755
Development overhead costs	1,295	906
Non-cash compensation expense related to stock options	829	918
Total antisense drug development	$ 11,346	$ 8,091

Antisense drug development expenditures were $10.5 million for the three months ended March 31, 2009 compared to $7.2 million for the same period in 2008, both amounts excluding non-cash compensation expense related to stock options. We attribute the increase primarily to the development of mipomersen, including the broad Phase 3 program, and increases in our metabolic disease development projects. Development overhead costs were $1.3 million for the three months ended March 31, 2009, compared to $906,000 for the same period in 2008. The increase in overhead costs was a result of the additional expenses needed to support 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 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 clinical 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, 15 of our 19 drug candidates, which substantially reduces our development costs. As part of our collaboration with Genzyme, we will over time transition the development responsibility to Genzyme and Genzyme will be responsible for the commercialization of mipomersen. We will contribute up to the first $125 million in funding for the development costs of mipomersen. Thereafter we and Genzyme will share development costs equally. Our initial development funding commitment and the shared funding will end when the program is profitable.

Manufacturing and Operations

Expenditures in our manufacturing and operations function consist primarily of personnel costs, specialized chemicals for oligonucleotide manufacturing, laboratory supplies and outside services. This function is responsible for providing drug supplies to antisense drug discovery and antisense drug development, including the analytical testing to satisfy good laboratory and good manufacturing practices requirements.

Our manufacturing and operations expenses were as follows (in thousands):

	Three Months Ended March 31,	
	2009	2008
Manufacturing and operations	$ 2,804	$ 2,608
Non-cash compensation expense related to stock options	325	260
Total manufacturing and operations	$ 3,129	$ 2,868

Manufacturing and operations expenses for the three months ended March 31, 2009 were $2.8 million and were slightly higher compared to $2.6 million for the same period in 2008, both amounts excluding non-cash compensation expense related to stock options.

R&D Support

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

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

	Three Months Ended March 31,	
	2009	2008
Personnel costs	$ 1,967	$ 1,472
Occupancy	1,622	1,501
Depreciation and amortization	1,221	1,120
Insurance	225	246
Other	673	(261)
Non-cash compensation expense related to stock options	720	641
Total R&D support costs	$ 6,428	$ 4,719

R&D support costs for the three months ended March 31, 2009 were $5.7 million compared to $4.1 million for the same period in 2008, both amounts excluding non-cash compensation expense related to stock options. The increase was primarily a result of $750,000 we received from Ercole in March 2008 as repayment of a convertible note that we had previously expensed and an increase in personnel costs.

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

	Three Months Ended March 31,	
	2009	2008
Drug Discovery and Development	$ 6,135	$ 4,719
Regulus Therapeutics	293	—
Total R&D support costs	$ 6,428	$ 4,719

As part of Regulus' conversion from an LLC to a C-Corporation in January 2009, we began providing Regulus research and development and general and administrative services under the terms of a services agreement. Under the terms of the services agreement, we allocate a portion of our R&D support costs to Regulus and include this allocation in Regulus' research and development expenses.

General and Administrative Expenses

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 legal, human resources, investor relations, finance and Regulus' general and administrative expenses. Additionally, we include in 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.

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

	Three Months Ended March 31,	
	2009	2008
General and administrative expenses	$ 3,234	$ 2,264
Non-cash compensation expense related to stock options	443	567
Total general and administrative expenses	$ 3,677	$ 2,831

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

	Three Months Ended March 31,	
	2009	2008
Drug Discovery and Development	$ 3,018	$ 2,616
Regulus Therapeutics	659	215
Total general and administrative expenses	$ 3,677	$ 2,831

General and administrative expenses for the three months ended March 31, 2009 were $3.2 million compared to $2.3 million for the same period in 2008, both amounts excluding non-cash compensation expense related to stock options. The increase was primarily a result of an increase in additional expenses to support the expansion of our clinical development programs and increase in Regulus' general and administrative expenses in 2009. We discuss expenses related to Regulus in a separate section below.

Regulus Therapeutics

The following table sets forth information on Regulus' operating expenses (in thousands):

	Three Months Ended March 31,	
	2009	2008
Research and development expenses	$ 2,156	$ 1,005
General and administrative expenses	657	76
Non-cash compensation expense related to stock options	(310)	446
Total Regulus' operating expenses	$ 2,503	$ 1,527

Operating expenses for Regulus were $2.8 million for the quarter ended March 31, 2009 compared to $1.1 million for the same period in 2008, both amounts excluding non-cash compensation expense related to stock options. The increase was primarily related to Regulus' continued efforts to build its team to support its internal microRNA programs and the efforts associated with its GSK collaboration, which began in April 2008. With the strategic alliance with GSK, it is anticipated that Regulus' expenses will increase over its run rate going forward as Regulus advances its research and development activities.

Investment Income

Investment income for the three months ended March 31, 2009 totaled $2.2 million compared to $3.0 million for the same period in 2008. The decrease in investment income was primarily due to the lower average returns on our investments resulting from the current market conditions.

Interest Expense

Interest expense for the three months ended March 31, 2009 was $3.1 million and was slightly higher compared to $2.9 million for the same period in 2008. In 2009, we adopted a new accounting standard, FSP 14-1, related to our 2 5/8% convertible notes. This new standard requires us to assign a value to our convertible debt equal to the estimated fair value of a similar debt instrument without the conversion feature, which results in us recording our convertible debt at a discount. FSP 14-1 then requires us to amortize the resulting debt discount over the expected life of the debt as additional non-cash interest expense. FSP 14-1 requires retrospective application to all periods presented. Accordingly, the amount of interest expense we recorded in our statement of operations for the first quarter of 2009 and 2008 increased by $1.7 million and $1.5 million, respectively. This new standard did not impact our cash, cash equivalents and short-term investments but decreased the carrying value of our $162.5 million convertible notes to $119.7 million and $118.0 million at March 31, 2009 and December 31, 2008, respectively, with corresponding increases to shareholders' equity. For additional information about FSP 14-1, see *Note 5, Long-Term Obligations*, in the Notes to the Condensed Consolidated Financial Statements.

Income Tax Benefit

Even though we finished the first quarter of 2009 with a net loss from continuing operations, we had taxable income, which is primarily a result of the significant upfront payments that we received from our strategic alliance with Genzyme in 2008 and the gain we recognized on the sale of Ibis to AMI earlier this year. SFAS 109 requires us to record an income tax benefit of $717,000 on a line called "Income Tax Benefit" as part of our financial results from continuing operations because we will be using the tax benefits generated from our current year loss from continuing operations to offset a portion of our taxable income.

Net Income (Loss) from Continuing Operations attributable to Isis Pharmaceuticals, Inc. Common Stockholders

The following table sets forth computations for our net income (loss) from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders (in thousands):

	Three Months Ended March 31,	
	2009	2008
Net loss from continuing operations, net of income tax benefit	$ (814)	$ (6,105)
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	913	883
Net income (loss) from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ 99	$ (5,222)

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Net income from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders for the quarter ended March 31, 2009 was $99,000, compared to net loss of $5.2 million for the same period in 2008. The improvement in our net loss from continuing operations was primarily driven by the improvement in our net operating results.

Net Income (Loss) from Discontinued Operations

In 2008, AMI purchased approximately 18.6% of the issued and outstanding common stock of Ibis for a total purchase price of $40 million. In December 2008, we, Ibis and AMI executed a stock purchase agreement. Under this agreement, AMI purchased the remaining equity in Ibis from us for $175 million. We, Ibis and AMI completed the acquisition on January 6, 2009.

We reflect Ibis as discontinued operations because Ibis meets the criteria for a component of an entity under SFAS 144. Accordingly, we have presented the operating results of Ibis in our Consolidated Statements of Operations as discontinued operations and we have reclassified all prior periods. Net income from discontinued operations for the three months ended March 31, 2009 was $171.7 million, compared to net loss from discontinued operations of $564,000 for the same period in 2008. Net income from discontinued operations for the first quarter of 2009 primarily consists of the $202.5 million gain less income taxes. SFAS 109 requires us to allocate our 2009 tax expense between discontinued operations and continuing operations in our Condensed Consolidated Statement of Operations. Since the sale of Ibis to AMI was a discrete event that occurred in the first quarter of 2009, SFAS 109 requires us to record the total amount of our estimated income tax expense for discontinued operations in the first quarter of this year. Further, we are required to gross up this amount by the projected annual tax benefit we expect to record as part of our loss from continuing operations in 2009, which is described in the *Income Tax Benefit* section above. This means that in addition to the tax expense for the gain on the sale of Ibis, discontinued operations also includes the tax expense for other timing differences, which principally consists of the timing difference associated with the upfront funding we received from Genzyme. Accordingly, we have recorded tax expense of $30.7 million in discontinued operations in the first quarter of 2009.

Net Income (Loss) and Net Income (Loss) Per Share attributable to Isis Pharmaceuticals, Inc. Common Stockholders

Net income attributable to Isis Pharmaceuticals, Inc. common stockholders for the three months ended March 31, 2009 was $171.8 million, compared to net loss of $5.8 million for the same period in 2008. Basic and diluted net income per share attributable to Isis Pharmaceuticals, Inc. common stockholders for the three months ended March 31, 2009 was $1.76 per share and $1.57 per share, respectively. Basic and diluted net loss per share attributable to Isis Pharmaceuticals, Inc. common stockholders for the three months ended March 31, 2008 was $0.06 per share. Our net income and net income per share for the first quarter of 2009 was significantly improved over our net loss and net loss per share for the same period in 2008 primarily due to the gain we recognized when we sold Ibis to AMI.

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 March 31, 2009, we have earned approximately $728.7 million in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through March 31, 2009, we have raised net proceeds of approximately $809.0 million from the sale of our equity securities and we have borrowed approximately $558.5 million under long-term debt arrangements to finance a portion of our operations.

At March 31, 2009, we had cash, cash equivalents and short-term investments of $652.2 million and stockholders' equity of $302.7 million. In comparison, we had cash, cash equivalents and short-term investments of $491.0 million and stockholders' equity of $147.4 million as of December 31, 2008. At March 31, 2009, we had consolidated working capital of $527.2 million, compared to $393.7 million at December 31, 2008. The $175 million we received from AMI in the first quarter of 2009 primarily led to the increase in our consolidated working capital.

As of March 31, 2009, our debt and other obligations totaled $134.0 million, compared to $130.0 million at December 31, 2008. The increase in our debt and other obligations was primarily due to our $2.7 million additional draw down on our equipment financing arrangement and $1.7 million non-cash amortization of the debt discount recorded in the first quarter of 2009 as a result of adopting FSP 14-1. In addition, as a result of adopting FSP 14-1, the carrying balance of our 2 5/8% convertible notes decreased to $119.7 million and $118.0 million at March 31, 2009 and December 31, 2008, respectively. For additional information about FSP 14-1, see *Note 5, Long-Term Obligations*, in the Notes to the Condensed Consolidated Financial Statements. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

The following table summarizes our contractual obligations as of March 31, 2009. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt 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
GSK Convertible Promissory Note, including accrued interest	$ 5.2	$ —	$ 5.2	$ —	$ —
Equipment Financing Arrangement	$ 8.7	$ 2.9	$ 5.7	$ 0.1	$ —
Other Obligations	$ 0.4	$ —	$ —	$ —	$ 0.4
Operating Leases	$ 17.2	$ 3.3	$ 4.3	$ 2.1	$ 7.5

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Our contractual obligations consist primarily of our publicly traded convertible debt. In addition, we also have a convertible promissory note Regulus issued to GSK, an equipment financing arrangement and other obligations.

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. We included the issuance costs in our balance sheet and are amortizing these costs to interest expense over the life of the debt. 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 our common stock at a conversion price of $14.63 per share. We 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 also are able to require us 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 and unpaid interest.

In connection with the strategic alliance with GSK in April 2008, Regulus issued a convertible promissory note to GSK in exchange for $5 million in cash. The convertible note bears interest at the prime rate, which was 3.25% at March 31, 2009. The note plus interest will convert into Regulus common stock in the future if Regulus achieves a minimum level of financing with institutional investors. In addition, we and Alnylam are guarantors of the note, and if the note does not convert or Regulus does not repay the note in cash by April 2011, we, Alnylam and Regulus may elect to repay the note plus interest with shares of each company's common stock.

In October 2008, we entered into a loan agreement related to an equipment financing. Under the loan agreement, we may borrow up to approximately $10 million in principal to finance the purchase of equipment. The $10 million includes the $600,000 Ibis borrowed in October 2008 that was fully repaid in the first quarter of 2009. Each loan under the loan agreement will have a term of approximately three years, with principal and interest payable monthly. We calculate interest on amounts we borrow under the loan agreement based upon the three year interest rate swap at the time we make each draw down plus 4%. We are using the equipment purchased under the loan agreement as collateral. In October 2008, we drew down $6.6 million in principal under the loan agreement with interest rate of 7.22%. In March 2009, we drew down an additional $2.7 million in principal under this loan agreement with interest rate of 6.28%. We have now drawn down the full amount available under the loan. The carrying balance under this loan agreement at March 31, 2009 and December 31, 2008 was $8.7 million and $6.5 million, respectively.

In addition to contractual obligations, we had outstanding purchase orders as of March 31, 2009 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. You should consider carefully the following information about the risks described below, together with the other information contained in this report and in our other public filings in evaluating our business. 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, 2008.

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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 generally exceeded our revenue since we were founded in January 1989. As of March 31, 2009, we had accumulated losses of approximately $679.4 million and stockholders' equity of approximately $302.7 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from research grants and the sale or licensing of our 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.

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 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, ATL, Atlantic Pharmaceuticals, BMS, iCo, Lilly, Merck, OncoGenex, OMJP and Teva. In addition, in January 2008 we entered a major strategic alliance with Genzyme in which Genzyme will develop and commercialize mipomersen. If any of these pharmaceutical companies stop funding and/or developing these products, our business could suffer and we may not have, or be willing to dedicate, 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, such as our collaborations with Genzyme, OMJP and BMS, these collaborations may not continue or result in commercialized drugs, or may not progress as quickly as we anticipated.

For example, a collaborator such as Genzyme, OMJP, or BMS, 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 its own drugs under development.

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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 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 assumptions 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.

For example, in April 2008 the FDA provided guidance regarding approval requirements for mipomersen. The FDA indicated that reduction of LDL-cholesterol is an acceptable surrogate endpoint for accelerated approval of mipomersen for use in patients with homozygous familial hypercholesterolemia, or hoFH. The FDA will require data from two ongoing preclinical studies for carcinogenicity to be included in the hoFH filing, which is now anticipated to take place in 2010. The FDA also indicated that for broader indications in high risk, high cholesterol patients an outcome study would be required for approval. This FDA guidance caused us to revise our development plans and timelines and, as a result, to accelerate our planned outcome trial.

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.

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 its 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 for the first 18 months. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain unresolved.

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. As of March 31, 2009, we had cash, cash equivalents and short-term investments equal to $652.2 million. 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:

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- 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; 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.

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 us. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. In addition, failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel.

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding March 31, 2009, the market price of our common stock ranged from $9.90 to $19.29 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.

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In such an event, we may be held liable for any resulting damages, and any 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 the coverage or coverage limits of our insurance policies may not 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, development or manufacturing facilities, it could delay our progress developing and commercializing our drugs.

We manufacture our research and clinical supplies in a separate manufacturing facility located in Carlsbad, California. The facilities and the equipment we use to research, develop and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. 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.

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.

In addition, our collaboration agreement with Genzyme regarding mipomersen provides that if we are acquired, Genzyme may elect to purchase all of our rights to receive payments under the mipomersen collaboration agreement for a purchase price to be mutually agree to by us and Genzyme, or, if we cannot agree, a fair market value price determined by an independent investment banking firm. This provision may make it more difficult or complicated for us to enter into an acquisition agreement with a potential acquirer.

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. For example, we registered for resale 4.25 million shares of our common stock issuable upon the exercise of the warrant we originally issued to Symphony GenIsis Holdings. In addition, 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 public market may have an adverse effect on the price of our securities.

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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 SEC, the Public Company Accounting Oversight Board (PCAOB) or the Nasdaq Global Market. Any such action could adversely affect our financial results and the market price of our common stock.

Negative conditions in the global credit markets and financial services and other industries may adversely affect our business.

The continuing deterioration in the global credit markets, the financial services industry and the U.S. capital markets, the U.S. economy as a whole have been experiencing a period of substantial turmoil and uncertainty characterized by unprecedented intervention by the U.S. federal government and the failure, bankruptcy, or sale of various financial and other institutions. The impact of these events on our business and the severity of the current economic crisis is uncertain. It is possible that the current crisis in the global credit markets, the U.S. capital markets, the financial services industry and the U.S. economy may adversely affect our business, vendors and prospects as well as our liquidity and financial condition. More specifically, our insurance carriers and insurance policies covering all aspects of our business may become financially unstable or may not be sufficient to cover any or all of our losses and may not continue to be available to us on acceptable terms, or at all.

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, including mipomersen and ISIS 113715. If any of our drugs in clinical studies, including 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 these and other drugs and our stock price could decline.

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

Successful results in preclinical or early human clinical trials, including the 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 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 or Phase 3 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, even if approved for commercialization, doctors may not use our products to treat patients. We currently have one commercially approved 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 would be required to establish large-scale commercial manufacturing capabilities either on our own or through a third party manufacturer. In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. We

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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, including mipomersen and ISIS 113715, or result in FDA enforcement action after approval that could limit the commercial success of our potential products, including mipomersen and ISIS 113715.

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;
- more effective than our drugs; or
- more convenient to use 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.

Disagreements between Alnylam and us regarding the development of our microRNA technology may cause significant delays and other impediments in the development of this technology, which could negatively affect the value of the technology and our investment in Regulus.

Regulus is a jointly owned company that we and Alnylam established to focus on the discovery, development, and commercialization of microRNA. As part of this joint venture, we exclusively licensed to Regulus our intellectual property rights covering microRNA. Regulus is operated as an independent company and governed by a board of directors. We and Alnylam can elect an equal number of directors to serve on the Regulus Board. Regulus researches and develops microRNA projects and programs pursuant to an operating plan that is approved by the board. Any disagreements between Alnylam and us regarding a development decision or any other decision submitted to Regulus' board may cause significant delays in the development and commercialization of our microRNA technology and could negatively affect the value of our investment in Regulus.

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

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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.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

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

ITEM 4. CONTROLS AND PROCEDURES

As of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of March 31, 2009. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 2009.

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

On February 11, 2008, we notified Bruker Daltonics, Ibis' manufacturing and commercialization partner for the T5000 System, that we were initiating the formal dispute resolution process under Ibis' agreement with them. We asserted that Bruker's performance of its manufacturing, commercialization and product service obligations are unsatisfactory and fail to meet their obligations under this agreement. Executive level negotiations and formal mediation efforts failed to achieve resolution of this dispute. On May 22, 2008, Bruker filed a complaint against Isis Pharmaceuticals, Inc. and Ibis Biosciences, Inc. in Superior Court of Middlesex County, Massachusetts alleging monetary damages due to breach of contract by us and Ibis. We and Ibis filed an Answer, Affirmative Defenses and Counterclaim on July 14, 2008, alleging breach of contract by Bruker. Discovery is in its early stage. We will continue to represent and defend Ibis Biosciences in this matter.

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

Not applicable

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

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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	Amended and Restated License and Collaboration Agreement among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics Inc. dated January 1, 2009 (with certain confidential information deleted).
10.2	Founding Investor Rights Agreement among the Registrant, Alnylam Pharmaceuticals, Inc. and Regulus Therapeutics Inc. dated January 1, 2009 (with certain confidential information deleted).
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.

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Isis Pharmaceuticals, Inc.

(Registrant)

SIGNATURES

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

Signatures	Title	Date
/s/ Stanley T. Crooke Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	May 7, 2009
/s/ B. Lynne Parshall B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	May 7, 2009

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

Execution

AMENDED AND RESTATED LICENSE AND COLLABORATION AGREEMENT

This Amended and Restated License and Collaboration Agreement (the "***Agreement***") is entered into as of the 1st day of January, 2009 (the "***Amendment 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 INC.** (formerly Regulus Therapeutics LLC), a Delaware corporation, with its principal place of business at 1896 Rutherford Road, Carlsbad, California 92008 ("***Regulus***").

RECITALS

WHEREAS, Isis and Alnylam each granted a license to Regulus in accordance with that certain License and Collaboration Agreement dated September 6, 2007 (the "***Original License Agreement***");

WHEREAS, as of the Amendment Effective Date, Alnylam, Isis and Regulus converted Regulus from a Delaware limited liability company into a Delaware corporation; and

WHEREAS, as a result of this corporate conversion, Isis, Alnylam, and Regulus now desire to amend and restate the Original License Agreement, as provided herein.

AGREEMENT

NOW, THEREFORE, 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 (i) use and exploit its Licensed IP solely to support its own internal Research in the Alnylam Field**,** and (ii) grant Permitted Licenses. The exclusive license granted to Regulus by Isis pursuant to Section 2.2(a) is subject to Isis' retained right to (i) use and exploit its Licensed IP solely to support its own internal Research in the Isis Field**,** and (ii) grant Permitted Licenses. 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.

5.7 Payment of Royalties. Following any dissolution or winding-up of Regulus that results in no successor entity to Regulus, any royalties, milestones and/or sublicense fees due to Regulus by a Licensor in connection with an Opt-In Election under this Agreement, will be reduced by [***] percent ([***]%) and this amount will instead be payable by the Licensor required to pay such fee directly to the other Licensor (the "***Receiving Licensor***"); *provided*, *however*, if the Receiving Licensor has pass-through obligations with respect to a royalty

payment, milestone or sublicense fee, the payment to the Receiving Licensor will not be reduced to an amount less than the amount of the pass-through obligation.(1)

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 Investor Rights 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.

(1) This Section 5.7 was taken from Section 10.7 of the LLC 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 Investor Rights 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 Investor Rights 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 Investor Rights Agreement and partially on a non-indemnified claim or based partially on a claim indemnified by one Party under this Agreement or the Investor Rights Agreement and partially on a claim indemnified by another Party(ies) under this Agreement or the Investor Rights 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 Amendment Effective Date: (a) it is a corporation 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 Amendment 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 Founding Investor*" (as defined in the Investor Rights 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 Founding Investor 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 Investor Rights Agreement) of such Licensor's Shares (as defined in the Investor Rights Agreement) and registerable securities, if any, 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 Investor Rights 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 Investor Rights 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, including without limitation the Original License Agreement. For clarity, the Parties acknowledge and agree that the Original License Agreement remains in effect in accordance with its terms with respect to the period between September 6, 2007 and the Amendment Effective Date. 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 Investor Rights 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.

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IN WITNESS WHEREOF, the Parties hereby execute this Agreement as of the date first written above.

ALNYLAM PHARMACEUTICALS, INC.

By: /s/ Barry Greene
Name: Barry Greene
Title: President & COO

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall
Name: B. Lynne Parshall
Title: COO & CFO

REGULUS THERAPEUTICS INC.

By: /s/ Kleanthis G. Xanthopoulos
Name: Kleanthis G. Xanthopoulos
Title: President & CEO

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 "***Amendment Effective Date***" has the meaning set forth in the Preamble.

1.7 "***Approved Mimic***" will have the meaning set forth in Section 1.61.

1.8 "***Approved Precursor Antagonist***" will have the meaning set forth in Section 1.61.

1.9 "***Bankruptcy Code***" will have the meaning set forth in Section 16.3.

1.10 "***Business Day***" means a day on which the banks in New York, New York are open for business.

1.11 "***Buy-Out***" will have the meaning set forth in the Investor Rights Agreement.

1.12 "***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.

1.13 "***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.

1.14 "***Combination Product***" will have the meaning set forth in Section 1.67.

1.15 "***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.

1.16 "***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.

1.17 "***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.

1.18 "***Completion***" means, with respect to any clinical trial, the locking of the database pertaining to such clinical trial.

1.19 "***Confidential Information***" will have the meaning set forth in the Investor Rights Agreement.

1.20 "***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.

1.21 "***Controlling Party***" will have the meaning set forth in Section 2.4(d).

1.22 "***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.

1.23 "***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.

1.24 "***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.

1.25 "***Development Project***" will have the meaning set forth in Section 4.4.

1.26 "***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.

1.27 "***Disclosing Party***" will have the meaning set forth in the Investor Rights Agreement.

1.28 "***Effective Date***" means September 6, 2007, the date on which the Parties entered into the Original License Agreement.

1.29 "***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.

1.30 "***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.

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

1.32 "***Field***" means treatment and/or prophylaxis of any or all Indications.

1.33 "***GAAP***" means United States Generally Accepted Accounting Principles, consistently applied.

1.34 "***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.

1.35 "***[***]***" means a [***].

1.36 "***Hatch-Waxman Act***" will have the meaning set forth in Section 9.3(a)(i)(A).

1.37 "***High Terms***" will have the meaning set forth in Section 5.4.

1.38 "***In-License Agreement***" will have the meaning set forth in Section 2.4(b).

1.39 "***In-License Summary***" will have the meaning set forth in Section 2.4(b).

1.40 "***IND***" means an Investigational New Drug Application or similar foreign application or submission for approval to conduct human clinical investigations.

1.41 "***Indication***" means any disease or condition, or sign or symptom of a disease or condition, or symptom associated with a disease or syndrome.

1.42 "***Initial Opt-In Election Period***" will have the meaning set forth in Section 5.3.

1.43 "***Intellectual Property***" will have the meaning set forth in the Investor Rights Agreement.

1.44 "***Invalidity Claim***" will have the meaning set forth in Section 9.4.

1.45 "***Investor Rights Agreement***" means the Founding Investor Rights Agreement of Regulus among the Parties, dated as of the Amendment Effective Date, as the same may be amended from time to time after the Amendment Effective Date.

1.46 "***Isis***" will have the meaning set forth in the Preamble.

1.47 "***Isis Field***" will have the meaning set forth in Section 2.3(b).

1.48 "***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.

1.49 "***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.

1.50 "***Licensed IP***" means, with respect to a Licensor, such Licensor's Licensed Know-How and Licensed Patent Rights.

1.51 "***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).

1.52 "***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).

1.53 "***Licensor***" will have the meaning set forth in the Preamble.

1.54 "***Licensor Indemnitees***" will have the meaning set forth in Section 11.1.

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 Investor Rights 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 Investor Rights 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 Investor Rights 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 Amended and Restated Services Agreement by and between Regulus, Alnylam and Isis dated the Amendment Effective Date, as the same may be amended from time to time after the Amendment 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 encumbrances 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 encumbrances 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 encumbrances 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
Upfont	[***]	[***]	***[***]***				***[***]***	[***]	[***]
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
Upfont	[***]	[***]	***[***]***				***[***]***	[***]	[***]
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
Upfont	[***]	[***]	***[***]***				***[***]***	[***]	[***]
IND filing	[***]	[***]	***[***]***				***[***]***	[***]	[***]
Completion of Phase IIa	[***]	[***]	***[***]***			[***]	***[***]***	[***]	[***]
Phase III start	[***]	[***]	***[***]***			[***]	***[***]***	[***]	[***]
			[***]	[***]	[***]	[***]	***[***]***	[***]	[***]
			[***]	[***]	[***]	[***]	***[***]***	[***]	[***]
FDA filing	[***]		***[***]***	[***]	[***]	[***]	***[***]***	[***]	[***]
EU filing	[***]		***[***]***	[***]	[***]	[***]	***[***]***	[***]	[***]
FDA approval	[***]		***[***]***	[***]	[***]	[***]	***[***]***	[***]	[***]
EU approval	[***]		***[***]***	[***]	[***]	[***]	***[***]***	[***]	[***]
			[***]	[***]	[***]	[***]	***[***]***	[***]	[***]
Total	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**

Exhibit 2

Alnylam Agreement Summaries

[attached]

Exhibit 2

Alnylam Summaries

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.

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	$	[***]

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· 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:

	Percentage due to GI
· Sublicense granted	[***]%
· 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").

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

Execution

REGULUS THERAPEUTICS INC.

FOUNDING INVESTOR RIGHTS AGREEMENT

REGULUS THERAPEUTICS INC.

FOUNDING INVESTOR RIGHTS AGREEMENT

THIS FOUNDING INVESTOR RIGHTS AGREEMENT (the "Agreement") is entered into as of the 1st day of January 2009, by and among **Regulus Therapeutics Inc.**, a Delaware corporation (the ***"Company"***) on the one hand, and **Isis Pharmaceuticals, Inc.**, a Delaware Corporation (***"Isis"***) and **Alnylam Pharmaceuticals, Inc.**, a Delaware corporation (***"Alnylam"***) who are each holders of the Company's Series A Preferred Stock (the ***"Preferred Stock"***) on the other hand. Isis and Alnylam may be referred to hereinafter collectively as the ***"Founding Investors"*** and each individually as a ***"Founding Investor"***. The Company, Isis and Alnylam may be referred to hereinafter collectively as the ***"Parties"*** and each individually as a ***"Party"***.

RECITALS

WHEREAS, the Company was formerly a Delaware limited liability company with the Founding Investors as its only members;

WHEREAS, the Company converted to a Delaware corporation in January 2009;

WHEREAS, in connection with the Company's conversion to a Delaware corporation, the Founding Investors received the Preferred Stock in exchange for their membership interests in the limited liability company; and

WHEREAS, in connection with the issuance of the Preferred Stock, the parties desire to enter into this Agreement in order to grant registration, information rights, buy-out rights and other rights to the Founding Investors as set forth below.

NOW, THEREFORE, in consideration of these premises and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties hereto agree as follows:

SECTION 1. DEFINITIONS.

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

SECTION 2. RESTRICTIONS ON TRANSFER.

No Founding Investor 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 Founding Investor's Shares or Registrable Securities, 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 Section 2.

2.1 Restrictions on Transfer Before Initial Offering. Except as provided in this Section 2, before the Company's Initial Offering, each Founding Investor agrees that it may not

and will not Transfer its Shares or Registrable Securities without the prior written consent of the other Founding Investor.

2.2 Restrictions on Transfer After Initial Offering. Each Holder agrees not to make any disposition of all or any portion of the Shares or Registrable Securities unless and until:

(a) there is then in effect a registration statement under the Securities Act covering such proposed disposition and such disposition is made in accordance with such registration statement; or

(b) (i) The transferee has agreed in writing to be bound by the terms of this Agreement, (ii) such Holder will have notified the Company of the proposed disposition and will have furnished the Company with a detailed statement of the circumstances surrounding the proposed disposition, and (iii) if reasonably requested by the Company, such Holder will have furnished the Company with an opinion of counsel, reasonably satisfactory to the Company, that such disposition will not require registration of such shares under the Securities Act. It is agreed that the Company will not require opinions of counsel for transactions made pursuant to Rule 144, except in unusual circumstances. After its Initial Offering, the Company will not require any transferee pursuant to Rule 144 to be bound by the terms of this Agreement if the shares so transferred do not remain Registrable Securities hereunder following such transfer.

2.3 Exempt Transfers. Notwithstanding the provisions of Sections 2.1 and 2.2 above, no such restriction will apply to a transfer by a Founding Investor that is:

(a) a Transfer by a Founding Investor to an Affiliate of such Founding Investor; *provided*, *however*, that (i) the Affiliate of such transferring Founding Investor must have the resources, assets, experience, qualifications, permits and other rights necessary to perform under this Agreement

and each of the Ancillary Agreements and (ii) the transferee will agree in writing to be subject to the terms of this Agreement to the same extent as if it were an original Founding Investor hereunder.

(b) Transfer pursuant to a Change in Control of such Founding Investor. In the event of a Change in Control of a Founding Investor, the other Founding Investor may initiate a Buy-Out pursuant to Section 4.

2.4 Stock Legends. Each certificate representing Shares or Registrable Securities will be stamped or otherwise imprinted with legends substantially similar to the following (in addition to any legend required under applicable state securities laws):

> THE SECURITIES REPRESENTED HEREBY HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933 (THE "***ACT***") AND MAY NOT BE OFFERED, SOLD OR OTHERWISE TRANSFERRED, ASSIGNED, PLEDGED OR HYPOTHECATED UNLESS AND UNTIL REGISTERED UNDER THE ACT OR UNLESS THE COMPANY HAS RECEIVED AN OPINION OF COUNSEL SATISFACTORY TO THE COMPANY AND ITS COUNSEL THAT SUCH

> REGISTRATION IS NOT REQUIRED.
>
> THE SALE, PLEDGE, HYPOTHECATION OR TRANSFER OF THE SECURITIES REPRESENTED BY THIS CERTIFICATE IS SUBJECT TO THE TERMS AND CONDITIONS OF A CERTAIN INVESTOR RIGHTS AGREEMENT BY AND BETWEEN THE STOCKHOLDER AND THE COMPANY. COPIES OF SUCH AGREEMENT MAY BE OBTAINED UPON WRITTEN REQUEST TO THE SECRETARY OF THE COMPANY.

(a) The Company will be obligated to promptly reissue unlegended certificates at the request of any Holder thereof if the Company has completed its Initial Offering and the Holder has obtained an opinion of counsel (which counsel may be counsel to the Company) reasonably acceptable to the Company to the effect that the securities proposed to be disposed of may lawfully be so disposed of without registration, qualification and legend, *provided that* the second legend listed above will be removed only at such time as the Holder of such certificate is no longer subject to any restrictions hereunder.

(b) Any legend endorsed on an instrument pursuant to applicable state securities laws and the stop-transfer instructions with respect to such securities will be removed upon receipt by the Company of an order of the appropriate blue sky authority authorizing such removal.

SECTION 3. COVENANTS OF THE COMPANY.

3.1 Financial Information and Reporting.

(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 Company will maintain a system of internal accounting controls which are sufficient to provide reasonable assurance that (w) transactions are executed in accordance with the Company's signature authority policy; (x) transactions are recorded as necessary to permit preparation of the financial statements of the Company and to maintain accountability for the Company's assets; (y) access to the Company's assets is permitted only in accordance with management's authorization; and (z) the reporting of the Company's assets is compared with existing assets at regular intervals. The Company's financial statements will be audited annually by an independent nationally recognized public accounting firm approved by the Company's Board of Directors.

(b) *During Consolidation Period*. For so long as (1) Isis' independent auditors advise Isis that Isis should consolidate Regulus' financial statements with Isis' financial statements or (2) Regulus is using Isis' financial systems (the ***"Consolidation Period"***) Regulus will do the following:

(i) Commencing with respect to the fiscal year ending December 31, 2008, and for each fiscal year during the term hereof, the Company will deliver or mail to each Founding Investor the audited annual financial statements of the Company at least [***] ([***]) [***] prior to the earliest date by which either Founding Investor 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 Founding Investor 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.

(ii) For each fiscal quarter during the term hereof, the Company will deliver or mail to each Founding Investor 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 [***] ([***]) days after the end of each fiscal quarter of the Company (or such earlier time as may be required by a Founding Investor to satisfy its reporting obligations under law, including without limitation, the rules and regulations of the SEC).

(iii) Commencing with the month ending on January 31, 2009, the Company will deliver to each Founding Investor 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 a Founding Investor to satisfy its reporting obligations under law, including without limitation, the rules and regulations of the SEC).

(iv) The income statements and balance sheets referred to in this Section 3.1 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.

(v) The Company will use the same accounting firm as Isis uses to audit its financial statements.

(vi) The Company's principal executive officer and principal financial officer, or persons performing similar functions, will provide certifications to Isis corresponding to those required under Sections 302 and 906 of the Sarbanes-Oxley Act of 2002, and the Company will provide to Isis an attestation report of its auditors with respect to the Company's internal controls, as may be requested by Isis' external auditors.

(vii) If after reasonable discussions in good faith, the Company's audit committee and Isis' audit committee cannot resolve any dispute with respect to accounting policies and practices for the Company's financial reporting, the Parties agree that they will apply the accounting policy or practice proposed by Isis' audit committee.

(c) *After the Consolidation Period*. After the Consolidation Period and until neither Isis nor Alnylam is required to record their respective share of Regulus' profit/loss,

Regulus will provide Isis and Alnylam the information as specified on **EXHIBIT E** attached hereto.

(d) Once Isis and Alnylam are no longer required to record their respective share of Regulus' income/losses, Regulus will not be required to provide the information to Isis and Alnylam outlined in Section 3.1(c) above. However, Regulus will provide to Isis and/or Alnylam any financial information reasonably requested by either company so that such company can determine if an impairment in Regulus exists, and Regulus will make its management available to Isis and/or Alnylam for reasonable inquiries regarding its financials.

3.2 Tax Matters.

(a) The Company 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. With respect to the Company's tax return for the fiscal year ended December 31, 2008, the Company will provide a draft of such tax return to each Founding Investor within a reasonable amount of time prior to filing such return to allow each Founding Investor an opportunity to review and comment on such return. In addition, the Company will give due consideration to each Founding Investor's comments regarding the tax return for the year ended December 31, 2008.

(b) Each Founding Investor may request from the Company any information reasonably necessary for the Founding Investor 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 Founding Investor.

3.3 Confidentiality of Records. Each Founding Investor agrees to use the same degree of care as such Founding Investor uses to protect its own confidential information to keep confidential and not disclose to any party any information furnished to such Founding Investor pursuant to Section 3.1 and 3.2 hereof that the Company identifies as being confidential or proprietary (so long as such information is not in the public domain), except that such Founding Investor may disclose such proprietary or confidential information (i) to any partner, subsidiary or parent of such Founding Investor as long as such partner, subsidiary or parent is advised of and agrees or has agreed to be bound by the confidentiality provisions of this Section 3.3 or comparable restrictions; (ii) at such time as it enters the public domain through no fault of such Founding Investor; (iii) that is communicated to it free of any obligation of confidentiality; (iv) that is developed by Founding Investor or their respective agents independently of and without reference to any confidential information communicated by the Company; or (v) as required by applicable law. Upon request by the Company, each Founding Investor agrees to enter into a separate confidentiality agreement with the Company.

3.4 Reservation of Common Stock. The Company will at all times reserve and keep available, solely for issuance and delivery upon the conversion of the Preferred Stock, all Common Stock issuable from time to time upon such conversion.

3.5 Board of Directors. The 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"***). Isis will have the right to designate [***] ([***]) Directors who need not be Independent Directors (the ***"Isis Directors"***). The President of the Company will, at all times while in office, be a Director. The remaining two members will be independent industry representatives approved by the other Directors then serving on the Board. Other than the President, each Director will serve at the pleasure of the Founding Investor designating such Director until such Director's removal by the designating Founding Investor or such Director's resignation. If there is a vacancy on the Board, the vacancy will be filled by the Founding Investor, if any, who initially designated the Director, except if the vacancy is caused by the termination of the President, such vacancy will be filled when the then existing Board appoints the new President. Any Founding Investor may remove, at any time and for any reason, any or all of the Directors designated by such Founding Investor and, subject to the Independent Director requirements, designate in lieu thereof any individual(s) to serve the remainder of the relevant term.

(a) *Observers*. The right to attend all or particular meetings of the Board (***"Observer Rights"***) may be granted to any Person designated by a Founding Investor upon the approval of the other Founding Investor (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 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 Founding Investor 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.

(b) *Other Attendees*. Any Director may invite a subject matter expert to attend any meeting of the 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.

(c) The Directors designated as of the Effective Date are set forth on **EXHIBIT B** hereto.

3.6 Directors' Liability and Indemnification. The Company's Certificate of Incorporation and Bylaws will provide (a) for elimination of the liability of a Director to the maximum extent permitted by law and (b) for indemnification of Directors for acts on behalf of the Company to the maximum extent permitted by law. In addition, the Company will enter into and use its best efforts to at all times maintain reasonable and customary indemnification agreements with each of its Directors to indemnify such directors to the maximum extent permissible under applicable law.

3.7 Operating Plan. The Company will use commercially reasonable efforts to operate the Company in accordance with the Approved Operating Plan (as defined below). The

initial Operating Plan, dated April 30, 2008 attached hereto as **EXHIBIT C** (the ***"Initial Operating Plan"***), will be deemed the ***"Approved Operating Plan"*** for the period beginning on September 6, 2007 and ending on December 31, 2009 (such period, the ***"Initial Commitment Period"***).

(a) No later than September 30, 2009, and no later than September 30 in each fiscal year thereafter, Regulus' management will prepare and submit to the 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"***).

(b) Each Proposed Operating Plan that has been prepared and submitted by Regulus' management in accordance with Section 3.7(a) will be considered at the first meeting of the Board following its submission and will be subject to the approval of the Board. The Chairperson will call a special meeting of the 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 Board will be considered the "***Approved Operating Plan***" for all purposes of this Agreement until amended or replaced.

(c) If, after the Initial Commitment Period, the Board is unable to approve a Proposed Operating Plan that has been prepared and submitted by Regulus' management in accordance with Section 3.7(a) within three months following the date such Proposed Operating Plan is submitted for approval (a ***"Stalemate"***), either Founding Investor may initiate a Buy-Out in accordance with Section 4; *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 Founding Investor 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.

3.8 Scientific Advisory Board. The Company will maintain 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 **EXHIBIT B**. Any changes to the composition of the Scientific Advisory Board, including the removal or appointment of the chairperson, will be approved by the Board. The SAB will meet at least at least three time a year 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 Board, President or Chief Scientific Officer; and (iii) advising the Company with respect to research and development decisions, as requested by the Board, President or Chief Scientific Officer.

3.9 Termination of Covenants. All covenants of the Company contained in Section 3 of this Agreement (other than the provisions of Section 3.1 and 3.3) will expire and terminate as to each Founding Investor upon the earlier of (i) the effective date of the registration statement pertaining to an Initial Offering or (ii) upon a Liquidation Event, Acquisition or Asset Transfer

(in each case as defined in the Company's Certificate of Incorporation as such may be amended from time to time).

SECTION 4. BUY-OUT.

4.1 Right to Initiate Buy-Out. Within (a) solely in the event of a Stalemate occurring after the end of the Initial Commitment Period (as further described in Section 3.7(c), the [***] ([***]) day period following such Stalemate, (b) at any time, whether before or after the end of the Initial Commitment Period, during the [***] ([***]) day period following notice from a Founding Investor that it has entered into a binding agreement providing for a Change of Control of such Founding Investor (such [***] ([***]) or [***] ([***]) day period, a ***"Buy-Out Notice Period"***), or (c) as provided for in the License Agreement, either Founding Investor (in the case of (a)), the Founding Investor receiving the notice of a Change in Control (in the case of (b)), or the Founding Investor or Founding Investors as specified in the License Agreement (in the case of (c) (in each case, the ***"Initiating Founding Investor"***) has the right, exercisable upon written notice to the Company and the other Founding Investor (the ***"Buy-Out Notice"***), to initiate the sale of the Company or the distribution the Company's assets, including the Company Intellectual Property and Company's rights in Licensed IP, in accordance with the terms set forth on **EXHIBIT D** (the ***"Buy-Out"***).

4.2 Voting Agreement; Cooperation. If any Founding Investor initiates a Buy-Out under Section 4.1, each Founding Investor agrees to vote or act with respect to their Shares, Registrable Securities and designated members of the Board so as to authorize and approve the Buyout unless Exhibit D expressly allows a Founding Investor to withhold such vote or action. Each Party further agrees to assist the other Parties in every proper way to consummate the Buy-Out, effect the Buy-Out, including but not limited to executing and delivering such documents and performing such other acts as a Party may reasonably request in connection with effecting the Buy-Out.

4.3 Preservation of Intent. If any term, covenant or condition of this Section 4 or Exhibit D or the application thereof to any Party or circumstance, to any extent, is invalid or unenforceable, then (a) the remainder of this Section 4 and Exhibit D, or the application of such term, covenant or condition to Parties or circumstances other than those as to which it is invalid or unenforceable, will not be affected thereby and each term, covenant or condition of this Section 4 and Exhibit D will be valid and be enforced to the fullest extent permitted by law; and (b) the Parties hereto covenant and agree to renegotiate any such term, covenant or application thereof in good faith in order to provide a reasonably acceptable alternative to the term, covenant or condition of this Section 4 and Exhibit D or the application thereof that is invalid or unenforceable, it being the intent of the Parties that the basic purposes of this Section 4 and Exhibit D are to be effectuated.

4.4 Termination of Buy-Out. The provisions set forth in this Section 4 will expire and terminate upon the effective date of the registration statement pertaining to an Initial Offering.

SECTION 5. RIGHTS OF FIRST REFUSAL

5.1 Subsequent Offerings. Subject to applicable securities laws, each Founding Investor will have a right of first refusal to purchase its *pro rata* share of all Equity Securities, as defined below, that the Company may, from time to time, propose to sell and issue after the date of this Agreement, other than the Equity Securities excluded by Section 5.6 hereof. Each Founding Investor's *pro rata* share is equal to the ratio of (a) the number of shares of the Company's Common Stock (including all shares of Common Stock issuable or issued upon conversion of the Shares or upon the exercise of outstanding warrants or options) of which such Founding Investor is deemed to be a holder immediately prior to the issuance of such Equity Securities to (b) the total number of shares of the Company's outstanding Common Stock (including all shares of Common Stock issued or issuable upon conversion of the Shares or upon the exercise of any outstanding warrants or options) immediately prior to the issuance of the Equity Securities. The term "***Equity Securities***" will mean (i) any Common Stock, Preferred Stock or other security of the Company, (ii) any security convertible into or exercisable or exchangeable for, with or without consideration, any Common Stock, Preferred Stock, or other security (including any option to purchase such a convertible security), (iii) any security carrying any warrant or right to subscribe to or purchase any Common Stock, Preferred Stock or other security or (iv) any such warrant or right.

5.2 Exercise of Rights. If the Company proposes to issue any Equity Securities, it will give each Founding Investor written notice of its intention, describing the Equity Securities, the price and the terms and conditions upon which the Company proposes to issue the same. Each Founding Investor will have [***] ([***]) days from the giving of such notice to agree to purchase its *pro rata* share of the Equity Securities for the price and upon the terms and conditions specified in the notice by giving written notice to the Company and stating therein the quantity of Equity Securities to be purchased. Notwithstanding the foregoing, the Company will not be required to offer or sell such Equity Securities to any Founding Investor who would cause the Company to be in violation of applicable federal securities laws by virtue of such offer or sale.

5.3 Issuance of Equity Securities to Other Persons. The Company will have [***] ([***]) days thereafter to sell the Equity Securities in respect of which the Founding Investor's rights were not exercised, at a price not lower and upon general terms and conditions not materially more favorable to the purchasers thereof than specified in the Company's notice to the Founding Investors pursuant to Section 5.2 hereof. If the Company has not sold such Equity Securities within [***] ([***]) days of the notice provided pursuant to Section 5.2, the Company will not thereafter issue or sell any Equity Securities, without first offering such securities to the Founding Investors in the manner provided above.

5.4 Termination and Waiver of Rights of First Refusal. The rights of first refusal established by this Section 5 will not apply to, and will terminate upon the earlier of (i) the effective date of the registration statement pertaining to the Company's Initial Offering or (ii) an Acquisition. Notwithstanding Section 7.5 hereof, the rights of first refusal established by this Section 5 may be amended, or any provision waived with and only with the written consent of the Company and the Founding Investors holding a majority of the Registrable Securities held by all Founding Investors.

5.5 Assignment of Rights of First Refusal. The rights of first refusal of each Founding Investor under this Section 5 may be assigned to the same parties, subject to the same restrictions as any transfer of registration rights pursuant to Section 6.7.

5.6 Excluded Securities. The rights of first refusal established by this Section 5 will have no application to any of the following Equity Securities:

(a) shares of Common Stock and/or options, warrants or other Common Stock purchase rights and the Common Stock issued pursuant to such options, warrants or other rights issued to employees, officers or directors of, or consultants or advisors to, the Company or any subsidiary pursuant to stock purchase or stock option plans or other arrangements that are approved by the Board of Directors;

(b) stock issued or issuable pursuant to any rights or agreements, options, warrants or convertible securities outstanding as of the date of this Agreement; and stock issued pursuant to any such rights or agreements granted after the date of this Agreement, so long as the rights of first refusal established by this Section 5 were complied with, waived, or were inapplicable pursuant to any provision of this Section 5.6 with respect to the initial sale or grant by the Company of such rights or agreements;

(c) any Equity Securities issued for consideration other than cash pursuant to a merger, consolidation, acquisition or similar business combination approved by the Board of Directors;

(d) any Equity Securities issued in connection with any stock split, stock dividend or recapitalization by the Company;

(e) any Equity Securities issued pursuant to any equipment loan or leasing arrangement, real property leasing arrangement, or debt financing from a bank or similar financial or lending institution approved by the Board of Directors;

(f) any Equity Securities that are issued by the Company pursuant to a registration statement filed under the Securities Act;

(g) any Equity Securities that are issued by the Company in connection with any underwritten public offering;

(h) any Equity Securities issued in connection with strategic transactions involving the Company and other entities, including, without limitation (i) joint ventures, manufacturing, marketing or distribution arrangements or (ii) technology transfer or development arrangements; *provided* that the issuance of shares therein has been approved by the Company's Board of Directors; and

(i) Any Equity Securities issued to third-party service providers in exchange for or as partial consideration for services rendered to the Company.

SECTION 6. REGISTRATION RIGHTS; MARKET STAND-OFF.

6.1 Piggyback Registrations. The Company will notify all Holders of Registrable Securities in writing at least fifteen (15) days prior to the filing of any registration statement under the Securities Act for purposes of a public offering of securities of the Company (including, but not limited to, registration statements relating to secondary offerings of securities of the Company, but excluding Special Registration Statements) and will afford each such Holder an opportunity to include in such registration statement all or part of such Registrable Securities held by such Holder. Each Holder desiring to include in any such registration statement all or any part of the Registrable Securities held by it will, within fifteen (15) days after the above-described notice from the Company, so notify the Company in writing. Such notice will state the intended method of disposition of the Registrable Securities by such Holder. If a Holder decides not to include all of its Registrable Securities in any registration statement thereafter filed by the Company, such Holder will nevertheless continue to have the right to include any Registrable Securities in any subsequent registration statement or registration statements as may be filed by the Company with respect to offerings of its securities, all upon the terms and conditions set forth herein.

(a) Underwriting. If the registration statement of which the Company gives notice under this Section 6.3 is for an underwritten offering, the Company will so advise the Holders of Registrable Securities. In such event, the right of any such Holder to include Registrable Securities in a registration pursuant to this Section 6.3 will be conditioned upon such Holder's participation in such underwriting and the inclusion of such Holder's Registrable Securities in the underwriting to the extent provided herein. All Holders proposing to distribute their Registrable Securities through such underwriting will enter into an underwriting agreement in customary form with the underwriter or underwriters selected for such underwriting by the Company. Notwithstanding any other provision of this Agreement, if the underwriter determines in good faith that marketing factors require a limitation of the number of shares to be underwritten, the number of shares that may be included in the underwriting will be allocated, first, to the Company; and second, to the Holders on a *pro rata* basis based on the total number of Registrable Securities held by the Holders; provided, however, that such reduction will not be permitted unless such registration does not include shares of any other selling stockholders. If any Holder disapproves of the terms of any such underwriting, such Holder may elect to withdraw therefrom by written notice to the Company and the underwriter, delivered at least ten (10) business days prior to the effective date of the registration statement. Any Registrable Securities excluded or withdrawn from such underwriting will be excluded and withdrawn from the registration. For any Holder which is a partnership, limited liability company or corporation, the partners, retired partners, members, retired members and stockholders of such Holder, or the estates and family members of any such partners, retired partners, members and retired members and any trusts for the benefit of any of the foregoing persons will be deemed to be a single "Holder," and any *pro rata* reduction with respect to such "Holder" will be based upon the aggregate amount of shares carrying registration rights owned by all entities and individuals included in such "Holder," as defined in this sentence.

(b) Right to Terminate Registration. The Company will have the right to terminate or withdraw any registration initiated by it under this Section 6.1 whether or not any

Holder has elected to include securities in such registration. The Registration Expenses of such withdrawn registration will be borne by the Company in accordance with Section 6.3 hereof.

6.2 Form S-3 Registration. In case the Company receives from any Holder or Holders of Registrable Securities a written request or requests that the Company effect a registration on Form S-3 (or any successor to Form S-3) or any similar short-form registration statement and any related qualification or compliance with respect to all or a part of the Registrable Securities owned by such Holder or Holders, the Company will:

(a) promptly give written notice of the proposed registration, and any related qualification or compliance, to all other Holders of Registrable Securities; and

(b) as soon as practicable, effect such registration and all such qualifications and compliances as may be so requested and as would permit or facilitate the sale and distribution of all or such portion of such Holder's or Holders' Registrable Securities as are specified in such request, together with all or such portion of the Registrable Securities of any other Holder or Holders joining in such request as are specified in a written request given within fifteen (15) days after receipt of such written notice from the Company; *provided*, *however*, that the Company will not be obligated to effect any such registration, qualification or compliance pursuant to this Section 6.2:

(i) if Form S-3 is not available for such offering by the Holders;

(ii) if the Holders, together with the holders of any other securities of the Company entitled to inclusion in such registration, propose to sell Registrable Securities and such other securities (if any) at an aggregate price to the public of less than fifteen million dollars ($15,000,000);

(iii) if within thirty (30) days of receipt of a written request from any Holder or Holders pursuant to this Section 6.2, the Company gives notice to such Holder or Holders of the Company's intention to make a public offering within ninety (90) days, other than pursuant to a Special Registration Statement;

(iv) if the Company will furnish to the Holders a certificate signed by the Chairman of the Board of Directors of the Company stating that in the good faith judgment of the Board of Directors of the Company, it would be seriously detrimental to the Company and its stockholders for such Form S-3 registration to be effected at such time, in which event the Company will have the right to defer the filing of the Form S-3 registration statement for a period of not more than one hundred twenty (120) days after receipt of the request of the Holder or Holders under this Section 6.2; *provided*, that such right to delay a request will be exercised by the Company not more than twice in any twelve (12) month period;

(v) if the Company has, within the twelve (12) month period preceding the date of such request, already effected one (1) registration on Form S-3 for the Holders pursuant to this Section 6.2, or

(vi) in any particular jurisdiction in which the Company would be required to qualify to do business or to execute a general consent to service of process in effecting such registration, qualification or compliance.

(c) Subject to the foregoing, the Company will file a Form S-3 registration statement covering the Registrable Securities and other securities so requested to be registered as soon as practicable after receipt of the requests of the Holders.

6.3 Expenses of Registration. Except as specifically provided herein, all Registration Expenses incurred in connection with any registration, qualification or compliance pursuant to Section 6.1 or 6.2 herein will be borne by the Company. All Selling Expenses incurred in connection with any registrations hereunder, will be borne by the holders of the securities so registered *pro rata* on the basis of the number of shares so registered. The Company will not, however, be required to pay for expenses of any registration proceeding begun pursuant to Section 6.2, the request of which has been subsequently withdrawn by the Initiating Holders unless (a) the withdrawal is based upon material adverse information concerning the Company of which the Initiating Holders were not aware at the time of such request or (b) the Holders of a majority of Registrable Securities agree to deem such registration to have been effected as of the date of such withdrawal for purposes of determining whether the Company will be obligated pursuant to Section 6.2(b)(v), as applicable, to undertake any subsequent registration, in which event such right will be forfeited by all Holders). If the Holders are required to pay the Registration Expenses, such expenses will be borne by the holders of securities (including Registrable Securities) requesting such registration in proportion to the number of shares for which registration was requested. If the Company is required to pay the Registration Expenses of a withdrawn offering pursuant to clause (a) above, then such registration will not be deemed to have been effected for purposes of determining whether the Company will be obligated pursuant to Section 6.2(b)(v) to undertake any subsequent registration.

6.4 Obligations of the Company. Whenever required to effect the registration of any Registrable Securities, the Company will, as expeditiously as reasonably possible:

(a) prepare and file with the SEC a registration statement with respect to such Registrable Securities and use all commercially reasonable efforts to cause such registration statement to become effective, and, upon the request of the Holders of a majority of the Registrable Securities registered thereunder, keep such registration statement effective for up to thirty (30) days or, if earlier, until the Holders have completed the distribution related thereto; provided, however, that at any time, upon written notice to the participating Holders and for a period not to exceed sixty (60) days thereafter (the "Suspension Period"), the Company may delay the filing or effectiveness of any registration statement or suspend the use of any registration statement (and the Initiating Holders hereby agree not to offer or sell any Registrable Securities pursuant to such registration statement during the Suspension Period) if the Company reasonably believes that there is or may be in existence material nonpublic information or events involving the Company, the failure of which to be disclosed in the prospectus included in the registration statement could result in a Violation (as defined below). In the event that the Company will exercise its right to delay the filing or effectiveness or suspend the use of a registration hereunder, the applicable time period during which the

registration statement is to remain effective will be extended by a period of time equal to the duration of the Suspension Period. The Company may extend the Suspension Period for an additional consecutive sixty (60) days with the consent of the Holders of a majority of the Registrable Securities registered under the applicable registration statement, which consent will not be unreasonably withheld. If so directed by the Company, all Holders registering shares under such registration statement will (i) not offer to sell any Registrable Securities pursuant to the registration statement during the period in which the delay or suspension is in effect after receiving notice of such delay or suspension; and (ii) use their commercially reasonable efforts to deliver to the Company (at the Company's expense) all copies, other than permanent file copies then in such Holders' possession, of the prospectus relating to such Registrable Securities current at the time of receipt of such notice. Notwithstanding the foregoing, the Company will not be required to file, cause to become effective or maintain the effectiveness of any registration statement other than a registration statement on Form S-3 that contemplates a distribution of securities on a delayed or continuous basis pursuant to Rule 415 under the Securities Act.

(b) Prepare and file with the SEC such amendments and supplements to such registration statement and the prospectus used in connection with such registration statement as may be necessary to comply with the provisions of the Securities Act with respect to the disposition of all securities covered by such registration statement for the period set forth in subsection (a) above.

(c) Furnish to the Holders such number of copies of a prospectus, including a preliminary prospectus, in conformity with the requirements of the Securities Act, and such other documents as they may reasonably request in order to facilitate the disposition of Registrable Securities owned by them.

(d) Use its commercially reasonable efforts to register and qualify the securities covered by such registration statement under such other securities or Blue Sky laws of such jurisdictions as will be reasonably requested by the Holders; *provided* that the Company will not be required in connection therewith or as a condition thereto to qualify to do business or to file a general consent to service of process in any such states or jurisdictions.

(e) In the event of any underwritten public offering, enter into and perform its obligations under an underwriting agreement, in usual and customary form, with the managing underwriter(s) of such offering. Each Holder participating in such underwriting will also enter into and perform its obligations under such an agreement.

(f) Notify each Holder of Registrable Securities covered by such registration statement at any time when a prospectus relating thereto is required to be delivered under the Securities Act of the happening of any event as a result of which the prospectus included in such registration statement, as then in effect, includes an untrue statement of a material fact or omits to state a material fact required to be stated therein or necessary to make the statements therein not misleading in the light of the circumstances then existing. The Company will use commercially reasonable efforts to amend or supplement such prospectus in order to cause such prospectus not to include any untrue statement of a material fact or omit to

state a material fact required to be stated therein or necessary to make the statements therein not misleading in the light of the circumstances then existing.

(g) Use its commercially reasonable efforts to furnish, on the date that such Registrable Securities are delivered to the underwriters for sale, if such securities are being sold through underwriters, (i) an opinion, dated as of such date, of the counsel representing the Company for the purposes of such registration, in form and substance as is customarily given to underwriters in an underwritten public offering, addressed to the underwriters, if any, and (ii) a letter, dated as of such date, from the independent certified public accountants of the Company, in form and substance as is customarily given by independent certified public accountants to underwriters in an underwritten public offering addressed to the underwriters.

6.5 Delay of Registration; Furnishing Information.

(a) No Holder will have any right to obtain or seek an injunction restraining or otherwise delaying any such registration as the result of any controversy that might arise with respect to the interpretation or implementation of this Section 6.

(b) It will be a condition precedent to the obligations of the Company to take any action pursuant to Section 6.1 or 6.2 that the selling Holders will furnish to the Company such information regarding themselves, the Registrable Securities held by them and the intended method of disposition of such securities as will be required to effect the registration of their Registrable Securities.

(c) The Company will have no obligation with respect to any registration requested pursuant to Section 6.2 if the number of shares or the anticipated aggregate offering price of the Registrable Securities to be included in the registration does not equal or exceed the number of shares or the anticipated aggregate offering price required to originally trigger the Company's obligation to initiate such registration as specified in Section 6.2.

6.6 Indemnification. In the event any Registrable Securities are included in a registration statement under Section 6.1 or 6.2:

(a) To the extent permitted by law, the Company will indemnify and hold harmless each Holder, the partners, members, officers and directors of each Holder, as applicable, any underwriter (as defined in the Securities Act) for such Holder and each person, if any, who controls such Holder or underwriter within the meaning of the Securities Act or the Exchange Act, against any losses, claims, damages, or liabilities (joint or several) to which they may become subject under the Securities Act, the Exchange Act or other federal or state law, insofar as such losses, claims, damages or liabilities (or actions in respect thereof) arise out of or are based upon any of the following statements, omissions or violations (collectively a "***Violation***") by the Company: (i) any untrue statement or alleged untrue statement of a material fact contained in such registration statement or incorporated by reference therein, including any preliminary prospectus or final prospectus contained therein or any amendments or supplements thereto, (ii) the omission or alleged omission to state therein a material fact required to be stated therein, or necessary to make the statements therein not misleading, or

(iii) any violation or alleged violation by the Company of the Securities Act, the Exchange Act, any state securities law or any rule or regulation promulgated under the Securities Act, the Exchange Act or any state securities law in connection with the offering covered by such registration statement; and the Company will reimburse each such Holder, partner, member, officer, director, underwriter or controlling person for any legal or other expenses reasonably incurred by them in connection with investigating or defending any such loss, claim, damage, liability or action; *provided however*, that the indemnity agreement contained in this Section 6.6(a) will not apply to amounts paid in settlement of any such loss, claim, damage, liability or action if such settlement is effected without the consent of the Company, which consent will not be unreasonably withheld, nor will the Company be liable in any such case for any such loss, claim, damage, liability or action to the extent that it arises out of or is based upon a Violation which occurs in reliance upon and in conformity with written information furnished expressly for use in connection with such registration by such Holder, partner, member, officer, director, underwriter or controlling person of such Holder.

(b) To the extent permitted by law, each Holder will, if Registrable Securities held by such Holder are included in the securities as to which such registration qualifications or compliance is being effected, indemnify and hold harmless the Company, each of its directors, its officers and each person, if any, who controls the Company within the meaning of the Securities Act, any underwriter and any other Holder, as applicable, selling securities under such registration statement or any of such other Holder's partners, directors or officers or any person who controls such Holder, against any losses, claims, damages or liabilities (joint or several) to which the Company or any such director, officer, controlling person, underwriter or other such Holder, or partner, director, officer or controlling person of such other Holder may become subject under the Securities Act, the Exchange Act or other federal or state law, insofar as such losses, claims, damages or liabilities (or actions in respect thereto) arise out of or are based upon any of the following statements: (i) any untrue statement or alleged untrue statement of a material fact contained in such registration statement or incorporated reference therein, including any preliminary prospectus or final prospectus contained therein or any amendments or supplements thereto, (ii) the omission or alleged omission to state therein a material fact required to be stated therein, or necessary to make the statements therein not misleading, or (iii) any violation or alleged violation by the Company of the Securities Act (collectively, a "***Holder Violation***"), in each case to the extent (and only to the extent) that such Holder Violation occurs in reliance upon and in conformity with written information furnished by such Holder under an instrument duly executed by such Holder and stated to be specifically for use in connection with such registration; and each such Holder will reimburse any legal or other expenses reasonably incurred by the Company or any such director, officer, controlling person, underwriter or other Holder, or partner, officer, director or controlling person of such other Holder in connection with investigating or defending any such loss, claim, damage, liability or action if it is judicially determined that there was such a Holder Violation; *provided, however,* that the indemnity agreement contained in this Section 6.6(b) will not apply to amounts paid in settlement of any such loss, claim, damage, liability or action if such settlement is effected without the consent of the Holder, which consent will not be unreasonably withheld; *provided further*, that in no event will any indemnity under this Section 6.6 exceed the net proceeds from the offering received by such Holder, as applicable.

(c) Promptly after receipt by an indemnified party under this Section 6.6 of notice of the commencement of any action (including any governmental action), such indemnified party will, if a claim in respect thereof is to be made against any indemnifying party under this Section 6.6, deliver to the indemnifying party a written notice of the commencement thereof and the indemnifying party will have the right to participate in, and, to the extent the indemnifying party so desires, jointly with any other indemnifying party similarly noticed, to assume the defense thereof with counsel mutually satisfactory to the parties; *provided, however,* that an indemnified party will have the right to retain its own counsel, with the fees and expenses thereof to be paid by the indemnifying party, if representation of such indemnified party by the counsel retained by the indemnifying party would be inappropriate due to actual or potential differing interests between such indemnified party and any other party represented by such counsel in such proceeding. The failure to

deliver written notice to the indemnifying party within a reasonable time of the commencement of any such action will relieve such indemnifying party of any liability to the indemnified party under this Section 6.6 to the extent, and only to the extent, prejudicial to its ability to defend such action, but the omission so to deliver written notice to the indemnifying party will not relieve it of any liability that it may have to any indemnified party otherwise than under this Section 6.6.

(d) If the indemnification provided for in this Section 6.6 is held by a court of competent jurisdiction to be unavailable to an indemnified party with respect to any losses, claims, damages or liabilities referred to herein, the indemnifying party, in lieu of indemnifying such indemnified party thereunder, will to the extent permitted by applicable law contribute to the amount paid or payable by such indemnified party as a result of such loss, claim, damage or liability in such proportion as is appropriate to reflect the relative fault of the indemnifying party on the one hand and of the indemnified party on the other in connection with the Violation(s) or Holder Violation(s) that resulted in such loss, claim, damage or liability, as well as any other relevant equitable considerations. The relative fault of the indemnifying party and of the indemnified party will be determined by a court of law by reference to, among other things, whether the untrue or alleged untrue statement of a material fact or the omission to state a material fact relates to information supplied by the indemnifying party or by the indemnified party and the parties' relative intent, knowledge, access to information and opportunity to correct or prevent such statement or omission; *provided*, *that* in no event will any contribution by a Holder, as applicable, hereunder exceed the net proceeds from the offering received by such Holder, as applicable.

(e) The obligations of the Company and Holders under this Section 6.6 will survive completion of any offering of Registrable Securities, as applicable, in a registration statement and, with respect to liability arising from an offering to which this Section 6.6 would apply that is covered by a registration filed before termination of this Agreement, such termination. No indemnifying party, in the defense of any such claim or litigation, will, except with the consent of each indemnified party, consent to entry of any judgment or enter into any settlement which does not include as an unconditional term thereof the giving by the claimant or plaintiff to such Indemnified Party of a release from all liability in respect to such claim or litigation.

6.7 Assignment of Registration Rights. The rights to cause the Company to register Registrable Securities pursuant to this Section 6 may be assigned by a Holder to a transferee or assignee of Registrable Securities (for so long as such shares remain Registrable Securities) that (a) is a subsidiary, parent, general partner, limited partner, retired partner, member or retired member, stockholder or other affiliate of a Holder that is a corporation, partnership or limited liability company, (b) acquires all of such Holders Registrable Securities in connection with the sale of all or substantially all of such Holder's business, or (c) acquires at least two hundred thousand (200,000) shares of Registrable Securities (as adjusted for stock splits and combinations); or (d) is an entity affiliated by common control (or other related entity) with such Holder *provided, however,* (i) the transferor will, within ten (10) days after such transfer, furnish to the Company written notice of the name and address of such transferee or assignee and the securities with respect to which such registration rights are being assigned and (ii) such transferee will agree to be subject to all restrictions set forth in this Agreement.

6.8 Limitation on Subsequent Registration Rights. Other than as provided in Section 5.10, after the date of this Agreement, the Company will not enter into any agreement with any holder or prospective holder of any securities of the Company that would grant such holder rights to demand the registration of shares of the Company's capital stock, or to include such shares in a registration statement that would reduce the number of shares includable by the Holders.

6.9 "Market Stand-Off" Agreement. Each Holder hereby agrees that such Holder, as the case may be, will not sell, transfer, make any short sale of, grant any option for the purchase of, or enter into any hedging or similar transaction with the same economic effect as a sale, any Common Stock (or other securities) of the Company held by such Holder (other than those included in the registration) during (i) the 180-day period following the effective date of the Initial Offering (or such longer period, not to exceed 34 days after the expiration of the 180-day period, as the underwriters or the Company will request in order to facilitate compliance with NASD Rule 2711 or NYSE Member Rule 472 or any successor rule), and (ii) the 90-day period following the effective date of a registration statement of the Company filed under the Securities Act (or such longer period, not to exceed 18 days after the expiration of the 90-day period, as the underwriters or the Company will request in order to facilitate compliance with NASD Rule 2711); *provided*, that, with respect to (i) and (ii) above, all officers, directors of the Company and all entities who hold Common Stock (or Securities Convertible into Common Stock) in an amount that is greater than 1% of the Company's then issued and outstanding Common Stock are bound by and have entered into similar agreements. The obligations described in this Section 6.9 will not apply to a Special Registration Statement.

6.10 Agreement to Furnish Information. Each Holder hereby agrees to execute and deliver such other agreements as may be reasonably requested by the Company or the underwriter that are consistent with such Holder's obligations under Section 6.9, as applicable, or that are necessary to give further effect thereto. In addition, if requested by the Company or the representative of the underwriters of Common Stock (or other securities) of the Company, each Holder will provide, within ten (10) days of such request, such information as may be required by the Company or such representative in connection with the completion of any public offering of the Company's securities pursuant to a registration statement filed under the Securities Act. The obligations described in Section 6.9 and this Section 6.10 will not apply to a Special

Registration Statement. The Company may impose stop-transfer instructions with respect to the shares of Common Stock (or other securities) subject to the foregoing restriction until the end of said day period. Each Holder agrees that any transferee of any shares of Registrable Securities will be bound by Sections 6.9 and 6.10. The underwriters of the Company's stock are intended third party beneficiaries of Sections 6.9 and 6.10 and will have the right, power and authority to enforce the provisions hereof as though they were a party hereto.

6.11 Rule 144 Reporting. With a view to making available to the Holders, as applicable, the benefits of certain rules and regulations of the SEC which may permit the sale of the Registrable Securities to the public without registration, the Company agrees to use its best efforts to:

(a) Make and keep public information available, as those terms are understood and defined in SEC Rule 144 or any similar or analogous rule promulgated under the Securities Act, at all times after the effective date of the first registration filed by the Company for an offering of its securities to the general public;

(b) File with the SEC, in a timely manner, all reports and other documents required of the Company under the Exchange Act; and

(c) So long as a Holder owns any Registrable Securities, as applicable, furnish to such Holder forthwith upon request: a written statement by the Company as to its compliance with the reporting requirements of said Rule 144 of the Securities Act, and of the Exchange Act (at any time after it has become subject to such reporting requirements); a copy of the most recent annual or quarterly report of the Company filed with the Commission; and such other reports and documents as a Holder may reasonably request in connection with availing itself of any rule or regulation of the SEC allowing it to sell any such securities without registration.

6.12 Termination of Registration Rights. The right of any Holder to request registration or inclusion of Registrable Securities in any registration pursuant to Sections 6.1 or 6.2 hereof will terminate upon the earlier of: (i) the date three (3) years following an Initial Offering; or (ii) following the Initial Offering, such time as all Registrable Securities issuable or issued upon conversion of the Shares held by and issuable to such Holder (and its affiliates) may be sold pursuant to Rule 144 during any ninety (90) day period. Upon such termination, such shares will cease to be "Registrable Securities" hereunder for all purposes.

SECTION 7. MISCELLANEOUS.

7.1 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.

7.2 Successors and Assigns. Except as otherwise expressly provided herein, the provisions hereof will inure to the benefit of, and be binding upon, the parties hereto and their respective successors, assigns, heirs, executors, and administrators and will inure to the benefit of and be enforceable by each person who will be a holder of Registrable Securities from time to time; *provided*, *however*, that prior to the receipt by the Company of adequate written notice of

the transfer of any Registrable Securities specifying the full name and address of the transferee, the Company may deem and treat the person listed as the holder of such shares in its records as the absolute owner and holder of such shares for all purposes, including the payment of dividends or any redemption price.

7.3 Entire Agreement. This Agreement, together with the Ancillary Agreements, including the exhibits and schedules hereto and thereto, constitutes the entire agreement among the Founding Investors 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 Founding Investors, and the termination or cancellation of any such other agreement or contract will have no effect on this Agreement or any Ancillary Agreement.

7.4 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.

7.5 Amendment and Waiver.

(a) Except as otherwise expressly provided, this Agreement may be amended or modified, and the obligations of the Company and the rights of the Holders under this Agreement may be waived, only upon the written consent of (i) the Company, and (ii) a 2/3 majority of shares held by the Founding Investors.

(b) For the purposes of determining the number of Holders or Founding Investors entitled to vote or exercise any rights hereunder, the Company will be entitled to rely solely on the list of record holders of its stock as maintained by or on behalf of the Company.

7.6 Delays or Omissions. It is agreed that no delay or omission to exercise any right, power, or remedy accruing to any party, upon any breach, default or noncompliance by another party under this Agreement will impair any such right, power, or remedy, nor will it be construed to be a waiver of any such breach, default or noncompliance, or any acquiescence therein, or of any similar breach, default or noncompliance thereafter occurring. It is further agreed that any waiver, permit, consent, or approval of any kind or character on any party's part of any breach, default or noncompliance under the Agreement or any waiver on such party's part of any provisions or conditions of this Agreement must be in writing and will be effective only to the extent specifically set forth in such writing. All remedies, either under this Agreement, by law, or otherwise afforded to any party, will be cumulative and not alternative.

7.7 Notices. 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.

7.8 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. If any action at law or in equity is necessary to enforce or interpret the terms of any of this Agreement, 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 7.8, "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.

7.9 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 Securities Act or to any 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.

7.10 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, 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.

7.11 Aggregation of Stock. All shares of Registrable Securities held or acquired by affiliated entities or persons or persons or entities under common management or control will be aggregated together for the purpose of determining the availability of any rights under this Agreement.

7.12 Specific Performance. The failure of any party to this Agreement to perform its agreements and covenants hereunder, including but not limited to Section 4, 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 7.12 is without prejudice to any other rights that the Founding Investors and the Company hereto may have for any failure to perform this Agreement.

7.13 Termination. This Agreement will terminate and be of no further force or effect upon the earlier of (i) a Liquidation Event, Acquisition or Asset Transfer; or (ii) the date three (3) years following the Closing of the Initial Offering that results in the conversion of all outstanding shares of Preferred Stock.

[THIS SPACE INTENTIONALLY LEFT BLANK]

IN WITNESS WHEREOF, the parties hereto have executed this **FOUNDING INVESTOR RIGHTS AGREEMENT** as of the date set forth in the first paragraph hereof.

COMPANY:

REGULUS THERAPEUTICS INC.

By: /s/ Kleanthis G. Xanthopoulos

FOUNDING INVESTORS:

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall

ALNYLAM PHARMACEUTICALS, INC.

By: /s/ Barry Greene

EXHIBIT A

DEFINITONS

1.1 ***"Ancillary Agreements"*** means the License Agreement and the Services Agreement each as amended from time to time.

1.2 ***"Change of Control"*** means, with respect to a Founding Investor (the "Affected Founding Investor"), the earlier of (x) the public announcement of and (y) the closing of: (a) a merger, reorganization or consolidation involving the Affected Founding Investor 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 Founding Investor's assets or business relating to this Agreement. Any Founding Investor will notify each other Founding Investor within two (2) Business Days of entering into an agreement which, if consummated, would result in a Change of Control.

1.3 ***"Common Stock"*** means the Common Stock of the Company.

1.4 ***"Exchange Act"*** means the Securities Exchange Act of 1934, as amended.

1.5 ***"Form S-3"*** means such form under the Securities Act as in effect on the date hereof or any successor or similar registration form under the Securities Act subsequently adopted by the SEC which permits inclusion or incorporation of substantial information by reference to other documents filed by the Company with the SEC.

1.6 ***"Holder"*** means any person owning of record Registrable Securities that have not been sold to the public or any assignee of record of such Registrable Securities in accordance with Section 6.7 hereof.

1.7 ***"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 Founding Investor designating such Director, or (ii) an officer or employee of, or immediate family member of any officer or employee of, the Company.

1.8 ***"Initial Offering"*** means the Company's first firm commitment underwritten public offering of its Common Stock registered under the Securities Act.

1.9 ***"License Agreement"*** means that certain Amended and Restated License and Collaboration Agreement by and among the Company, Alnylam and Isis dated January 1, 2008, as amended from time to time.

1.10 ***"Person"*** means a natural person, company, corporation, partnership, trust or other organization or legal entity of any type, whether or not formally organized.

1.11 ***"Register," "registered,"*** and ***"registration"*** refer to a registration effected by preparing and filing a registration statement in compliance with the Securities Act, and the declaration or ordering of effectiveness of such registration statement or document.

1.12 ***"Registrable Securities"*** means (a) Common Stock issuable or issued upon conversion of the Shares and (b) any Common Stock issued as (or issuable upon the conversion or exercise of any warrant, right or other security which is issued as) a dividend or other distribution with respect to, or in exchange for or in replacement of, such above-described securities. Notwithstanding the foregoing, Registrable Securities will not include any securities (i) sold by a person to the public either pursuant to a registration statement or Rule 144, (ii) sold in a private transaction in which the transferor's rights under Section 6 of this Agreement are not assigned or (iii) eligible for resale pursuant to Rule 144 without volume limitations.

1.13 ***"Registrable Securities then outstanding"*** will be the number of shares of Common Stock that are Registrable Securities and either (a) are then issued and outstanding or (b) are issuable pursuant to then exercisable or convertible securities.

1.14 ***"Registration Expenses"*** will mean all expenses incurred by the Company in complying with Sections 6.1 or 6.2, including, without limitation, all registration and filing fees, printing expenses, fees and disbursements of counsel for the Company, reasonable fees and disbursements not to exceed ten thousand dollars ($10,000) of a single special counsel for the Holders, if applicable, blue sky fees and expenses and the expense of any special audits incident to or required by any such registration (but excluding the compensation of regular employees of the Company which will be paid in any event by the Company).

1.15 ***"SEC"*** or ***"Commission"*** means the Securities and Exchange Commission.

1.16 ***"Securities Act"*** will mean the Securities Act of 1933, as amended.

1.17 ***"Selling Expenses"*** will mean all underwriting discounts and selling commissions applicable to the sale.

1.18 ***"Shares"*** will mean the Company's Preferred Stock issued pursuant to the Purchase Agreement held from time to time by the Founding Investors and their permitted assigns.

1.19 ***"Special Registration Statement"*** will mean (i) a registration statement relating to any employee benefit plan or (ii) with respect to any corporate reorganization or transaction under Rule 145 of the Securities Act, any registration statements related to the issuance or resale of securities issued in such a transaction or (iii) a registration related to stock issued upon conversion of debt securities.

EXHIBIT B

INITIAL DIRECTORS AND INITIAL SAB MEMBERS

Board of Directors:

Name	Title
Kleanthis G. Xanthopoulos, Ph.D.	President, Regulus Therapeutics LLC
David Baltimore, Ph.D.	Independent Director nominated by Alnylam
Stelios Papadopoulos, Ph.D.	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

SAB Members:

Name	Title
David Baltimore, Ph.D.	Member and Chairperson
David Bartel, Ph.D.	Member
Scott Hammond, Ph.D.	Member
Markus Stoffel, M.D., Ph.D.	Member
Thomas Tuschl, Ph.D.	Member
Philip Zamore, Ph.D.	Member

EXHIBIT C

OPERATING PLAN

[***]

EXHIBIT D

TERMS OF BUY-OUT

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

1.1 Negotiated Resolution. Following the Company's receipt of the Buy-Out Notice, the Founding Investors will take all actions necessary to cause the sale of the Company to a Third Party or a Founding Investor (whether through merger, acquisition of 100% of the Equity Securities or purchase of all or substantially all of the assets of the Company) (a ***"Sale"***). The Company promptly thereafter will retain a reputable investment bank chosen by mutual agreement (such agreement not to be unreasonably withheld, conditioned or delayed) of the Founding Investors and the Company (the ***"Investment Banker"***) to assist with the valuation and possible Sale of the Company; *provided, however*, that in the event that due to then-current market conditions a Sale would be impractical because it would be reasonably like to result in proceeds from such Sale to either Founding Investor that are substantially below such Founding Investor's cost basis in its investment in the Company, as determined based on the written advice of the Investment Banker (***"Poor Market Conditions"***), then the Founding Investors will mutually determine whether notwithstanding such market conditions to attempt to Sell the Company to a Third Party or a Founding Investor; *and, provided, further however*, that, notwithstanding anything in this Exhibit D or Section 4.2 to the contrary, neither Founding Investor 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 Founding Investors and the Company, which will be documented in a separate written agreement among the parties (a ***"Sale Agreement"***).

1.2 Non-Negotiated Resolution.

(a) If (i) Poor Market Conditions exist and the Founding Investors do not determine pursuant to Section 1.1 to attempt a Sale of the Company, or (ii) the Founding Investors have not within [***] ([***]) days after the Company's receipt of the Buy-Out Notice, or such longer period as mutually agreed to by the Founding Investors (such period, the "Buy-Out Negotiation Period"), executed a Sale Agreement, the Company will, except as otherwise set forth in this Section 1.2, distribute and assign to the Founding Investors, or their designated Affiliate, jointly, in accordance with Pro Rata Share, all of the Company's rights, interests and assets, other than any contracts and/or arrangements between the Company and Third Parties that the 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 1.2 will apply. For purposes of this Exhibit D, ***"Pro Rata Share"*** means, with respect to each Investor at any particular moment, the ratio of (a) the number of shares of the Company's Common Stock (not including any shares of Common Stock issuable or issued upon conversion of the Shares or upon the exercise of outstanding warrants or options) of which such Investor is deemed to be a holder immediately prior to the moment in question to (b) the total number of shares of the Company's outstanding

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Common Stock (not including any shares of Common Stock issued or issuable upon conversion of the Shares or upon the exercise of any outstanding warrants or options) immediately prior to the moment in question.

(b) Distribution of Intellectual Property.

(i) Upon the distribution of the Company's assets pursuant to this Section 1.2, each Founding Investor 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 Founding Investor has obtained a license in connection with an Opt-In Election or obtains a license pursuant to Section 1.2(d) or 1.2(e), the licenses to the Distributed IP under this Section 1.2(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 1.2(d) or 1.2(e); and (z) to the extent that a Founding Investor has obtained a license in connection with Section 2.3 of the License Agreement, the licenses to the Distributed IP under this Section 1.2(b) will be subject to such license granted to such Founding Investor. For purposes of this Section 1.2(b)(i), "co-exclusive" means that such license is exercisable by each Founding Investor or its designated Affiliate, and that the Company retains no rights to exercise any such licensed Intellectual Property.

(ii) The rights granted to each Founding Investor in this Section 1.2(b) will be (1) royalty-bearing, as set forth in Section 1.2(b)(iii) below, and (2) sublicenseable solely (A) to such Founding Investor's Affiliates or (B) by such Founding Investor 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 Exhibit D, and will provide that any such sublicensee will not further sublicense except on terms consistent with this clause; (y) such Founding Investor 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 Exhibit D and (z) in the event of a material default by any of its sublicensees under a sublicense agreement, such Founding Investor will inform the Company and the other Founding Investor and will take such action, after consultation with such other parties, which, in such Founding Investor's reasonable business judgment, will address such default.

(iii) Each Founding Investor will, to the extent it, its Affiliates and/or Sublicensees develop a Royalty-Bearing Product under Intellectual Property distributed from the Company to the Founding Investor pursuant to this Section 1.2(b) that does not become subject to Section 1.2(d) or 1.2(e): (x) pay to the other Founding Investor (or its designated Affiliate) a royalty of [***]% on Net Sales of such Royalty-Bearing Products sold by the selling Founding Investor, 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

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other payments payable to Third Parties in respect of the exercise of such license by such selling Founding Investor, its Affiliates and/or Sublicensees, including without limitation any amounts payable by either Founding Investor or the Company to its Third Party licensors with respect to the license and sublicense granted to such Founding Investor pursuant to this Section 1.2(b). The royalty-paying Founding Investor will use Commercially Reasonable Efforts to benefit from offsets to the amounts payable to such Founding Investor's Third Party licensors.

(c) Retained Assets and Rights. Following the distribution of the Company's assets pursuant to this Section 1.2, the Company will not maintain any interest in or right to any assets of the Company, including Intellectual Property, except to the extent the Board determines is necessary to maintain Third Party Contracts or its obligations to Opt-In Parties or Founding Investors 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 1.2.

(d) Research Program Selection and Transfer.

(i) Within [***] ([***]) Business Days following the distribution of the Company's assets in accordance with Section 1.2(a) and (b), the non-Initiating Founding Investor will submit a bid, consisting [***] (***"First Selection Right Bid"***), to the Initiating Founding Investor to obtain the first right to select a Research Program from the most recent Program/Project List with respect to which such Founding Investor desires to acquire exclusive rights; *provided, however*, that in the event the non-Initiating Founding Investor does not submit such a bid with [***] ([***]) Business Days, the Initiating Founding Investor may assume the rights of the non-Initiating Founding Investor set forth in this Section 1.2(d) with respect to the First Selection Right Bid. The Initiating Founding Investor will have [***] ([***]) Business Days to notify the non-Initiating Founding Investor of its acceptance or rejection of such First Selection Right Bid.

(ii) If the Initiating Founding Investor accepts such First Selection Right Bid,

(1) The non-Initiating Founding Investor will have the right, upon payment to the Initiating Founding Investor of the [***] set forth in the First Selection Right Bid (which [***] 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 Founding Investor will obtain the license set forth in clause (vi) below under Intellectual Property directed to such Selected Program; and.

(2) Each of the Founding Investors, starting with the Initiating Founding Investor, will then take turns selecting (by written notice within [***] ([***]) Business Days following the last selection by the other Founding Investor) a Research Program (other than the Selected Program), until all Research Programs on the Program/Project List have been selected by the Founding Investors (and each such selected Research Program is a "Selected Program" hereunder), and each Founding Investor will obtain the rights set forth in clause (vi) below under Intellectual Property directed to the Research Program selected by such Founding Investor.

(iii) If the Initiating Founding Investor rejects such First Selection Right Bid, such Founding Investor will submit to the non-Initiating Founding Investor, 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 Founding Investor will have [***] ([***]) Business Days to accept or reject such counterbid.

(iv) If the non-Initiating Founding Investor accepts such counterbid, the Initiating Founding Investor will have the right, upon payment to the non-Initiating Founding Investor 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 Founding Investor will obtain from the non-Initiating Founding Investor the rights set forth in clause (vi) below with respect to the Research Program selected by such Founding Investor.

(v) If the non-Initiating Founding Investor rejects such counterbid, then such non-Initiating Founding Investor will submit, concurrently with such notice of rejection, its counterbid to the Initiating Founding Investor's counterbid, which counterbid must be higher than the Initiating Founding Investor'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 Founding Investor will grant to the other Founding Investor 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 Founding Investor 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 1.2(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 Exhibit D, and will provide that any such Sublicensee will not further sublicense except on terms consistent with this clause; (y) such Founding Investor 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 Exhibit D and (z) in the event of a material default by any of its Sublicensees under a sublicense agreement, such Founding Investor will inform the Company and the other Founding Investor and will take such action, after consultation with such other Parties, which, in such Founding Investor's reasonable business judgment, will address such default.

(viii) Each Founding Investor selecting a Selected Program will (1) pay to the other Founding Investor (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

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Third Parties in respect of the exercise of such license by such selling Founding Investor, its Affiliates and/or Sublicensees, including without limitation any amounts payable by either Founding Investor or the Company to its Third Party licensors with respect to the licenses granted to such Founding Investor pursuant to Section 1.2(a). The royalty-paying Founding Investor will use Commercially Reasonable Efforts to benefit from offsets to the amounts payable to such Founding Investor's Third Party licensors.

(ix) Each Founding Investor will assign or exclusively license to the other Founding Investor, to the fullest extent possible, all of its rights and obligations in assets, other than Intellectual Property, distributed by the Company to the Founding Investors pursuant to Section 1.2(a), to the extent such assets are solely related to any of the other Founding Investor's Selected Programs. In the event any such assets are related to Selected Programs of both Founding Investors, each Founding Investors will assign to or exclusively license the other, to the fullest extent possible, the rights to such assets as they relate to the other Founding Investor'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 1.2(a), the non-Initiating Party (the ***"Bidding Party"***) will have the right to submit to the other Founding Investor a bid, which need not be limited to a [***] (***"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 1.2(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

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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 Founding Investor to which a counterbid is submitted determines in good faith that the terms of such counterbid are not more favorable to such Founding Investor, taken as a whole, than the terms offered in such Founding Investor's most-recent prior bid, by at least [***]% (as measured by industry standards), then at any time within the [***] ([***]) day period during which such Founding Investor may accept or reject such counterbid, such Founding Investor (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 Founding Investors. If the Founding Investors 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 Board) will select a Qualified Third Party within [***] ([***]) Business Days after the end of such initial [***] ([***]) Business Day period and will promptly notify the Founding Investors of the Qualified Third Party selected. The Founding Investors 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 Founding Investors within [***] ([***]) Business Days following submission of such dispute to such Qualified Third Party. Such Qualified Third Party's determination will be binding on the Founding Investors. 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 Founding Investor against whom the Qualified Third Party finds will bear the costs of such Qualified Third Party.

(vi) Each Founding Investor will grant to the other Founding Investor 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 Founding Investor 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,

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and consistent with, the terms and conditions of this Exhibit D, and will provide that any such Sublicensee will not further sublicense except on terms consistent with this clause; (2) such Founding Investor 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 Exhibit D and (3) in the event of a material default by any of its Sublicensees under a sublicense agreement, such Founding Investor will inform the Company and the other Founding Investor and will take such action, after consultation with such other Parties, which, in such Founding Investor's reasonable business judgment, will address such default.

(viii) Each Founding Investor will assign or exclusively license to the other Founding Investor, to the fullest extent possible, all of its rights and obligations in assets, other than Intellectual Property, distributed by the Company to the Founding Investors pursuant to Section 1.2(a) to the extent such assets are solely related to any of the other Founding Investor's Selected Development Projects. In the event any such assets are related to Development Programs of both Founding Investors, each Founding Investor will assign to the other, to the fullest extent possible, the rights to such assets as they relate to the other Founding Investor'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 1.2, the Company will not be dissolved if, in the discretion of the 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 1.2, 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 Founding Investor 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 Founding Investor under this Section 1.2, at such Founding Investor'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

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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.

1.3 Section 365(n) of the Bankruptcy Code. All rights and licenses granted under this Exhibit D and Section 4 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.

EXHIBIT E

FINANCIAL REQUIREMENT FOR EQUITY ACCOUNTING

Once Regulus is no longer consolidated into Isis' financials and is not using Isis' financial systems, then Regulus may hire its own auditors subject to the requirements below that are necessary to ensure that Isis and Alnylam receive in a timely manner the information each needs to record its share of Regulus' income/losses.

1. Regulus' auditors will be an independent registered public accounting firm of recognized national standing.

2. Regulus will provide Isis and Alnylam the audited annual financial statements of Regulus no later than [***] ([***]) weeks after the end of each fiscal year, including the related notes thereto. The financial statements include the following:

    a. A balance sheet of Regulus as of the close of such fiscal year.
    b. A statement of net income for such fiscal year.
    c. A statement of cash flows for such fiscal year.
    d. The related notes thereto.
    e. These financial statements will contain in comparative form the figures for the previous fiscal year.
    f. An opinion of Regulus' auditors that the above financial statements present fairly, in all material respects, the financial position of Regulus and its results of operations and cash flows. Also, that the financial statements have been prepared in conformity with GAAP and that the audit by Regulus' auditors has been made in accordance with generally accepted auditing standards and that audit provides a reasonable basis for the auditors' opinion.

3. Regulus will provide Isis and Alnylam an unaudited balance sheet of Regulus as of the end of each quarter and unaudited statements of income and cash flows of Regulus for such quarter and for the current fiscal year to the end of such fiscal quarter within [***] ([***]) calendar days after the end of each fiscal quarter of Regulus, including the related notes thereto.

    a. The financial statements will be those outlined in 2(a) — (f) above.
    b. These financial statements will be reviewed by Regulus' auditors, which review will be complete prior to Regulus providing the above financial statements to Isis and Alnylam.
    c. These financial statements will include a certificate signed by the CEO and CFO of Regulus stating that these financial statements were prepared in conformity with GAAP from the books and records of Regulus and that there were no changes in the internal control environment of Regulus that would materially affect the integrity of these statements.

4. Regulus will provide Isis and Alnylam with an unaudited balance sheet of Regulus as of the end of each month and unaudited statements of income and of cash flows of Regulus for such month and for the current fiscal year to the end of such month promptly following Regulus' completion of the review of its financial statements for such month (other than the last month of any fiscal quarter).

a. The financial statements will be those outlined in 2(a) — (f) above, excluding 2(d).

5. The financial statements referred to above will be accompanied by the report thereon of the independent accountants engaged by Regulus as described in 2(f) above. Additionally, Regulus will provide to Isis and/or Alnylam any supplemental schedules reasonably required by either company, and Regulus will make its management available to Isis and/or Alnylam for reasonable inquiries regarding its financials.

6. Regulus will provide Isis and Alnylam with any certificate that may be reasonably necessary to meet Isis' and Alnylam's SOX 404 requirements.

7. If Isis' and/or Alnylam's filing requirements change, all three companies together will review the timing outlined above. If filing requirements for either Isis or Alnylam are accelerated, Regulus agrees to provide the information in #2 and #3 above on the timeline that Isis and/or Alnylam reasonably determines is necessary to meet its filing requirements.

An extra section break has been inserted above this paragraph. Do not delete this section break if you plan to add text after the Table of Contents/Authorities. Deleting this break will cause Table of Contents/Authorities headers and footers to appear on any pages following the Table of Contents/Authorities.

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: May 7, 2009

/s/ Stanley T. Crooke

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

EXHIBIT 31.2

CERTIFICATION

I, B. Lynne Parshall, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: May 7, 2009

/s/ B. Lynne Parshall

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

Exhibit 32.1

CERTIFICATION

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

1. The Company's Quarterly Report on Form 10-Q for the period ended March 31, 2009, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: May 7, 2009

/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.