UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended June 30, 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 August 3, 2009 was 98,330,836

ISIS PHARMACEUTICALS, INC.
FORM 10-Q

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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)

	June 30, 2009 (Unaudited)	December 31, 2008 (1)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 215,789	$ 217,918
Short-term investments	421,722	273,080
Contracts receivable	783	4,121
Inventories	2,779	2,718
Other current assets	6,439	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	647,512	518,384
Property, plant and equipment, net	26,636	17,371

Licenses, net	15,714	16,861
Patents, net	15,709	16,260
Deposits and other assets	3,590	3,900
Total assets	$ 709,161	$ 572,776
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 6,659	$ 5,710
Accrued compensation	4,460	6,835
Income taxes payable	23,233	—
Accrued liabilities	8,422	9,557
Current portion of long-term obligations	2,995	2,065
Current portion of deferred contract revenue	82,092	92,662
Liabilities from discontinued operations	—	7,870
Total current liabilities	127,861	124,699
2 5/8% convertible subordinated notes	121,464	117,993
Long-term obligations, less current portion	10,643	9,938
Long-term deferred contract revenue	143,376	172,766
Total liabilities	403,344	425,396
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 98,158,360 and 97,172,380 shares issued and outstanding at June 30, 2009 and December 31, 2008, respectively	98	97
Additional paid-in capital	972,697	960,361
Accumulated other comprehensive income	2,324	982
Accumulated deficit	(682,268)	(851,216)
Total Isis Pharmaceuticals, Inc. stockholders' equity	292,851	110,224
Noncontrolling interest in Regulus Therapeutics Inc.	12,966	4,737
Noncontrolling interest in Ibis Biosciences, Inc. — discontinued operations	—	32,419
Total stockholders' equity	305,817	147,380
Total liabilities and stockholders' equity	$ 709,161	$ 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 June 30,		Six Months Ended June 30,	
	2009	2008 (1)	2009	2008 (1)
Revenue:				
Research and development revenue under collaborative agreements	$ 30,768	$ 23,556	$ 60,453	$ 41,262
Licensing and royalty revenue	224	6,147	2,115	6,815
Total revenue	30,992	29,703	62,568	48,077
Expenses:				
Research and development	32,146	25,288	60,688	47,071
General and administrative	3,673	3,334	7,350	6,165
Total operating expenses	35,819	28,622	68,038	53,236
Income (loss) from operations	(4,827)	1,081	(5,470)	(5,159)
Other income (expense):				
Investment income	1,678	2,302	3,812	5,336
Interest expense	(3,155)	(2,920)	(6,236)	(5,818)
Gain on investments	2,612	—	2,671	—
Income (loss) from continuing operations, before income tax benefit (expense)	(3,692)	463	(5,223)	(5,641)
Income tax benefit (expense)	(61)	—	656	—
Net income (loss) from continuing operations, net of income tax benefit (expense)	(3,753)	463	(4,567)	(5,641)

Discontinued operations:				
Loss from discontinued operations	—	(5,165)	(29)	(5,729)
Gain on sale of Ibis Biosciences, Inc., net of tax	—	—	171,773	—
Net income (loss) from discontinued operations, net of tax	—	(5,165)	171,744	(5,729)
Net income (loss)	(3,753)	(4,702)	167,177	(11,370)
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	857	965	1,771	1,848
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (2,896)	$ (3,737)	$ 168,948	$ (9,522)
Basic net income (loss) per share:				
Net income (loss) from continuing operations	$ (0.03)	$ 0.02	$ (0.03)	$ (0.04)
Net income (loss) from discontinued operations	—	(0.06)	1.76	(0.06)
Basic net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.03)	$ (0.04)	$ 1.73	$ (0.10)
Shares used in computing basic net income (loss) per share	98,116	94,675	97,820	92,737
Diluted net income (loss) per share:				
Net income (loss) from continuing operations	$ (0.03)	$ 0.02	$ 0.02	$ (0.04)
Net income (loss) from discontinued operations	—	(0.06)	1.54	(0.06)
Diluted net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.03)	$ (0.04)	$ 1.56	$ (0.10)
Shares used in computing diluted net income (loss) per share	98,116	94,675	111,608	92,737

(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)

	Six Months Ended June 30,	
	2009	2008
Net cash (used in) provided by operating activities	$ (44,716)	$ 252,756
Investing activities:		
Purchases of short-term investments	(406,873)	(129,033)
Proceeds from the sale of short-term investments	258,424	92,728
Purchases of property, plant and equipment	(10,215)	(4,209)
Acquisition of licenses and other assets	(1,481)	(1,253)
Purchases of strategic investments	(349)	—
Proceeds from the sale of strategic investments	2,848	—
Net cash used in investing activities	(157,646)	(41,767)
Financing activities:		
Net proceeds from issuance of equity	7,627	4,724
Proceeds from equipment financing arrangement	2,705	—
Proceeds from issuance of convertible promissory note to GSK	—	5,000
Principal payments on debt and capital lease obligations	(1,166)	(3,569)
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	40,000
Proceeds from Alnylam's capital contribution to Regulus Therapeutics Inc.	10,000	—
Net cash provided by financing activities	194,166	96,117
Net (decrease) increase in cash and cash equivalents	(8,196)	307,106
Cash and cash equivalents at beginning of period	223,985	138,614
Cash and cash equivalents at end of period	$ 215,789	$ 445,720
Supplemental disclosures of cash flow information:		
Interest paid	$ 2,396	$ 2,308
Income taxes paid	$ 6,805	$ —
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 914	$ 1,467

See accompanying notes.

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ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
June 30, 2009
(Unaudited)

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three and six month periods ended June 30, 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 6, *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") and 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 condensed 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.

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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 consider all liquid investments with maturities of ninety days or less when purchased to be cash equivalents. Our short-term investments have initial maturities of greater than ninety days from date of purchase. We classify our securities as "available-for-sale" in accordance with SFAS 115, *Accounting for Certain Investments in Debt and Equity Securities.* We carry our available-for-sale securities at fair market value based upon prices for identical or similar items on the last day of the fiscal period. We record unrealized gains and losses as a separate component of stockholders' equity and include net realized gains and losses in gain on investments. We use the specific identification method to determine the cost of securities sold.

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 first half of 2009 and 2008. During the second quarter of 2009, we sold all of the common stock of OncoGenex Pharmaceuticals Inc. that we owned resulting in a realized gain of $2.5 million.

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 half of 2009 and 2008. Total inventory, which consisted of raw materials, was $2.8 million and $2.7 million as of June 30, 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 half of 2009 and 2008, we recorded a non-cash charge of $351,000 and $644,000, 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;
- GlaxoSmithKline convertible promissory note;
- Dilutive stock options; and
- Warrants issued to Symphony GenIsis Holdings LLC

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

As we incurred a loss for the three months ended June 30, 2009, 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 June 30, 2009			
Basic and diluted net loss per share:			
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (2,896)		
Net income (loss) from discontinued operations	—		
Total basic and diluted net loss	$ (2,896)	98,116	$ (0.03)

	Numerator: Net Income (Loss)	Denominator: Shares	Amount
For the six months ended June 30, 2009			
Basic net income per share:			
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (2,796)		
Net income from discontinued operations, net of taxes	171,744		
Total basic net income	$ 168,948	97,820	$ 1.73
Diluted net income per share:			
Dilutive stock options	—	2,322	
$2^5/_8$% convertible subordinated notes, net of tax	4,776	11,111	
GSK convertible promissory note, net of tax	25	170	
Warrants issued to Symphony GenIsis Holdings LLC	—	185	
Net income from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders plus assumed conversions	2,005		
Net income from discontinued operations, net of taxes	171,744		
Total diluted net income	$ 173,749	111,608	$ 1.56
Potentially dilutive securities not included above since they are anti-dilutive:			
Anti-dilutive stock options		4,148	

As we incurred a loss for the three and six months ended June 30, 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 June 30, 2008			
Basic and diluted net loss per share:			
Net income from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ 1,428		
Net loss from discontinued operations	(5,165)		
Total basic and diluted net loss	$ (3,737)	94,675	$ (0.04)

For the six months ended June 30, 2008			
Basic and diluted net loss per share:			
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (3,793)		
Net loss from discontinued operations	(5,729)		
Total basic and diluted net loss	$ (9,522)	92,737	$ (0.10)

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 June 30, 2009, we had collaborative arrangements with eight entities that we consider to be variable interest entities under FIN 46R. For the six months ended June 30, 2009, our condensed consolidated financial statements include one variable interest entity, Regulus, for which we were the primary beneficiary. For the six months ended June 30, 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.

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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 six months ended June 30, 2009 (in thousands):

	Isis Pharmaceuticals, Inc. Stockholders' Equity					Noncontrolling Interests		
	Common stock		Additional paid in capital	Accumulated other comprehensive income	Accumulated deficit	Regulus	Ibis	Total stockholders' equity
Description	**Shares**	**Amount**						
Balance at December 31, 2008	97,172	$ 97	$ 960,361	$ 982	$ (851,216)	$ 4,737	$ 32,419	$ 147,380
Comprehensive income:								
Net income (loss)	—	—	—	—	168,948	(1,771)	—	167,177
Change in unrealized gains	—	—	—	2,990	—	—	—	2,990
Reclassification adjustment for realized gains included in net income	—	—	—	(1,648)	—	—	—	(1,648)
Comprehensive income	—	—	—	—	—	—	—	168,519
Options exercised and employee stock purchase plan issuances	986	1	7,626	—	—	—	—	7,627
Share-based compensation expense	—	—	4,710	—	—	—	—	4,710
Sale of Ibis to AMI	—	—	—	—	—	—	(32,419)	(32,419)
Alnylam's capital contribution to noncontrolling interest	—	—	—	—	—	10,000	—	10,000
Balance at June 30, 2009	98,158	$ 98	$ 972,697	$ 2,324	$ (682,268)	$ 12,966	$ —	$ 305,817

The following table presents the statement of changes in stockholders' equity in conformity with the requirements of SFAS 160 for the six months ended June 30, 2008 (in thousands):

	Isis Pharmaceuticals, Inc. Stockholders' Equity					Noncontrolling Interests		
	Common stock		Additional paid in capital	Accumulated other comprehensive income	Accumulated deficit	Regulus	Ibis	Total stockholders' equity
Description	**Shares**	**Amount**						
Balance at December 31, 2007	87,239	$ 87	$ 882,633	$ 538	$ (833,044)	$ 9,371	$ —	$ 59,585
Comprehensive loss:								
Net loss	—	—	—	—	(9,522)	(1,848)	(896)	(12,266)
Change in unrealized gains	—	—	—	2,192	—	—	—	2,192
Comprehensive loss	—	—	—	—	—	—	—	(10,074)
Options exercised and employee stock purchase plan issuances	627	—	4,725	—	—	—	—	4,725
Warrants exercised	2,580	3	(3)	—	—	—	—	—
Share-based compensation expense	—	—	7,765	—	—	—	—	7,765
Issuance of common stock to Genzyme	5,000	5	49,956	—	—	—	—	49,961
AMI's capital contribution to noncontrolling interest	—	—	—	—	—	—	34,521	34,521
Balance at June 30, 2008	95,446	$ 95	$ 945,076	$ 2,730	$ (842,566)	$ 7,523	$ 33,625	$ 146,483

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 expense 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 6, *Long-Term Obligations*.

Subsequent Events

In May 2009, the Financial Accounting Standards Board ("FASB") issued SFAS 165, *Subsequent Events*. This statement establishes general standards of accounting for and disclosure of events that occur after the balance sheet date but before an entity issues its financial statements. This statement is effective for interim or annual periods ending after June 15, 2009. We adopted SFAS 165 for the quarter ending June 30, 2009. Although the adoption of SFAS 165 did not impact our financial condition, results of operations, or cash flow, SFAS 165 requires us to provide the date through which we have evaluated subsequent events, as well as whether that date is the date we issued our financial statements or the date our financial statements were available for us to issue. We have evaluated subsequent events occurring through August 6, 2009, which represents the date we issued our financial statements.

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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 employee 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 six months ended June 30, 2009 and 2008, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Six Months Ended June 30,	
	2009	2008
Risk-free interest rate	1.8%	3.1%
Dividend yield	0.0%	0.0%
Volatility	56.9%	55.0%
Expected Life	4.9 years	4.6 years

ESPP:

	Six Months Ended June 30,	
	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

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 and six months ended June 30, 2009 and 2008 (in thousands, except per share data) was allocated as follows:

	Three Months Ended June 30,		Six Months Ended June 30	
	2009	2008	2009	2008
Research and development	$ 2,879	$ 2,866	$ 5,138	$ 5,582
General and administrative	686	674	1,130	1,241
Non-cash compensation expense related to stock options included in continuing operations	3,565	3,540	6,268	6,823
Non-cash compensation expense (benefit) related to stock options included in discontinued operations	—	466	(1,558)	942
Total	$ 3,565	$ 4,006	$ 4,710	$ 7,765
Basic stock-based compensation expense, per share:				
Net loss per share included in continuing operations	$ (0.04)	$ (0.04)	$ (0.06)	$ (0.07)
Net income per share included in discontinued operations	—	—	0.01	(0.01)
Total	$ (0.04)	$ (0.04)	$ (0.05)	$ (0.08)
Diluted stock-based compensation expense, per share:				
Net loss per share included in continuing operations	$ (0.04)	$ (0.04)	$ (0.06)	$ (0.07)
Net income per share included in discontinued operations	—	—	0.02	(0.01)
Total	$ (0.04)	$ (0.04)	$ (0.04)	$ (0.08)

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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. The seconded employees of Isis 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 and all options issued by Alnylam. Regulus records the expenses associated with these options on its books.

As of June 30, 2009, total unrecognized compensation cost related to Isis' and Regulus' non-vested stock-based compensation plans was $15.7 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 1.4 years.

Impact of recently issued accounting standards

In June 2009, the FASB issued SFAS 167, *Amendments to FASB Intepretation No. 46(R)*. This Statement amends Interpretation 46(R) to replace the quantitative-based risks and rewards calculation for determining which enterprise, if any, has a controlling financial interest in a variable interest entity with an approach focused on identifying which enterprise has the power to direct the activities of a variable interest entity that most significantly impact the

entity's economic performance and (1) the obligation to absorb losses of the entity or (2) the right to receive benefits from the entity. This statement is effective for interim and annual periods that begin after November 15, 2009, and will be effective for our fiscal year 2010. We are currently evaluating the impact of adopting SFAS 167 on our results of operations and financial position.

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 for the first half 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):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2009	2008	2009	2008
Revenue	$ —	$ 3,258	$ —	$ 6,237
Total operating expenses	—	7,472	35	13,041
Loss from operations	—	(4,214)	(35)	(6,804)
Other income, net	—	(1,742)	—	179
Loss attributed to noncontrolling interest in Ibis Biosciences, Inc.	—	791	6	896
Loss from discontinued operations	—	(5,165)	(29)	(5,729)
Gain on sale of Ibis Biosciences, Inc., net of tax	—	—	171,773	—
Net income (loss) from discontinued operations, net of tax	$ —	$ (5,165)	$ 171,744	$ (5,729)

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At December 31, 2008, we had the following assets and liabilities classified 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. Investments

In April 2009, the FASB issued FSP FAS 115-2 and FAS 124-2 ("FSP FAS 115-2/124-2"), *Recognition and Presentation of Other-Than-Temporary Impairments.* FSP FAS 115-2/124-2 provides additional guidance designed to create greater clarity and consistency in accounting for and presenting other-than-temporary impairments on debt securities. We adopted FSP FAS 115-2/124-2 for the quarter ending June 30, 2009. Although the adoption of FSP FAS 115-2/124-2 did not impact our financial condition, results of operations, or cash flow, FSP FAS 115-2/124-2 requires us to provide the following annual disclosures required by SFAS 115, *Accounting for Certain Investments in Debt and Equity Securities*, on a quarterly basis.

As of June 30, 2009, our excess cash is primarily invested in commercial paper and debt instruments with strong credit ratings of financial institutions, corporations, U.S. government agencies and the U.S. Treasury. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

The following table summarizes the contract maturity of the available-for-sale securities we held as of June 30, 2009:

One year or less	83%
After one year but within five years	17%
Total	100%

We have an ownership interest of less than 20% in each of five private companies and two public companies with which we conduct business. The companies are Antisense Therapeutics Limited and iCo Therapeutics Inc., which are publicly-traded, and Santaris Pharma A/S, formerly Pantheco A/S, Achaogen, Inc., Atlantic Pharmaceuticals Limited, Altair Therapeutics Inc. and Excaliard Pharmaceuticals, Inc., which are privately-held. We account for

securities in the privately-held companies under the cost method of accounting according to APB 18. During the second quarter of 2009, we sold all of the common stock of OncoGenex that we owned resulting in a realized gain of $2.5 million.

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The following is a summary of our investments (in thousands):

June 30, 2009	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value
Short-term investments:				
Corporate debt securities	$ 127,766	$ 333	$ (146)	$ 127,953
Debt securities issued by U.S. government agencies	152,676	476	(9)	153,143
Debt securities issued by the U.S. Treasury	69,861	55	—	69,916
Debt securities issued by states of the United States and political subdivisions of the states	275	—	—	275
Total securities with a maturity of one year or less	350,578	864	(155)	351,287
Corporate debt securities	21,826	127	(120)	21,833
Debt securities issued by U.S. government agencies	43,442	76	(20)	43,498
Debt securities issued by U.S. Treasury	5,094	10	—	5,104
Total securities with a maturity of more than one year	70,362	213	(140)	70,435
Subtotal	$ 420,940	$ 1,077	$ (295)	$ 421,722
Equity securities:				
Current portion	$ 1,229	$ 1,542	$ —	$ 2,771
Long-term portion	625	—	—	625
Subtotal	$ 1,854	$ 1,542	$ —	$ 3,396
	$ 422,794	$ 2,619	$ (295)	$ 425,118

December 31, 2008	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Short-term investments:					
Corporate debt securities	$ 111,569	$ 150	$ (307)	$ —	$ 111,412
Debt securities issued by U.S. government agencies	111,112	838	(19)	—	111,931
Debt securities issued by the U.S. Treasury	12,939	44	—	—	12,983
Debt securities issued by states of the United States and political subdivisions of the states	275	—	—	—	275
Total securities with a maturity of one year or less	235,895	1,032	(326)	—	236,601
Corporate debt securities	13,608	5	(371)	—	13,242
Debt securities issued by U.S. government agencies	23,199	56	(18)	—	23,237
Total securities with a maturity of more than one year	36,807	61	(389)	—	36,479
Subtotal	$ 272,702	$ 1,093	$ (715)	$ —	$ 273,080
Equity securities:					
Current portion	$ 2,380	$ 604	$ —	$ (1,163)	$ 1,821
Long-term portion	625	—	—	—	625
Subtotal	$ 3,005	$ 604	$ —	$ (1,163)	$ 2,446
	$ 275,707	$ 1,697	$ (715)	$ (1,163)	$ 275,526

Investments we consider to be temporarily impaired at June 30, 2009 are as follows (in thousands):

		Less than 12 months of temporary impairment	
	Number of Investments	Estimated Fair Value	Unrealized Losses
Corporate debt securities	16	$ 48,860	$ (266)
Debt securities issued by U.S. government agencies	6	20,113	(28)
Debt securities issued by states of the United States and political subdivisions of the states	1	275	(1)
Total temporarily impaired securities	23	$ 69,248	$ (295)

We believe that the decline in value of these securities is temporary and primarily related to the change in market interest rates since purchase. We intend to hold these securities to maturity and anticipate full recovery of amortized cost with respect to these securities at maturity.

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5. 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.

In April 2009, the FASB issued 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.* FSP FAS 157-4 provides guidelines for making fair value measurements more consistent with the principles presented in SFAS 157. We adopted FSP FAS 157-4 for the quarter ending June 30, 2009. Although the adoption of FSP FAS 157-4 did not impact our financial condition, results of operations, or cash flow, FSP FAS 157-4 requires us to provide additional disclosures as part of our financial statements.

In accordance with SFAS 157, we measure our assets that SFAS 157 requires us to measure at fair value on a recurring basis using the inputs below. In addition, we disclose the following major security types as required under FSP FAS 157-4 at June 30, 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 (1)	$ 176,680	$ 176,680	$ —	$ —
Corporate debt securities (1)	149,786	—	149,786	—
Debt securities issued by U.S. government agencies (1)	196,641	—	196,641	
Debt securities issued by the U.S. Treasury (1)	75,020	75,020	—	—
Debt securities issued by states of the United States and political subdivisions of the states (1)	275	—	275	—
Equity securities (2)	2,771	2,771	—	—
Total	$ 601,173	$ 254,471	$ 346,702	$ —

(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.

6. 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 June 30, 2009 and December 31, 2008, the principal and accrued interest payable on the notes was $162.5 million and $1.6 million, respectively. For the six months ended June 30, 2009, we included 11.1 million shares of our common stock in the computation of diluted net income per share for the conversion of the 2⅝% notes. We did not include any shares in the diluted net loss per share calculation for the three months ended June 30, 2009 and the three and six months ended June 30, 2008 because the effect would have been anti-dilutive.

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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 accounting 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 2⅝% notes was 9.3%. As a result, we retrospectively adjusted the carrying value of the 2⅝% 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 three and six months ended June 30, 2008 to reflect our nonconvertible debt borrowing rate as follows (in thousands):

	As Originally	As	Effect of Change	Effect of Change

	Reported	Adjusted		per share (Basic and Diluted)
Interest expense:				
Three months ended June 30, 2008	$ 1,391	$ 2,920	$ 1,529	$ 0.02
Six months ended June 30, 2008	$ 2,788	$ 5,818	$ 3,030	$ 0.03

As a result of adopting FSP 14-1, interest expense for the three months ended June 30, 2009 includes $1.7 million, or $0.02 for basic and diluted per share, of non-cash interest expense related to the amortization of the debt discount and $3.3 million, or $0.03 for basic and diluted per share for the six months ended June 30, 2009.

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 June 30, 2009 and December 31, 2008 was $8.0 million and $6.5 million, respectively.

7. 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.

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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 half 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 first half of 2009. As a result we recorded an income tax benefit of $656,000 for the first half of 2009.

At June 30, 2009, our balance sheet includes an income tax payable of $23.2 million. In the second half of 2009, as our loss from continuing operations increases, we will record an income tax benefit using the calculation above. The income tax benefit we record 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 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.

8. 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.

Technology Development Satellite Company Collaborations

Alnylam Pharmaceuticals, Inc.

In April 2009, we and Alnylam amended our strategic collaboration and license agreement to form 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 amended collaboration and license agreement, Alnylam paid us an upfront license fee of $11 million, which we are amortizing over the three year period of our performance obligation based on the research plan included in the agreement. Alnylam will also pay us up to $20 million in additional license fees, which Alnylam will pay 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 is funding research activities at a minimum of $3 million each year for three years with research and 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 could potentially receive milestones, totaling up to $18.5 million per product, together with royalty payments. Also, initially we are eligible to receive up to 50 percent of any sublicense payments due to Alnylam based on Alnylam's 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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Our Condensed Consolidated Balance Sheets at June 30, 2009 included deferred revenue of $10.4 million related to our agreement with Alnylam and none at December 31, 2008. During the three and six months ended June 30, 2009, we generated revenue from our relationship with Alnylam totaling $1.3 million and $2.3 million, respectively, compared to $4.6 million for the same periods in 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 increased by the $10 million Alnylam contributed.

9. 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):

	Drug Discovery and Development	Regulus	Total
Three Months Ended June 30, 2009			
Revenue:			
Research and development	$ 29,643	$ 1,125	$ 30,768
Licensing and royalty	224	—	224
Total segment revenue	$ 29,867	$ 1,125	$ 30,992
Loss from operations	$ (3,127)	$ (1,700)	$ (4,827)
Three Months Ended June 30, 2008			
Revenue:			
Research and development	$ 22,900	$ 656	$ 23,556
Licensing and royalty	6,147	—	6,147

Total segment revenue	$ 29,047	$ 656	$ 29,703
Income (loss) from operations	$ 2,948	$ (1,867)	$ 1,081

	Drug Discovery and Development	Regulus	Total
Six Months Ended June 30, 2009			
Revenue:			
Research and development	$ 58,690	$ 1,763	$ 60,453
Licensing and royalty	2,115	—	2,115
Total segment revenue	$ 60,805	$ 1,763	$ 62,568
Loss from operations	$ (1,906)	$ (3,564)	$ (5,470)
Total assets as of June 30, 2009	$ 681,651	$ 27,510	$ 709,161
Six Months Ended June 30, 2008			
Revenue:			
Research and development	$ 40,514	$ 748	$ 41,262
Licensing and royalty	6,815	—	6,815
Total segment revenue	$ 47,329	$ 748	$ 48,077
Loss from operations	$ (1,857)	$ (3,302)	$ (5,159)
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.

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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 June 30,		Six Months Ended June 30,	
	2009	2008	2009	2008
Partner A	54%	29%	53%	31%
Partner B	22%	30%	22%	35%
Partner C	7%	14%	7%	13%
Partner D	4%	16%	4%	10%

Contract receivables from three significant partners comprised approximately 38%, 19% and 18% of contract receivables at June 30, 2009. Contract receivables from three significant partners comprised approximately 25%, 18% and 14% of contract receivables at December 31, 2008.

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 31 of this Report.

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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 Bristol-Myers Squibb Company, or BMS, Genzyme, Eli Lilly and Company and Ortho-McNeil-Janssen Pharmaceuticals, Inc., or 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 Corp. 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 $346 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. Since 2007, 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.

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.

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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. When AMI completed the acquisition of Ibis, 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 half 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 reported positive top-line mipomersen Phase 3 data in patients with homozygous FH. The study met its primary endpoint, with a 25% reduction in LDL-C after 26 weeks of treatment, vs. 3% for placebo ($p<0.001$). The study also met each of its three secondary endpoints of reduction in apoB, total cholesterol and non-HDL-C.

- Genzyme continues to refine its regulatory strategy for mipomersen. 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.
- We and Genzyme completed enrollment in a Phase 3 study in heterozygous FH patients with coronary artery disease.

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

- We initiated a Phase 1 clinical study of ISIS-SGLT2Rx 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.
- OncoGenex reported results of a randomized Phase 2 trial of OGX-011 in patients with advanced prostate cancer showing a median survival in patients treated with OGX-011 plus docetaxel of 23.8 months compared to 16.9 months for patients treated with docetaxel alone.
- Altair reported a Phase 1 study that showed AIR645 was safe and well tolerated.
- Excaliard initiated a Phase 1 clinical study of EXC 001 for the local treatment of fibrosis.
- OncoGenex reported that OGX-427 was well tolerated as a monotherapy in a Phase 1 study and demonstrated declines in circulating tumor cells and evidence of reduction in tumor markers.
- Lilly recently completed its Phase 1 study of LY2181308 and presented data confirming that LY2181308 penetrates tumor tissue and reduces survivin mRNA and protein levels in tumor cells.

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.
- We were awarded a grant from the Michael J. Fox Foundation's Therapeutic Development Initiative program for the discovery and development of an antisense drug for the treatment of Parkinson's Disease.

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- 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.

We and our collaborators highlighted new antisense therapeutic programs and targets to treat metabolic diseases, including obesity, at the American Diabetes Association (ADA) scientific sessions.

- We presented new preclinical data on ISIS-SGLT2$_{Rx}$ showing robust and sustained reduction in SGLT2 levels that resulted in a significant reduction in blood glucose levels in multiple animal species.
- We and our collaborators presented data on a number of other promising new diabetes and anti-obesity targets demonstrating that reducing levels of these targets with antisense drugs can significantly lower blood glucose levels, increase the body's sensitivity to insulin, and reduce fat mass and body weight in animals.

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 RNA-based technologies and develop drugs that incorporate our technology 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 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.
- We earned milestone payments from Archemix because Archemix advanced drugs that incorporate our technology.

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.
- Regulus achieved its first milestone in its inflammatory disease collaboration with GSK.

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;

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- Determination of the proper valuation of investments in marketable securities and other equity investments;
- Estimations to assess the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determination of the proper valuation of inventory;
- Determination of the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimation of our net deferred income tax asset valuation allowance;
- Determination of the appropriateness of judgments and estimates used in allocating revenue and expenses to operating segments; and
- Estimations to determine the fair value of stock-based compensation, including the expected life of the option, the expected stock price volatility over the term of the expected life and estimated forfeitures.

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 expense 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 6, *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 and six months ended June 30, 2009 was $31.0 million and $62.6 million, respectively, compared to $29.7 million and $48.1 million for the same periods 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 three and six months ended June 30, 2008 only included one month of amortization of the $175 million license fee.

Our satellite companies also contributed to the increase in our revenue,

- Regulus earned revenue from its strategic alliance with GSK, including a $500,000 discovery milestone payment.
- We entered into a license agreement with Alnylam, which provided an $11 million license fee plus research funding. We began amortizing the license fee into revenue over the three year collaboration term in the second quarter.
- We received a $375,000 milestone payment from Alnylam for initiation of clinical trials on ALN-VSP.
- We earned $1.4 million of revenue when we sold drug to OncoGenex.

Collaborations with Alnylam, BMS, Genzyme, OMJP 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.

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Our revenue fluctuates based on the nature and timing of payments under agreements with our partners, including license fees, milestone-related payments and other payments, such as the bulleted items above. Assuming no new transactions, our revenue will decrease when the $50 million upfront payment we received from OMJP in 2007 is fully amortized in the third quarter of this year.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2009	2008	2009	2008
Drug Discovery and Development:				
Research and development revenue	$ 29,643	$ 22,900	$ 58,690	$ 40,514
Licensing and royalty revenue	224	6,147	2,115	6,815
	$ 29,867	$ 29,047	$ 60,805	$ 47,329
Regulus Therapeutics:				
Research and development revenue	$ 1,125	$ 656	$ 1,763	$ 748
	$ 1,125	$ 656	$ 1,763	$ 748
Total Revenue:				
Research and development revenue	$ 30,768	$ 23,556	$ 60,453	$ 41,262
Licensing and royalty revenue	224	6,147	2,115	6,815
	$ 30,992	$ 29,703	$ 62,568	$ 48,077

Drug Discovery & Development

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the three and six months ended June 30, 2009 was $29.6 million and $58.7 million, respectively, compared to $22.9 million and $40.5 million for the same periods 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 and six months ended June 30, 2009 was $224,000 and $2.1 million, respectively, compared to $6.1 million and $6.8 million for the same periods in 2008. Revenue was higher in 2008 primarily due to the $4.6 million and $1.4 million of sublicensing revenue we earned from Alnylam and ATL, respectively, in the second quarter of 2008 offset, in part, by 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 three and six months ended June 30, 2009 was $1.1 million and $1.8 million, respectively, compared to $656,000 and $748,000 for the same periods in 2008. The increase was primarily related to the $500,000 discovery milestone payment that Regulus received from its collaboration with GSK for demonstrating a pharmacological effect in immune cells by specific microRNA inhibition. 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 three and six months ended June 30, 2009 were $35.8 million and $68.0 million, respectively, compared to $28.6 million and $53.2 million for the same periods 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 broad Phase 3 clinical program for mipomersen, the lead drug in our cardiovascular franchise, expenses for Regulus as it builds its core team and expenses related to the expansion of our drug discovery activities into new therapeutic areas.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2009	2008	2009	2008
Drug Discovery and Development	$ 32,994	$ 26,099	$ 62,711	$ 49,186
Regulus Therapeutics	2,825	2,523	5,327	4,050
Total operating expenses	$ 35,819	$ 28,622	$ 68,038	$ 53,236

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.

Research and Development Expenses

Our research and development 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 June 30,		Six Months Ended June 30,	
	2009	2008	2009	2008
Research and development expenses	$ 29,267	$ 22,422	$ 55,550	$ 41,489
Non-cash compensation expense related to stock options	2,879	2,866	5,138	5,582
Total research and development expenses	$ 32,146	$ 25,288	$ 60,688	$ 47,071

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2009	2008	2009	2008
Drug Discovery and Development	$ 29,932	$ 23,682	$ 56,630	$ 44,153
Regulus Therapeutics	2,214	1,606	4,058	2,918
Total research and development expenses	$ 32,146	$ 25,288	$ 60,688	$ 47,071

For the three and six months ended June 30, 2009, we incurred total research and development expenses of $29.3 million and $55.6 million, respectively, compared to $22.4 million and $41.5 million for the same periods in 2008, all amounts excluding non-cash compensation expense related to stock options. We attribute the increase in expenses to the expansion of our clinical development programs, including additional expenses associated with the broad Phase 3 clinical program for mipomersen, the lead drug in our cardiovascular franchise, expenses for Regulus as it builds its core team and expenses related to the expansion of our drug discovery activities into new therapeutic areas. 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 our research and development activities described above.

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.

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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 June 30,		Six Months Ended June 30,	
	2009	2008	2009	2008
Antisense drug discovery	$ 6,009	$ 4,519	$ 11,398	$ 8,725
Non-cash compensation expense related to stock options	812	593	1,510	1,183
Total antisense drug discovery	$ 6,821	$ 5,112	$ 12,908	$ 9,908

Antisense drug discovery costs for the three and six months ended June 30, 2009 were $6.0 million and $11.4 million, respectively, compared to $4.5 million and $8.7 million for the same periods in 2008, all amounts excluding non-cash compensation expense related to stock options. The higher expenses in the first half of 2009 compared to the first half 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.

Antisense Drug Development

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

	Three Months Ended June 30,	Six Months Ended June 30,

	2009	2008	2009	2008
Mipomersen	$ 5,532	$ 3,070	$ 10,289	$ 6,581
Other antisense development products	3,814	4,035	8,278	6,790
Development overhead costs	1,151	840	2,447	1,747
Non-cash compensation expense related to stock options	939	860	1,768	1,778
Total antisense drug development	$ 11,436	$ 8,805	$ 22,782	$ 16,896

Antisense drug development expenditures were $10.5 million and $21.0 million for the three and six months ended June 30, 2009 compared to $7.9 million and $15.1 million for the same periods in 2008, all 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 other cardiovascular development projects. Development overhead costs were $1.2 million and $2.4 million for the three and six months ended June 30, 2009, compared to $840,000 and $1.7 million for the same periods 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.

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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 June 30,		Six Months Ended June 30,	
	2009	2008	2009	2008
Manufacturing and operations	$ 3,806	$ 2,825	$ 6,611	$ 5,432
Non-cash compensation expense related to stock options	374	306	699	566
Total manufacturing and operations	$ 4,180	$ 3,131	$ 7,310	$ 5,998

Manufacturing and operations expenses for the three and six months ended June 30, 2009 were $3.8 million and $6.6 million, respectively, compared to $2.8 million and $5.4 million for the same periods in 2008, all amounts excluding non-cash compensation expense related to stock options. The increase in expenses was primarily a result of an increase in personnel costs and lab expenses to support our expanded clinical development programs including our broad Phase 3 program for mimpomersen.

R&D Support

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

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2009	2008	2009	2008
Personnel costs	$ 1,930	$ 1,395	$ 3,898	$ 2,867
Occupancy	1,705	1,596	3,327	3,098
Depreciation and amortization	2,410	1,564	3,631	2,684
Insurance	233	206	457	452
Other	748	1,298	1,421	1,036
Non-cash compensation expense related to stock options	795	574	1,515	1,215
Total R&D support costs	$ 7,821	$ 6,633	$ 14,249	$ 11,352

R&D support costs for the three and six months ended June 30, 2009 were $7.0 million and $12.7 million, respectively, compared to $6.1 million and $10.1 million for the same periods in 2008, all amounts excluding non-cash compensation expense related to stock options. The increase was primarily a result of $750,000 we received from Ercole Biotech, Inc. in March 2008 as repayment of a convertible note that we had previously expensed, an increase in personnel costs and an increase in depreciation relating to upgrades made to our manufacturing facility which was completed in the second quarter of 2009.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2009	2008	2009	2008
Drug Discovery and Development	$ 7,494	$ 6,633	$ 13,629	$ 11,352
Regulus Therapeutics	327	—	620	—
Total R&D support costs	$ 7,821	$ 6,633	$ 14,249	$ 11,352

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.

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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 June 30,		Six Months Ended June 30,	
	2009	2008	2009	2008
General and administrative expenses	$ 2,987	$ 2,660	$ 6,220	$ 4,924
Non-cash compensation expense related to stock options	686	674	1,130	1,241
Total general and administrative expenses	$ 3,673	$ 3,334	$ 7,350	$ 6,165

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2009	2008	2009	2008
Drug Discovery and Development	$ 3,062	$ 2,417	$ 6,080	$ 5,033
Regulus Therapeutics	611	917	1,270	1,132
Total general and administrative expenses	$ 3,673	$ 3,334	$ 7,350	$ 6,165

General and administrative expenses for the three and six months ended June 30, 2009 were $3.0 million and $6.2 million, respectively, compared to $2.7 million and $4.9 million for the same periods in 2008, all amounts excluding non-cash compensation expense related to stock options. The increase was primarily a result of costs associated with our Bruker Daltonics Inc. litigation and the increase in Regulus' general and administrative expenses in 2009. For further information on the Bruker Daltonics litigation, see the Legal Proceedings section below. 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 June 30,		Six Months Ended June 30,	
	2009	2008	2009	2008
Research and development expenses	$ 2,256	$ 1,073	$ 4,411	$ 2,078
General and administrative expenses	480	662	1,137	739
Non-cash compensation expense/(benefit) related to stock options	89	788	(221)	1,233
Total Regulus' operating expenses	$ 2,825	$ 2,523	$ 5,327	$ 4,050

Operating expenses for Regulus were $2.7 million and $5.5 million for the three and six months ended June 30, 2009 compared to $1.7 million and $2.8 million for the same periods in 2008, all 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 and six months ended June 30, 2009 totaled $1.7 million and $3.8 million, respectively, compared to $2.3 million and $5.3 million for the same periods in 2008. The decrease in investment income was primarily due to the lower average returns on our investments resulting from the current market conditions offset by significantly higher average cash balances.

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Interest Expense

Interest expense for the three and six months ended June 30, 2009 was $3.2 million and $6.2 million, respectively, and was slightly higher compared to $2.9 million and $5.8 million for the same periods in 2008. In 2009, we adopted a new accounting standard, FSP 14-1, related to our 2 ⅝% convertible notes. As a result of adopting FSP 14-1, the amount of interest expense we recorded in our statement of operations for the three and six months ended June 30, 2009 increased by $1.7 million and $3.3 million, respectively, compared to an increase of $1.5 million and $3.0 million for the same periods in 2008. For additional information about FSP 14-1, see *Note 5, Long-Term Obligations*, in the Notes to the Condensed Consolidated Financial Statements.

Gain on Investments

Gain on investments for the three and six months ended June 30, 2009 was $2.6 million and $2.7 million, respectively, primarily reflecting the gain we realized on the sale of all of the common stock of OncoGenex that we owned. We did not recognize any gain on investments for the first half of 2008.

Income Tax Benefit (Expense)

Even though we finished the first half 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 expense of $61,000 and income tax benefit of $656,000 for the three and six months ended June 30, 2009 on a line called "Income Tax Benefit (Expense)" 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 June 30,		Six Months Ended June 30,	
	2009	2008	2009	2008
Net income (loss) from continuing operations, net of income tax benefit (expense)	$ (3,753)	$ 463	$ (4,567)	$ (5,641)
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	857	965	1,771	1,848
Net income (loss) from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (2,896)	$ 1,428	$ (2,796)	$ (3,793)

Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders for the three and six months ended June 30, 2009 was $2.9 million and $2.8 million, respectively, compared to net income of $1.4 million and net loss of $3.8 million for the same periods in 2008. The improvement in our net loss from continuing operations for the first half of 2009 compared to the first half of 2008 was primarily due to the $2.7 million gain on investments offset by the $1.5 million decrease in investment income.

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 six months ended June 30, 2009 was $171.7 million, compared to net loss from discontinued operations of $5.2 million and $5.7 million for the three and six months ended June 30, 2008. We did not recognize any net income (loss) from discontinued operations for the three months ended June 30, 2009. Net income from discontinued operations for the first half 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 (Expense)* 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 half of 2009.

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

Net loss attributable to Isis Pharmaceuticals, Inc. common stockholders for the three months ended June 30, 2009 was $2.9 million and net income for the six months ended June 30, 2009 was $168.9 million, compared to a net loss of $ 3.7 million and $9.5 million for the three and six months ended June 30, 2008. Basic and diluted net loss per share for the three months ended June 30, 2009 was $0.03 per share compared to $0.04 per share for the same

period in 2008. Basic and diluted net income per share for the six months ended June 30, 2009 was $1.73 per share and $1.56 per share, respectively, compared to basic and diluted net loss per share of $0.10 for the same period in 2008. The improvement in our net income and net income per share for the first half of 2009 over the same period in 2008 was 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 June 30, 2009, we have earned approximately $759.7 million in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through June 30, 2009, we have raised net proceeds of approximately $810.5 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 June 30, 2009, we had cash, cash equivalents and short-term investments of $637.5 million and stockholders' equity of $305.8 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 June 30, 2009, we had consolidated working capital of $519.7 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. In addition, during the first half of 2009, we received more than $31 million in cash from our corporate partnerships, including the $11 million upfront license fee that we received from our recently announced licensing and collaboration agreement with Alnylam.

As of June 30, 2009, our debt and other obligations totaled $135.1 million, compared to $130.0 million at December 31, 2008. The increase in our debt and other obligations was primarily due to the $2.7 million additional draw down on our equipment financing arrangement and $3.5 million non-cash amortization of the debt discount recorded in the first half of 2009 as a result of adopting FSP 14-1. 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 $121.5 million and $118.0 million at June 30, 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. 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 June 30, 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**
2⅝% Convertible Subordinated Notes	$ 162.5	$ —	$ —	$ —	$ 162.5
GSK Convertible Promissory Note, including accrued interest	$ 5.3	$ —	$ 5.3	$ —	$ —
Equipment Financing Arrangement	$ 8.0	$ 3.0	$ 5.0	$ —	$ —
Other Obligations	$ 0.4	$ —	$ —	$ —	$ 0.4
Operating Leases	$ 16.2	$ 3.3	$ 3.8	$ 2.1	$ 7.0

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 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. 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.

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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 June 30, 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 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 June 30, 2009 and December 31, 2008 was $8.0 million and $6.5 million, respectively.

In addition to contractual obligations, we had outstanding purchase orders as of June 30, 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.

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 June 30, 2009, we had accumulated deficit of approximately $682.3 million and stockholders' equity of approximately $305.8 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.

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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.

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.

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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 June 30, 2009, we had cash, cash equivalents and short-term investments equal to $637.5 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:

- 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.

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding June 30, 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.

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

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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 an 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 2⁵¤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.

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.

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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.

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;

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- 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 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.

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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 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 June 30, 2009. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to June 30, 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.

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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

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

On June 2, 2009, we held our Annual Meeting of Stockholders in Carlsbad, California for the following purposes:

(1) To elect two directors to serve as Class III directors of the Company until the 2012 Annual Meeting of Stockholders. For Director number one, Richard D. DiMarchi, the number of votes for and withheld was 89,973,374 and 910,494, respectively. For Director number two, Frederick T. Muto, the number of votes for and withheld was 87,952,198 and 2,931,670, respectively.

(2) To approve an amendment and restatement of the 2000 Employee Stock Purchase Plan ("ESPP") to (i) extend the ESPP so that it will terminate on June 2, 2019 (ii) limit the evergreen provision such that it only adds 150,000 shares to the ESPP each year (iii) limit the offering periods under the ESPP to a maximum of six months and (iv) impose a minimum six-month holding period on shares purchased under the ESPP. The number of votes for, against and abstaining was 68,892,670; 686,233 and 90,534, respectively.

(3) To ratify the appointment of Ernst & Young LLP as the Company's independent registered public accounting firm for the fiscal year ending December 31, 2009. The number of votes for, against and abstaining was 89,230,567; 1,456,001 and 197,297, respectively.

ITEM 5. OTHER INFORMATION

Not applicable

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Amended and Restated Strategic Collaboration and License Agreement dated April 28, 2009 between the Registrant and Alnylam Pharmaceuticals, Inc. (with certain confidential information deleted).
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.

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(Registrant)

SIGNATURES

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

Signatures	Title	Date
/s/ Stanley T. Crooke Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	August 6, 2009
/s/ B. Lynne Parshall B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	August 6, 2009

Exhibit 10.1

Execution Copy

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

AMENDED AND RESTATED STRATEGIC COLLABORATION AND LICENSE AGREEMENT

This Amended and Restated Strategic Collaboration and License Agreement (the "Agreement") is executed this April 28, 2009 (the "Restatement Date"), between ISIS PHARMACEUTICALS, INC., a Delaware corporation having an address at 1896 Rutherford Road, Carlsbad, CA 92008 ("Isis") and ALNYLAM PHARMACEUTICALS, INC., a Delaware corporation having an address at 300 Third Street, Cambridge, Cambridge, MA 02142 (together with its wholly owned subsidiaries Alnylam U.S., Inc., a Delaware corporation, and Alnylam Europe AG, a company organized under the laws of Germany, "Alnylam"). Isis and Alnylam may be referred to herein as the "Parties," or each individually as a "Party."

GUIDING PRINCIPLES

Isis is the leader in RNA-based drug discovery, has created technology, intellectual property, expertise, facilities and resources to discover and develop oligonucleotide drugs;

Alnylam is the leader in RNAi therapeutics, has developed and acquired intellectual property, expertise and technology in RNAi therapeutics, and is conducting research, drug discovery and development focused on Double Stranded RNA drugs;

Isis and Alnylam desire to create a long-term strategic relationship that will enhance the positions of both companies in RNA-based drug discovery;

Isis will continue to pursue RNA-based drug discovery technology very broadly including all potential mechanisms of action. Isis will work with Alnylam as Isis' primary means of participating in the potential value of Double Stranded RNA Products, and will not enter into any collaborations with Third Parties the primary purpose of which is to discover Double Stranded RNA Products;

Alnylam will focus on RNAi therapeutics and the use of Double Stranded RNA;

Isis and Alnylam are parties to the Strategic Collaboration and License Agreement dated March 11, 2004 (as amended to date, the "Original Agreement"); and

Isis and Alnylam now wish to amend and restate the Original Agreement primarily to expand the Original Agreement by providing each other exclusive licenses to research, develop and commercialize Single Stranded RNAi Products for a limited pool of gene targets, and co-exclusivity in the field of Single Stranded RNAi Compounds.

The objectives of the strategic relationship are to:

· Enhance the leadership of Alnylam in RNAi therapeutics.

· Enhance the potential of Alnylam to develop Double Stranded RNA drugs.
· Enhance the patent positions of each Party with respect to Double Stranded RNA drugs and Single Stranded RNAi Products.
· Provide Isis with a means for participating in the success of RNAi therapeutics.
· Provide each party with exclusive rights to research, develop and commercialize Single Stranded RNAi Products for a limited pool of gene targets, and provide each other co-exclusivity in the field of Single Stranded RNAi Compounds.

ARTICLE 1

DEFINITIONS; AMENDMENT AND RESTATEMENT

1.1 Capitalized terms used herein and not defined elsewhere herein have the meanings set forth in Exhibit 1.1.

1.2 Effective as of the Restatement Date, this Agreement restates and supersedes the Original Agreement as amended through the Restatement Date. The terms and conditions of the Original Agreement shall apply for the period from the Effective Date until the Restatement Date unless otherwise provided by this Agreement.

ARTICLE 2

EQUITY INVESTMENT

2.1 In connection with the Original Agreement, Isis purchased from Alnylam 1,666,667 shares of Series D Preferred Stock, at $6.00 per share (i.e., at an aggregate purchase price of $10,000,002).

ARTICLE 3

3.1 [Intentionally Deleted]

ARTICLE 4

COLLABORATIVE RESEARCH EFFORTS; PROTECTED TARGETS

4.1 Research Management Committee.

(a) To promote the success of the collaboration objectives and RNAi technology, the Parties will establish a Research Management Committee ("RMC"), which will be comprised of equal numbers of representatives of each of the Parties and will meet at least twice per calendar year, alternating venues between the vicinities of Cambridge, Massachusetts and Carlsbad, California, to share scientific direction and data, to coordinate basic research experiments, and to facilitate the guiding principles of the collaboration.

(b) Intellectual property representatives of each Party will be invited to participate in RMC meetings and such meetings will provide a forum to discuss patent prosecution and enforcement issues and to allocate responsibility for the filing and prosecution of any Joint Patents.

(c) Through the RMC, the Parties will update one another regarding the progress of the Research Program (as defined below), including a summary of the work

each Party has performed thereunder; and regarding their respective Future Chemistry and Motif and Mechanism Patents.

(d) The RMC will establish a written clearance policy that will govern any publication or presentation by a Party in which such Party proposes to include any previously undisclosed information or intellectual property Controlled by the other Party.

(e) The RMC and any subcommittees and working groups established by the RMC will dissolve at the end of the Research Term. Upon termination of the RMC, the Parties will agree upon a strategy to make decisions about the items in Sections 4.1 (b), (c), and (d).

4.2 Single Stranded RNAi Collaboration. Subject to Alnylam's early termination right set forth in Section 14.4, during the 3 year period following the Restatement Date (the "Research Term"), the Parties will collaborate in carrying out a research program focused on Single Stranded RNAi Compounds (the "Research Program"). The Parties may extend the Research Term by mutual written agreement.

(a) Research Plan. The Research Program will be carried out in accordance with a written research plan, including without limitation the Budget (as defined below), which research plan shall be mutually agreed upon by the Parties (the "Research Plan"). The initial outline of the Research Plan agreed to by the Parties as of the Restatement Date is hereby incorporated into this Agreement by reference and is made a part of this Agreement; provided, within [***] days of the Restatement Date, the Parties will complete and agree in writing on an initial Research Plan, including without limitation an initial Budget, which is hereby incorporated into this Agreement by reference and is made a part of this Agreement. The purpose of the Research Plan is to detail the responsibilities and activities of Isis and Alnylam with respect to carrying out the Research Program. The Research Plan will include a description of the specific activities to be performed by the Parties in support of the Research Program, the allocation of Isis FTEs and Alnylam FTEs to perform such activities, projected timelines for completion of such activities, and an applicable budget (the "Budget"). The Budget for the Research Program must be mutually agreed by the Parties and will be at least $3,000,000 per year during the Research Term, including without limitation budgeted costs of Isis FTEs and Alnylam FTEs, and external costs. Beginning in 2010, at least once during September of each year of the Research Term, the RMC will review the Research Plan and will amend the Research Plan, as may be necessary, from time to time. In addition, each Calendar Quarter the RMC will review the progress of the work under the Research Plan, including spending against the Budget, and recommend adjustments to the Budget as necessary to support the Research Plan. The Research Plan, including without limitation any Budget, may only be amended with the written approval of the RMC. If the activities contemplated by the Research Plan at any time do not justify the number of Isis FTEs allocated to the Research Program, the Parties will work in good faith to mutually agree to modify the scope of the Research Plan or adjust the number of Alnylam funded FTEs and related Budget; provided that the minimum Budget for the Research Plan shall be as set forth in this Section 4.2(a). For clarity, Alnylam shall not be required to agree to any Budget which exceeds $3,000,000 per year.

(b) Research Staffing. Subject to Alnylam's obligations under Section 4.2(c), the Research Plan will provide for (and Isis will supply) a minimum of [***] Isis FTEs per year during the initial two-year period of the Research Term to perform activities in support of the Research Program and a minimum of [***] Isis FTEs during the third year of the Research Program. Each Party will supply the number of FTEs the Research Plan specifies that such Party will supply, and will conduct the Research Program diligently and in good scientific manner, and in compliance with all applicable good laboratory practices, and applicable legal requirements, to attempt to achieve efficiently and expeditiously the objectives of the Research Program. Each Party will comply with all Applicable Laws, in the performance of work under this Agreement.

(c) Research Funding. Alnylam will fund 100% of the costs of conducting the Research Program in accordance with the Research Plan (collectively, the "Research Costs") to the extent that such Research Costs are incurred under the Budget, including without limitation FTEs (whether employed by Isis or Alnylam) plus any out-of-pocket expenses specified in the Research Plan. By [***], 2009 with respect to the second Calendar Quarter of 2009 and thereafter within [***] Days following [***] each Calendar Quarter, Alnylam will pay Isis [***] for the Alnylam-funded Isis FTEs assigned to the Research Program for such Calendar Quarter (a prorated amount shall be payable for any portion of a Calendar Quarter). With respect to any work to be performed in support of the Research Program during the [***] days following the Restatement Date, if the Parties have not agreed on an initial Research Plan, then Alnylam will make [***] payments for such work based on [***] Isis FTEs. No later than [***] days following the end of each Calendar Quarter, Isis will provide Alnylam with a report of the number of FTEs actually assigned to the Research Program with a summary of the FTEs who performed under the Research Program ("Actual FTE Costs") and a reasonably detailed accounting of all other Research Costs actually incurred by Isis during such Calendar

Quarter ("Actual External Costs"). Alnylam shall not be responsible for any Research Costs incurred by Isis that exceed the [***] amount in the Budget for the work specified in the Research Plan to be conducted by Isis ("Excess Amount"), unless the RMC approves an amendment to the Budget to include such Excess Amount. Similarly, (i) Alnylam will promptly provide Isis a summary of the Alnylam FTEs who performed under the Research Program for a given Calendar Quarter and a reasonably detailed accounting of all other Research Costs actually incurred by Alnylam during such Calendar Quarter, and (ii) Research Costs incurred by Alnylam that exceed the total amount in the Budget for the work specified in the Research Plan to be conducted by Alnylam will not reduce the amounts committed in the Budget to fund Isis' Research Costs. In addition, upon reasonable request, each Party shall provide the other Party with reasonable documentation of Research Costs incurred by such Party during the Research Term and shall grant the other Party reasonable audit rights consistent with the terms set forth in Section 9.3 in connection with such Research Costs.

(d) Materials Transfer. In order to facilitate the Research Program, either Party may provide to the other Party certain materials for use by the other Party in furtherance of the Research Program. All such materials shall be used by the receiving Party in accordance with the terms and conditions of this Agreement solely for purposes of performing its rights and obligations under this Agreement and the Research Plan, and the receiving Party shall not transfer such materials to any Third Party unless expressly

contemplated by this Agreement or the Research Plan, or upon the written consent of the supplying Party.

4.3 Enabled Targets for Single Stranded RNAi.

(a) Enabled Targets. Each Party will have a pool (with respect to either Party, an "Enabled Target Pool"; with respect to Isis, the "Isis Enabled Target Pool"; and, with respect to Alnylam, the "Alnylam Enabled Target Pool") each containing [***] [***] slots for which such Party can designate certain Gene Targets against which such Party intends to research, develop and commercialize a Single-Stranded RNAi Product (each such slot, an "Enabled Target Slot" and any Gene Target occupying such a slot, an "Enabled Target"); provided, however, that, each time a Party (the "Advancing Party") designates as a Development Candidate a Single Stranded RNAi Product Designed for one of such Advancing Party's Enabled Targets, then (i) such Enabled Target will be considered to have graduated from the Advancing Party's Enabled Target Pool (a "Graduated Enabled Target"), (ii) the Advancing Party will be permitted to designate a new Enabled Target to fill the open Enabled Target Slot in the Advancing Party's Enabled Target Pool, and (iii) so long as the Advancing Party continues to maintain an Active Program for the applicable Single Stranded RNAi Product Designed for the Graduated Enabled Target, such Graduated Enabled Target will remain an Enabled Target of such Advancing Party hereunder. For purposes of clarity, except as set forth in Sections 5.1(g)(i), 5.1(h)(i), 5.5, 6.6, 6.1(h)(i) and 6.1(i)(i), as applicable, neither Party may research, develop or commercialize a Single Stranded RNAi Product other than a Single Stranded RNAi Product Designed for one of such Party's Enabled Targets.

(b) Designating Enabled Targets. Within thirty (30) days following completion of *[***]*, the Parties will begin the process set forth below for selecting Enabled Targets for inclusion in each Party's Enabled Target Pool. For clarity, at no time may either Party designate a Gene Target which is in the other Party's Enabled Target Pool. Except as set forth in Section 4.3(e) below, the Parties will designate Enabled Targets by taking alternating turns (each Party's designation of a new Gene Target (a "Pick") or affirmative election not to designate an Enabled Target (a "Pass") shall be considered a "Turn"; and each round in which Isis and Alnylam have each Picked or Passed once shall be considered a "Round") in one or more Rounds, as necessary. For each Turn, a Party shall either Pick or Pass within five (5) Business Days (it being understood that if a Party does not provide affirmative notice of a Pick or Pass within such five (5) Business Day-period, then such Party shall be deemed to have "Passed" in such Turn). The Parties will complete Rounds until the Parties have either (i) both filled all of their respective Enabled Target Slots, or (ii) both elected to Pass in the same Round, thereby completing a Round (such point being the end of a "Selection Session", which Selection Session includes all of the Rounds completed since the end of the last Selection Session (or, in the case of the first Selection Session, all prior Rounds)). For purposes of clarity, either Party may, prior to Picking or Passing in such Party's Turn in any ongoing Round, remove any existing Gene Target(s) on its Enabled Target List in accordance with Section 4.3(d) and use its Pick in such Turn to Pick a different Gene Target as an Enabled Target on its Enabled Target List, subject to the [***] Enabled Target Slot limitation. Either Party may initiate a new Selection Session at any time by providing written notice to the other Party (such new Selection Session to begin on the

first Business Day following the 30th day following such notice). For each new Selection Session, the Party who gets to take the first Turn in the First Round will be determined in accordance with Section 4.3(c) below.

(c) Determining First Turn. Alnylam will take the first Turn in the first Round of the first Selection Session. Thereafter:

(i) If, immediately prior to the start of a Selection Session, one Party (the "Lopsided Party") has fewer Enabled Targets in its Enabled Target Pool than the number of Enabled Targets the other Party has in such other Party's Enabled Target Pool, then the Lopsided Party will take the first Turn in the First Round. In such event (1) in each Turn the Lopsided Party makes a [***] that is not a [***] the other Party [***] until both Parties have an [***] in their respective Enabled Target Pools (and then subsequent Rounds in the Selection Session will continue in accordance with Section 4.3(c)(iii) below with the other Party getting the first Pick in the first such subsequent Round); and (2) if the Lopsided Party [***] or [***] in a Turn, the other Party may Pick or Pass (and then any subsequent Rounds in the Selection Session will continue in accordance with Section 4.3(c)(iii) below).

(ii) If there is no Lopsided Party immediately prior to the start of a Selection Session, then the Party who was *not* the last Party to Pass in the prior Selection Session shall be the first Party to take the first Turn in the first Round of such new Selection Session (and then any subsequent Rounds in the Selection Session will continue in accordance with Section 4.3(c)(iii) below).

(iii) For any subsequent Rounds in a Selection Session, the Party who was not the first Party to take a Turn in the most previous Round will have the first Turn in the next Round.

(iv) The Parties have attached as Exhibit 4.3(c)(iv) examples of how the Parties intend this Section 4.3(c) to operate.

(d) Removing Enabled Targets. From time to time after the Restatement Date (except during the 30-day period immediately preceding a Selection Session or when a Lopsided Party is taking Turns under Section 4.3(c)(i)), each Party may remove a Gene Target from its Enabled Target Pool upon written notice to the other Party (which removal will create an open Enabled Target Slot). In addition, on an Enabled Target-by-Enabled Target basis, if the

applicable Party has not designated a Development Candidate comprising a Single Stranded RNAi Product Designed for the applicable Enabled Target before the [***]year anniversary of the date such Party added the applicable Enabled Target to such Party's Enabled Target Pool, then such Gene Target will be automatically removed from such Party's Enabled Target Pool. Once a Party removes a Gene Target from its Enabled Target Pool (whether voluntarily or by operation of this Section 4.3(d)), such Gene Target shall no longer be deemed an Enabled Target hereunder and the removing Party will be prevented from later adding such Gene Target to its Enabled Target Pool until [***] months have passed from the date such Gene Target was removed.

(e) Isis Protected Targets. Notwithstanding the foregoing, Alnylam may not designate as one of Alnylam's Enabled Targets any of the Gene Targets identified as an Isis Protected Target in the letter Isis issued to Alnylam on the Restatement Date (collectively, the "Isis Protected Targets").

(i) With respect to any Isis Protected Target Isis identified as an Isis Protected Target on the Restatement Date due to a contractual restriction that prevents or otherwise restricts Isis' ability to grant a license to Alnylam under Sections 5.1(g) and 5.1(h) (each an "Isis Partnered Excluded Target"), (1) Isis shall list in the above-reference letter such Isis Partnered Excluded Targets separately such that they are clearly distinguished from other Isis Protected Targets, (2) Isis shall diligently enforce the relevant terms governing Isis' rights to clear any contractual restrictions on such Isis Partnered Excluded Target, (3) once a particular contractual restriction clears or expires on such Isis Partnered Excluded Target, such Gene Target will no longer be considered an Isis Protected Target, such that Alnylam may then designate such Gene Target as one of its Enabled Targets in accordance with the terms of this Agreement, and (4) when practical (but at least every [***] months), Isis shall update the list of Isis Protected Targets to remove Gene Targets that are no longer Isis Partnered Excluded Targets.

(ii) For purposes of clarity, except as permitted under Sections 6.1(h)(i) and 6.1(i)(i), Isis may not research, develop or commercialize a Single-Stranded RNAi Product Designed for any Isis Protected Target unless such Isis Protected Target is designated as an Enabled Target by Isis pursuant to Section 4.3(b) above or the remainder of this Section 4.3(e)(ii). Notwithstanding anything in this Section 4.3 to the contrary, with respect to any Isis Partnered Excluded Target for which the applicable contractual restriction has cleared or expired (each, a "Cleared Target") (A) Isis shall not have the right to designate such a Cleared Target as one of its Enabled Targets until Isis has provided written notice to Alnylam of such clearance (as part of the regular updates contemplated in Section 4.3(e)(i) above or otherwise) (such notice, a "Clearance Notice"), and (B) in the first Selection Session following Alnylam's Receipt of the applicable Clearance Notice with respect to a particular Cleared Target, Isis may not Pick such Cleared Target as one of its Enabled Targets until and unless Alnylam has had a full Turn in such Selection Session in which it could Pick such Cleared Target as one of its Enabled Targets and does not elect to Pick such Cleared Target. For example, if two Gene Targets become Cleared Targets (and Alnylam receives a Clearance Notice related thereto) immediately prior to the start of a Selection Session and Isis has the first Turn, (1) Isis may not Pick either such Cleared Target in its first Turn, (2) in Alnylam's next Turn, Alnylam could Pick either such Cleared Target, and (3) once Alnylam opts to Pick a Gene Target (whether or not such Pick was for one of the two Cleared Targets) or Pass, Isis may then pick either of the remaining two such Cleared Targets that it was prohibited from Picking in its previous Turn.

(f) Confidentiality. The fact that a Party has designated or removed a particular Gene Target within its Enabled Target Pool is Confidential Information of such Party, subject to the provisions of Article 12. Neither Party shall disclose such Confidential Information of the other Party to any Third Party, including its Third Party collaborators, or use such Confidential Information of the other Party to guide its own (or its Third Party collaborators') decisions to pursue particular Gene Targets, but either

Party can use such Confidential Information to decline a Third Party's request for a license to such Gene Target. The Isis Protected Targets are Isis' Confidential Information.

(g) Review Designating Process. The Parties agree that on or about the three year anniversary of the Restatement Date, if either Party deems appropriate, the Parties will, in good faith, review the process for designating Enabled Targets for the purposes of improving the process for the mutual benefit of both Parties, and if necessary, amend this Section 4.3, to effect such improvements; provided, however, that either Party shall have the right to refuse any such changes in its sole discretion.

ARTICLE 5

LICENSES GRANTED BY ISIS TO ALNYLAM; AND CO-EXCLUSIVITY COVENANT

5.1 License Grants. Subject to the terms and conditions of this Agreement, including, but not limited to, the restrictions set forth in Section 5.3, Isis grants Alnylam the following licenses:

(a) Under Isis Current Motif and Mechanism Patents and Isis Current Chemistry Patents, a license to research, develop, make, have made, use, import, offer to sell and sell Double Stranded RNA and Double Stranded RNA Products.

(b) Subject to the terms of Section 11.8, under Isis Future Motif and Mechanism Patents, Isis Future Chemistry Patents and Isis' rights in Joint Patents, a license to research, develop, make, have made, use, import, offer to sell and sell Double Stranded RNA and Double Stranded RNA Products.

(c) Under the Isis Current Motif and Mechanism Patents and Isis Current Chemistry Patents, a license to research, develop, make, have made, use, import, offer to sell and sell MicroRNA Products.

(d) Subject to the terms of Section 11.8, under the Isis Future Motif and Mechanism Patents and Isis Future Chemistry Patents, a license to research, develop, make, have made, use, import, offer to sell and sell MicroRNA Products.

(e) A royalty-free, fully paid, license to practice any Know-How disclosed to Alnylam during the performance of this Agreement, subject to the non-disclosure but not the non-use provisions contained in Article 12.

(f) A fully paid, royalty-free license under Isis Manufacturing Patents to research, develop, make, have made, use and import Alnylam Products for Research Use.

(g) Under the Isis Current Motif and Mechanism Patents and Isis Current Chemistry Patents, a license to (i) research, develop, make, have made, use and import Single Stranded RNAi Compounds and Single Stranded RNAi Products for Research

Use, and (ii) research, develop, make, have made, use, import, offer to sell and sell Alnylam Single Stranded RNAi Products.

(h) Subject to the terms of Section 11.8, under Isis Future Motif and Mechanism Patents, Isis Future Chemistry Patents and Isis' rights in Joint Patents, a license to (i) research, develop, make, have made, use and import Single Stranded RNAi Compounds and Single Stranded RNAi Products for Research Use, and (ii) research, develop, make, have made, use, import, offer to sell and sell Alnylam Single Stranded RNAi Products.

(i) Under Isis' rights in Research Program Patents, a royalty-free license for any and all purposes, except to research, develop, make, have made, use, import, offer to sell or sell any (1) oligonucleotides (or chemically modified oligonucleotide analogs) designed to work via the RNase H 1 or 2 mechanism (including any oligonucleotide which has [***]), (2) Double Stranded RNA Products, (3) MicroRNA Products, (4) Single Stranded RNAi Products, or (5) Isis Single Stranded Products.

5.2 License Exclusivity, Territory and Sublicenses.

(a) Subject to the terms and conditions of this Agreement, including the restrictions set forth in Section 5.3, the licenses from Isis to Alnylam granted in Sections 5.1(a) and (b) are worldwide and co-exclusive (with Isis), with the exclusive right to grant Naked Sublicenses; the licenses from Isis to Alnylam granted in Sections 5.1 (c), (d), (e), (f), (g)(i), (h)(i) and (i) are worldwide and nonexclusive; and the licenses from Isis to Alnylam granted in Sections 5.1 (g)(ii) and (h)(ii) are worldwide and exclusive. Alnylam is not permitted to grant sublicenses under the licenses granted in Sections 5.1(a) through 5.1(e), except that Alnylam is permitted to grant (i) sublicenses in connection with a Bona Fide Drug Discovery Collaboration, (ii) sublicenses in connection with a Development Collaboration, (iii) Naked Sublicenses and (iv) sublicenses under the license granted in Section 5.1(e) in connection with the discovery, development or commercialization of any product. Furthermore, Alnylam is not permitted to grant sublicenses under the licenses granted in Section 5.1(f). Alnylam may grant sublicenses under Section 5.1(i), subject to Section 7.7.

(b) Alnylam may grant sublicenses under the licenses granted in Sections 5.1(g) and 5.1(h) only to further the research, development or commercialization of an Alnylam Single Stranded RNAi Product that Alnylam has performed on its own (or with Isis under the Research Plan) and [***] at least [***]% of the work to discover and develop the Alnylam Single Stranded RNAi Product through the [***] [***] (or a date that is earlier than the [***] if requested by Alnylam and approved in writing by Isis, such approval not to be unreasonably withheld).

(c) Alnylam cannot sublicense its right to grant Naked Sublicenses under this Agreement except that Alnylam may permit its sublicensees to grant further sublicenses in connection with a sublicense to further the research, development or commercialization of an Alnylam Product.

(d) Notwithstanding the foregoing, (i) Alnylam acknowledged and permits the license Isis granted [***], as amended through the Restatement Date, that granted [***] a nonexclusive license under Isis Current Motif and Mechanism Patents and Isis Current Chemistry Patents for the manufacture and sale of chemically modified oligonucleotides for [***] only and (ii) Isis may continue to grant licenses to Third Parties for the purpose of manufacturing and selling oligonucleotides; provided that, to the extent such licenses cover Double Stranded RNA or Single Stranded RNAi Compounds, Isis will restrict such licenses to [***].

5.3 Limitations on Licenses.

(a) The licenses granted under Section 5.1 above are not intended to grant any rights to Alnylam to practice the Isis Excluded Technology. If Alnylam wishes to license any Isis Excluded Technology for which Isis has the right to grant a license or sublicense, Isis will negotiate in good faith an appropriate license.

(b) Notwithstanding the licenses granted to Alnylam under Section 5.1, Isis retains its rights in the Isis Patent Rights and in the Joint Patents (i) exclusively for the Isis Reserved DS-Targets, and (ii) exclusively for the Isis Encumbered Targets. Once a particular contractual restriction expires on an Isis Encumbered Target, Alnylam's licenses under Section 5.1 will no longer be limited under this Section 5.3(b) for such target and such target shall no longer be an Isis Encumbered Target. Isis will update the [***] (as defined in the letter agreement dated March 9, 2004 between Alnylam and Isis) provided to Alnylam prior to the Effective Date and subsequent [***] provided to Alnylam from time to time to remove targets that are no longer Isis Encumbered Targets promptly upon receipt of a written request from Alnylam to update such [***], but will not be required to update such [***] more frequently than [***] a calendar quarter. In addition, the licenses granted by Isis to Alnylam under each of Sections 5.1(g)(i) and 5.1(h)(i) do not include the right to research, develop, make, have made, use, or import Single Stranded Compounds or Single Stranded RNAi Products, in each case that are Designed for Isis' Enabled Targets or the Isis Protected Targets.

(c) Licenses to Isis Patent Rights that are joint patents with Third Parties (i.e., invented by one or more Isis inventors and one or more non-Isis inventors) are licensed subject to the retained rights of any non-Isis inventors and their assignees and licensees. Any such retained rights of non-Isis inventors and their assignees and licensees existing as of the Restatement Date are set forth in Exhibit 5.3(c) attached hereto.

(d) Licenses to Isis Patent Rights that are subject to contractual obligations between Isis and Third Parties in effect as of the Restatement Date are licensed subject to the restrictions and other terms described in Exhibit 5.3(d) attached hereto. Alnylam hereby agrees to comply, and to cause its sublicensees to comply, with such restrictions and other terms.

5.4 Alnylam Covenant Regarding Sublicensing of Isis Patent Rights. Alnylam shall use good faith efforts to include sublicenses under the licenses under the Isis Patent Rights granted to Alnylam in Sections 5.1(a) and 5.1(b) in any Third Party collaboration

or license agreement in which Alnylam grants rights to develop and commercialize Double Stranded RNA Products, unless the technology covered by such licensed Isis Patent Rights would not reasonably be expected to advance the goals of such Third Party collaboration or license relationship.

5.5 Isis Covenant to Alnylam Regarding Co-Exclusivity for Single Stranded RNAi Products. Isis hereby covenants to Alnylam, that, after the Restatement Date, Isis will not itself, and will not grant to a Third Party a license under the Isis Current Motif and Mechanism Patents, Isis Current Chemistry Patents, Isis Future Motif and Mechanism Patents, Isis Future Chemistry Patents, the Co-Exclusive ssRNAi Patents, and/or Isis' rights in any Joint Patents or Research Program Patents to, research, develop, make, have made, use, import, offer to sell and sell Single Stranded RNAi Compounds or Single Stranded RNAi Products, except Isis may (i) research, develop, make, have made, use and import Single Stranded RNAi Compounds or Single Stranded RNAi Products for [***], (ii) grant a license to Controlled Contractors to support work under the Research Plan, (iii) grant a license to further the research, development or commercialization of an Isis Single Stranded Product, (iv) grant a license to further the research, development or commercialization of an Isis Single Stranded RNAi Product solely in conjunction with a permitted sublicense by Isis under Section 6.3; and (v) continue to grant licenses to Third Parties for the purpose of manufacturing and selling oligonucleotides; provided that, to the extent such licenses cover Single Stranded RNAi Compounds, Isis will restrict such licenses to [***]. For purposes of clarity, this Section 5.5 will not preclude Isis from (A) itself using the [***], or (B) granting any Third Party a license under the [***].

ARTICLE 6

LICENSES GRANTED BY ALNYLAM TO ISIS; AND CO-EXCLUSIVITY COVENANT

6.1 License Grants. Subject to the terms and conditions of this Agreement, including, but not limited to, the restrictions set forth in Section 6.5, Alnylam grants Isis the following licenses:

(a) A fully-paid, royalty-free, nonexclusive license under Alnylam Current Motif and Mechanism Patents and Alnylam Current Chemistry Patents to research, develop, make, have made, use and import Isis Products other than Isis Single Stranded RNAi Products for Research Use.

(b) Subject to the terms of Section 11.8, a fully paid, royalty-free nonexclusive license under Alnylam Future Motif and Mechanism Patents and Alnylam Future Chemistry Patents to research, develop, make, have made, use and import Isis Products other than Isis Single Stranded RNAi Products for Research Use.

(c) A nonexclusive license under Alnylam Current Motif and Mechanism Patents and Alnylam Current Chemistry Patents to research, develop, make, have made, use, import, offer to sell and sell Isis Single Stranded Products.

(d) Subject to the terms of Section 11.8, a nonexclusive license under Alnylam Future Motif and Mechanism Patents and Alnylam Future Chemistry Patents to research, develop, make, have made, use, import, offer to sell and sell Isis Single Stranded Products.

(e) Under the Alnylam Current Motif and Mechanism Patents and Alnylam Current Chemistry Patents, a nonexclusive license to research, develop, make, have made, use, import, offer to sell and sell MicroRNA Products.

(f) Subject to the terms of Section 11.8, under the Alnylam Future Motif and Mechanism Patents and Alnylam Future Chemistry Patents, a nonexclusive license to research, develop, make, have made, use, import, offer to sell and sell MicroRNA Products.

(g) A worldwide, royalty-free, fully paid, nonexclusive license to practice any Know-How disclosed to Isis during the performance of this Agreement, subject to the non-disclosure but not the non-use provisions contained in Article 12.

(h) A worldwide license under the Alnylam Current Motif and Mechanism Patents and Alnylam Current Chemistry Patents to (i) research, develop, make, have made, use and import Single Stranded RNAi Compounds and Single Stranded RNAi Products for Research Use, and (ii) research, develop, make, have made, use, import, offer to sell and sell Isis Single Stranded RNAi Products. The license granted to Isis under the foregoing clause (i) shall be non-exclusive, and the license granted to Isis under the foregoing clause (ii) shall be exclusive.

(i) Subject to the terms of Section 11.8, a worldwide license under Alnylam Future Motif and Mechanism Patents and Alnylam Future Chemistry Patents to (i) research, develop, make, have made, use and import Single Stranded RNAi Compounds and Single Stranded RNAi Products for Research Use, and (ii) research, develop, make, have made, use, import, offer to sell and sell Isis Single Stranded RNAi Products. The license granted to Isis under the foregoing clause (i) shall be non-exclusive, and the license granted to Isis under the foregoing clause (ii) shall be exclusive.

(j) Under Alnylam's rights in Research Program Patents, a royalty-free license for any and all purposes, except to research, develop, make, have made, use, import, offer to sell or sell any (1) oligonucleotides (or chemically modified oligonucleotide analogs) designed to work via the RNase H 1 or 2 mechanism (including any oligonucleotide which has [***]), (2) Double Stranded RNA Products, (3) MicroRNA Products, (4) Single Stranded RNAi Products, or (5) Isis Single Stranded Product.

6.2 License Option. For each Gene Target in the Isis DS-Target Pool (as further described below) Alnylam grants Isis an option to obtain (on a Reserved DS-Target-by-Reserved DS-Target basis), subject to the terms and conditions of this Agreement, including, but not limited to, the restrictions set forth in Section 6.5, a non-exclusive license under (i) Alnylam Current Motif and Mechanism Patents and Alnylam

Current Chemistry Patents and (ii) subject to the terms of Section 11.8, Alnylam Future Motif and Mechanism Patents, Alnylam Future Chemistry Patents and Alnylam's rights in Joint Patents, to research, develop, make, have made, use, import, offer for sale and sell Double Stranded RNA Products that are Isis Products.

(a) This option will expire on a Reserved DS-Target-by-Reserved DS-Target basis if Isis has not paid Alnylam the option fee set forth in Section 8.1 below before the earlier of (i) the [***] with respect to such Reserved DS-Target, (ii) the [***] anniversary of the date such Reserved DS-Target [***] or the [***] anniversary of the date such Reserved DS-Target [***] with a Third Party and Isis is contractually able to revoke such Third Party's rights or (iii) the date [***] with respect to such Reserved DS-Target.

(b) For any Reserved DS-Target for which Isis obtains a license from Alnylam under this Section 6.2, Isis will use Commercially Reasonable Efforts (either on its own or in an Antisense Drug Discovery Program or Development Collaboration) to develop and commercialize Double Stranded RNA Products that modulate such Reserved DS-Target.

6.3 Sublicenses.

(a) With respect to any license granted by Alnylam pursuant to Section 6.1(a), 6.1(b), or 6.2, Isis may only grant a sublicense to a Third Party solely for (i) the purpose of enabling such Third Party to collaborate with Isis in an Antisense Drug Discovery Program, or (ii) to develop and commercialize an Isis Product in a Development Collaboration. With respect to any license granted by Alnylam pursuant to Section 6.1(c), 6.1(d), 6.1(e), 6.1(f), 6.1(g), Isis may grant a sublicense to a Third Party in connection with the discovery, development or commercialization of any product. Isis may grant sublicenses under Section 6.1(j), subject to Section 8.5. With respect to the licenses granted by Alnylam pursuant to Section 6.1(h) and 6.1(i), Isis may only grant a sublicense to a Third Party to further the research, development or commercialization of an Isis Single Stranded RNAi Product that Isis has performed on its own (or with Alnylam under the Research Plan) and [***] at least [***]% of the work to discover and develop the Isis Single Stranded RNAi Product through the [***] (or a date that is earlier than the [***] if requested by Isis and approved in writing by Alnylam, such approval not to be unreasonably withheld).

(b) Notwithstanding anything in this Agreement to the contrary, Isis may not enter into any drug discovery collaboration the primary purpose of which is to discover Double Stranded RNA Products and/or to develop Double Stranded RNA Products to any point up to the [***].

6.4 DS-Target Pool.

(a) Reserved DS-Target Slots. On the Effective Date, Isis will have a pool (the "Isis DS-Target Pool") containing up to [***] slots for which Isis can designate certain Gene Targets solely for Antisense Drug Discovery Programs (each such slot, a "DS-Target Slot" and any Gene Target occupying such a slot, a "Reserved DS-Target");

provided, however, that on January 1 of each year starting with January 1, 2007, Isis will gain the right to purchase one additional DS-Target Slot by paying Alnylam $[***] per each additional DS-Target Slot. These rights are cumulative and, subject to Section 17.2(c) do not expire during the License Term. Furthermore, in the event that Isis pays the $[***] license option fee for a Reserved DS-Target pursuant to Section 8.1, such Reserved DS-Target will be considered to have graduated from the Isis DS-Target Pool, and, subject to Section 6.4(e), Isis will be permitted to designate a new Reserved DS-Target to fill the open DS-Target Slot in the Isis DS-Target Pool. For purposes of clarity, except as permitted under Sections 6.1(h)(i) and 6.1(i)(i), Isis may not research, develop or commercialize Single Stranded RNAi Products for a Reserved DS-Target unless such Reserved DS-Target is designated as an Enabled Target by Isis pursuant to Section 4.3(a) above.

(b) Initial Designations. The letter delivered by Isis to Alnylam on the Restatement Date sets forth the Reserved DS-Targets as of the Restatement Date.

(c) Removing/Adding DS-Targets. After the Restatement Date and no more than once in any [***] period (a "Target Reallocation Period"), Isis may do any of the following:

(i) Remove a Gene Target from the Isis DS-Target Pool (which, following such removal will create an open DS-Target Slot); or

(ii) Add a new Gene Target to any open DS-Target Slot (subject to the procedures and provisions of Section 6.4(e).

Notwithstanding the foregoing provisions of this Section 6.4(c), in any Target Reallocation Period, Isis cannot remove a number of Reserved DS-Targets that exceeds the number calculated by dividing the then current number of DS-Target Slots by [***] and rounding down to the nearest whole number. For the purpose of the limitation described in the immediately preceding sentence, removing a Gene Target from the Isis DS-Target Pool and then filling the open DS-Target Slot created by such removal shall count as a single removal. Once Isis removes a Gene Target from the Isis DS-Target Pool, Isis will be prevented from later adding such Gene Target to the Isis DS-Target Pool until [***] have passed from the date Isis removed such Gene Target.

(d) New Target Request. When Isis wishes to add a new Gene Target to occupy a vacant DS-Target Slot, it will provide Alnylam with written notice (the "Request Notice") of the Gene Target it wishes to add (the "Proposed Reserved DS-Target"). The Request Notice will include the gene name, and the NCBI accession number or nucleic acid sequence for the Proposed Reserved DS-Target.

(e) New Target Rejection/Approval. Within [***] of receipt of the Request Notice, Alnylam will give Isis written notice if any of the criteria set forth below applied to such Proposed Reserved DS-Target at the time of Alnylam's receipt of the Request Notice. If, at such time, the Proposed Reserved DS-Target is (i) subject to Alnylam's own Active Program [***], (ii) encumbered by a contractual obligation

between Alnylam and a Third Party that would preclude Alnylam from granting a license under Section 6.2 with respect to the Proposed Reserved DS-Target or (iii) the subject of Alnylam's good faith negotiations to enter into a contractual obligation within the [***] following receipt of the Request Notice with a Third Party (as supported by a written request from such Third Party) that would preclude Alnylam from granting a license under Section 6.2 with respect to the Proposed Reserved DS-Target, then the Proposed Reserved DS-Target will be rejected and will not become a Reserved DS-Target. If the Proposed Reserved DS-Target is not rejected under this subsection (e), the Proposed Reserved DS-Target will become an Isis Reserved DS-Target. Alnylam will promptly notify Isis in writing if a rejected Proposed Reserved DS-Target later becomes available to be designated as a Reserved DS-Target.

(f) [Intentionally Deleted].

(g) Diligence on Rejected Targets. If (i) Alnylam rejects a Proposed Reserved DS-Target under Section 6.4(e) above and (ii) Alnylam has [***] with respect to such rejected Proposed Reserved DS-Target by the [***] anniversary of the date Alnylam rejected such Proposed Reserved DS-Target if Alnylam is working on such target alone, or the [***] anniversary of the date Alnylam rejected such Proposed Reserved DS-Target if such rejected Proposed Reserved DS-Target is subject to a contractual obligation between Alnylam and a Third Party that would preclude Alnylam from granting a license under Section 6.2 with respect to the rejected Proposed Reserved DS-Target but Alnylam [***], then [***] such rejected Proposed Reserved DS-Target [***].

(h) Diligence Obligations in Third Party Contractual Obligations. With the goal of minimizing contractual encumbrances on Alnylam Patent Rights with respect to Gene Targets in the absence of a reasonable intent to discover and develop products that modulate such Gene Targets by Third Parties with which Alnylam enters into such contractual obligations, Alnylam intends to seek reasonable diligence obligations from Third Parties in negotiating contracts between Alnylam and such Third Parties that would constitute contractual obligations of Alnylam that would preclude Alnylam from granting licenses to Isis under Section 6.2 with respect to Proposed Reserved DS-Targets; or that would prevent Alnylam from granting Isis licenses with respect to Proposed Reserved DS-Targets; provided that Isis hereby acknowledges that such diligence obligations are often heavily negotiated in biotechnology license and collaboration agreements and that this Section 6.4(h) shall not prevent Alnylam from entering into contracts between Alnylam and Third Parties in accordance with Alnylam's reasonable business judgment.

(i) Confidentiality. The fact that Isis has designated or removed a particular Gene Target within the Isis DS-Target Pool is Confidential Information of Isis, or that Alnylam has rejected a particular Gene Target proposed for a DS-Target Slot or disallowed the redesignation of a particular Gene Target is Confidential Information of Alnylam, subject to the provisions of Article 12. Neither Party shall disclose such Confidential Information of the other Party to any Third Party, including its Third Party collaborators, or use such Confidential Information of the other Party to guide its own (or its Third Party collaborators') decisions to pursue particular Gene Targets, but Alnylam

can use such Confidential Information of Isis to decline a Third Party's request for a license to such Gene Target.

6.5 Limitations on Licenses.

(a) The licenses granted under Sections 6.1 and 6.2 above are not intended to grant any rights to Isis to practice the Alnylam Excluded Technology. If Isis wishes to license any Alnylam Excluded Technology for which Alnylam has the right to grant a sublicense, Alnylam will negotiate in good faith an appropriate license.

(b) Licenses to Alnylam Patent Rights that are joint patents with Third Parties (i.e., invented by one or more Alnylam inventors and one or more non-Alnylam inventors) are licensed subject to the retained rights of any non-Alnylam inventors and their assignees and licensees. There are no Alnylam Current Chemistry Patents or Alnylam Current Motif and Mechanism Patents subject to such retained rights.

(c) Licenses to Alnylam Patent Rights that are subject to contractual obligations between Alnylam and Third Parties in effect as of the Effective Date are licensed subject to the restrictions and other terms described in Exhibit 6.5(c) attached hereto. Isis hereby agrees to comply, and to cause its sublicensees to comply, with such restrictions and other terms.

(d) Notwithstanding anything to the contrary herein, the licenses to Alnylam Patent Rights hereunder initially shall not include licenses to Patents licensed by Alnylam from Stanford University under any agreement between Alnylam and Stanford University in effect as of the Restatement Date; provided that if any such licensed Patents become issued Patents, Isis shall have the option of expanding its licenses to Alnylam Patent Rights hereunder to include such issued Patents by notifying Alnylam of such election and agreeing to pay to Alnylam, in addition to all amounts otherwise payable to Alnylam hereunder (and without any right under Section 8.2 to reduce such otherwise payable amounts as a consequence of such additional payment amounts), all amounts that (i) become payable by Alnylam to Stanford University as a result of such expansion of Isis' licenses and Isis' (and its Affiliates' and sublicensees') exercise of its rights thereunder and (ii) are described on Exhibit 6.5(d) attached hereto.

(e) In addition, the licenses granted by Alnylam to Isis under each of Sections 6.1(h)(i), 6.1(i)(i) and 6.1(j) do not include the right to research, develop, make, have made, use, or import Single Stranded RNAi Compounds or Single Stranded RNAi Products, in each case that are Designed for Alnylam's Enabled Targets.

6.6 Alnylam Covenant to Isis Regarding Co-Exclusivity for Single Stranded RNAi Products. Alnylam hereby covenants to Isis, that, after the Restatement Date, Alnylam will not itself, and will not grant to a Third Party a license under the Alnylam Current Motif and Mechanism Patents, Alnylam Current Chemistry Patents, Alnylam Future Motif and Mechanism Patents, Alnylam Future Chemistry Patents, the Co-Exclusive ssRNAi Patents, and/or Alnylam's rights in any Joint Patents or Research Program Patents to, research, develop, make, have made, use, import, offer to sell and sell Single Stranded RNAi Compounds or Single Stranded RNAi Products, except

Alnylam may (i) research, develop, make, have made, use or import Single Stranded RNAi Compounds or Single Stranded RNAi Products for [***], (ii) grant a license to Controlled Contractors to support work under the Research Plan, (iii) grant a license to further the research, development or commercialization of an Alnylam Single Stranded RNAi Product solely in conjunction with a permitted sublicense by Alnylam under Section 5.2; and (iv) continue to grant licenses to Third Parties for the purpose of manufacturing and selling oligonucleotides; provided that, to the extent such licenses cover Single Stranded RNAi Compounds, Alnylam will restrict such licenses to [***]. For purposes of clarity, this Section 6.6 will not preclude Alnylam from (A) itself using the [***], or (B) granting any Third Party a license under the [***].

ARTICLE 7

LICENSE FEES AND ROYALTIES PAYABLE TO ISIS

7.1 License Fees.

(a) In connection with the Original Agreement, Alnylam paid Isis an initial, irrevocable, noncreditable and non-refundable license fee of $5,000,000.

(b) Alnylam will pay Isis an additional, irrevocable, noncreditable and non-refundable license fee of $11,000,000 within 5 Business Days following the Restatement Date.

7.2 Royalties.

(a) Subject to the terms and conditions of, and during the term of, this Agreement, Alnylam will pay to Isis royalties on sales of Alnylam Double Stranded RNA Products by Alnylam, its Affiliates or sublicensees (except Naked Sublicensees) equal to [***]% of Net Sales. Alnylam may reduce the royalty due under this section by [***]% of any additional royalties that Alnylam owes to Third Parties on such Alnylam Double Stranded RNA Product that arise from Alnylam acquiring access to new technologies after the Effective Date; provided, however that (a) the royalty due under this section can never be less than a floor of [***]% and (b) additional royalties arising as the result of the addition, pursuant to Section 11.8, of Isis Future Chemistry Patents or Isis Future Motif and Mechanism Patents to the Isis Patent Rights licensed to Alnylam cannot be used to reduce the royalty.

(b) Subject to the terms and conditions of, and during the term of, this Agreement, Alnylam will pay to Isis royalties on sales of Alnylam Single Stranded RNAi Products by Alnylam, its Affiliates or sublicensees equal to [***]% of Net Sales; provided, however, that if Alnylam is the subject of an Acquisition, the royalty payable under this Section 7.2(b) on the Net Sales of Alnylam Single Stranded RNAi Products after the date of such Acquisition will be [***]%.

7.3 Research and Development Milestones.

(a) Single Stranded Research Milestones. Alnylam, its Affiliates or sublicensees will pay to Isis the following milestone payments within [***] after the first achievement of each of the following events:

Milestone Event	Milestone Payment
The earlier of (i) first *In Vivo* Efficacy in Rodents and (ii) the 18-month anniversary of the Restatement Date	US$10,000,000
First *In Vivo* Efficacy in NHP	US$5,000,000
First Initiation of Phase I Trial	US$5,000,000

Alnylam shall have the right to prepay Isis any or all of the milestone payments set forth in this Section 7.3(a) prior to achievement of the corresponding milestone event(s), in which event such milestone event(s) shall be deemed to have been achieved as of the date of such early payment(s) by Alnylam, and such early payments will be irrevocable, noncreditable and non-refundable. If Alnylam decides to terminate this Agreement pursuant to Section 14.4, the terms of Section 14.4(d) shall apply. For purposes of clarity, Alnylam does not have the right to prepay any of the milestones set forth in Section 7.3(b) through 7.3(d) below.

(b) Single Stranded Development Milestones. Alnylam, its Affiliates or sublicensees will pay to Isis the following milestone payments for each Alnylam Single Stranded RNAi Product within [***] after the first achievement of each of the following events:

Milestone Event	Milestone Payment*
Initiation of Phase I Trial	US$[***]
Initiation of Phase III Trial	US$[***]
Filing NDA in U.S., EU or Japan	US$[***]
Marketing Approval in U.S., EU or Japan	US$[***]

*****If Alnylam is the subject of an Acquisition, any milestone payments under this Section 7.3(b) that were not due before the date of such Acquisition will [***] in amount.

Each milestone payment under this Section 7.3(b) will only be due on the [***] Alnylam Single Stranded RNAi Product that modulates a particular Gene Target to trigger such milestone payment, whether such milestone is achieved by Alnylam or an Affiliate or sublicensee of Alnylam.

(c) Double Stranded Development Milestones. Alnylam, its Affiliates or sublicensees (except Naked Sublicensees) will pay to Isis the following milestone payments for each Alnylam Double Stranded RNA Product within [***] [***] after the first achievement of each of the following events:

Milestone Event	Milestone Payment
Initiation of Phase I Trial	US$[***]
Initiation of Phase III Trial	US$[***]
Filing NDA	US$[***]

Each milestone payment under this Section 7.3(c) will only be due on the [***] Alnylam Double Stranded RNA Product that modulates a particular Gene Target to trigger such milestone payment, whether such milestone is achieved by Alnylam or an Affiliate or sublicensee of Alnylam.

(d) MicroRNA Milestone. Alnylam, its Affiliates or sublicensees will pay to Isis a milestone payment of US$[***] for the [***] MicroRNA Product that is an Alnylam Product that modulates a particular Gene Target within [***] after such MicroRNA Product reaches the initiation of [***], and not for any other MicroRNA Product that is an Alnylam Product that modulates the particular Gene Target.

7.4 Sublicensing Revenue on Naked Sublicenses and Single Stranded Sublicenses.

(a) With respect to Sublicense Revenue from each Naked Sublicense granted by Alnylam and its Affiliates under this Agreement, Alnylam will pay Isis within [***] following receipt by Alnylam of such Sublicense Revenue (i) fifty percent (50%) of all such Sublicense Revenue that does not constitute royalty payments, and (ii) [***] percent ([***]%) of the amount that remains of the total royalties received under such Naked Sublicense after Alnylam has paid the royalties that are due from Alnylam to any Third Parties in connection with such Naked Sublicense.

(b) Alnylam will pay Isis a percentage of Sublicense Revenue received by Alnylam and its Affiliates pursuant to sublicenses (or right to obtain a sublicense) granted by Alnylam to a Third Party as permitted by Section 5.2(b). Alnylam shall make such payment within [***] [***] following receipt by Alnylam of such Sublicense Revenue. Such percentage will be calculated based on the year in which Alnylam executes such sublicense agreement, and whether or not Alnylam executes such sublicense before or after the Product(s) that are the subject of such sublicense have met the [***] under Section 7.3(b), using the following table:

For Single Stranded RNAi Products Alnylam Sublicenses Before [***]

Year	2009-2011	2012-2013	2014-2015	2016-2017	2017+
Applicable Percentage	[***]%	[***]%	[***]%	[***]%	[***]%

For Single Stranded RNAi Products Alnylam Sublicenses [***] Such Products

Year	2009-2012	2013	2014	2015+
Applicable Percentage	[***]%	[***]%	[***]%	[***]%

(c) If Alnylam grants a sublicense (or right to obtain a sublicense) pursuant to which Alnylam will be required to pay Isis Sublicense Revenue under Section 7.4(b), then, so long as Alnylam pays Isis the applicable Sublicense Revenue when due, Alnylam [***] have to pay Isis [***] of the milestones that become due under Section 7.3(b) after the execution of such sublicense solely with respect to the Alnylam Single Stranded RNAi Product(s) that are being developed and commercialized under each such sublicense.

(d) Notwithstanding any of the foregoing, each of the applicable percentages set forth in the tables above in Section 7.3(b) for any and all periods following the [***] anniversary of the Restatement Date shall be recalculated by multiplying each such percentage by the fraction of X/Y, where X is [***] and Y is the total number of Isis Partnered Excluded Targets for which contractual restrictions have not expired or been cleared as of the [***] anniversary of the Restatement Date. Such recalculation shall be made on the thirtieth (30^{th}) day following the [***] anniversary of the Restatement Date, provided, however, that (i) no recalculation shall be made if the total number of Isis Partnered Excluded Targets for which contractual restrictions have not expired or been cleared as of the [***] anniversary of the Restatement Date is less than or equal to [***]; (ii) the applicable percentages, as so recalculated, shall apply only to all sublicenses entered into between Alnylam and a Third Party following the [***] anniversary of the Restatement Date; and (iii) this Section 7.4(d) shall not adjust the applicable percentages set forth in the tables above in Section 7.3(b) as they apply to any sublicenses entered into between Alnylam and a Third Party on or before the [***] anniversary of the Restatement Date.

7.5 Technology Access Fees from Bona Fide Collaborations.

(a) Alnylam will pay Isis a percentage of Technology Access Fees received by Alnylam and its Affiliates pursuant to Bona Fide Drug Discovery Collaborations and Development Collaborations entered into between Alnylam and a Third Party. Alnylam shall make such payment to Isis within [***][***] following receipt by Alnylam of such Technology Access Fees. Such percentage will be calculated based on the year in which Alnylam executes such Bona Fide Drug Discovery Collaboration or Development Collaboration agreement using the following table:

Year	2004/2005	2006	2007	2008+
Applicable Percentage	[***]%	[***]%	[***]%	[***]%

However, Alnylam may credit any milestone payments made by Alnylam under Section 7.3(c) above with respect to an Alnylam Double Stranded RNA Product against any Technology Access Fees that are later due under a Bona Fide Drug Discovery Collaboration or Development Collaboration that involves the same Alnylam Double Stranded RNA Product that triggered such milestone payment.

(b) Notwithstanding the foregoing, for any Bona Fide Drug Discovery Collaboration or Development Collaboration agreement, Alnylam will pay Isis a minimum fee, payable upon the first Alnylam Product other than a Single Stranded RNAi

Product developed pursuant to such Bona Fide Drug Discovery Collaboration agreement reaching [***] (in which event Alnylam shall pay Isis such minimum fee within [***] following such initiation of [***]) or within [***] after the execution of such Development Collaboration agreement, equal to the lesser of (i) $[***] or (ii) [***]% of the Technology Access Fees from such collaboration; provided, however that Alnylam may credit any amounts paid Isis pursuant to Section 7.5(a) above as the result of the same Bona Fide Drug Discovery Collaboration or Development Collaboration agreement against this minimum fee with such amounts credited only once, and provided further that if following such payment, additional Technology Access Fees are owed to Isis for such Bona Fide Drug Discovery Collaboration or Development Collaboration, the amounts paid under this Section 7.5(b) (after crediting of any previous Technology Access Fees paid under Section 7.5(a) in accordance with the immediately preceding proviso) will be creditable against such future Technology Access Fees.

7.6 Allocation of Sublicense Income and Technology Access Fees. Each time Alnylam enters a collaboration or license agreement (an "Isis IP Sublicense") pursuant to which Alnylam grants a sublicense under the Isis Patent Rights to a Third Party, the CEO of Isis and the CEO of Alnylam will in mutually discuss and agree in writing upon: (a) if the Isis IP Sublicense only relates Double Stranded RNA, a good faith determination as to whether such Isis IP Sublicense is a Naked Sublicense or a Bona Fide Drug Discovery Collaboration or Development Collaboration; and (b) if the Isis IP Sublicense relates to Double Stranded RNA and Alnylam Single Stranded RNAi Product(s), a good faith allocation of the consideration received by Alnylam under such Isis IP Sublicense between the consideration attributable to the components of such Isis IP Sublicense that relate to (i) Double Stranded RNA and (ii) Alnylam Single Stranded RNAi Product(s). Within [***] days following the execution of each Isis IP Sublicense, Alnylam, through its CEO, will provide Isis' CEO a reasonably detailed and accurate description of such Isis IP Sublicense for the purpose of enabling the CEOs to perform the determination and allocation described in this Section 7.6.

7.7 Revenue Sharing for Research Program Patents. Alnylam will pay Isis 50% of any payments received by Alnylam and its Affiliates pursuant to licenses granted by Alnylam to a Third Party under the Research Program Patents for any and all purposes, except to research, develop, make, have made, use, import, offer to sell or sell any (1) oligonucleotides (or chemically modified oligonucleotide analogs) designed to work via the RNase H 1 or 2 mechanism (including any oligonucleotide which has [***]), (2) Double Stranded RNA Products, (3) MicroRNA Products, (4) Single Stranded RNAi Products, or (5) Isis Single Stranded Product. Alnylam shall make such payment to Isis within [***] following receipt by Alnylam of such payments.

ARTICLE 8

LICENSE FEES, SUBLICENSE REVENUE AND ROYALTIES PAYABLE TO ALNYLAM

8.1 Option Fee. For each Isis Reserved DS-Target for which Isis exercises its option granted pursuant to Section 6.2, Isis will pay Alnylam an irrevocable,

noncreditable and non-refundable option fee of $[***] due upon the date of exercise. Isis may credit any $[***] payment made under Section 6.4(a) for the DS-Target Slot occupied by such Reserved DS-Target against this option fee. The option fee is only payable once per Gene Target.

8.2 Royalties.

(a) Subject to the terms and conditions of, and during the term of, this Agreement, Isis will pay to Alnylam royalties on sales of Double Stranded RNA Products that are Isis Products by Isis, its Affiliates or sublicensees equal to [***]% of Net Sales. Isis may reduce the royalty due under this section by [***]% of any additional royalties that Isis owes to Third Parties on such Double Stranded RNA Products that are Isis Products that arise from Isis acquiring access to new technologies after the Restatement Date; provided, however that (i) the royalty due under this section can never be less than a floor of [***]%, (ii) additional royalties arising as the result of the addition, pursuant Section 11.8, of Alnylam Future Chemistry Patents or Alnylam Future Motif and Mechanism Patents to the Alnylam Patent Rights licensed to Isis, or as the result of an expansion of Isis' licenses pursuant to Section 6.5(d), cannot be used to reduce the royalty and (iii) Isis shall not be entitled to reduce, pursuant to this sentence, its royalty obligation to Alnylam below a royalty obligation equal to the lesser of (y) Alnylam's aggregate royalty obligations [***] existing as of the Effective Date [***] [***] and (z) Alnylam's aggregate royalty obligations [***] [***] as such obligations may be reduced from time to time after the Effective Date.

(b) Subject to the terms and conditions of, and during the term of, this Agreement, Isis will pay to Alnylam royalties on Net Sales of Isis Single Stranded RNAi Products by Isis, its Affiliates or sublicensees equal to [***]% of Net Sales; provided, however, that if Isis is the subject of an Acquisition, the royalty payable under this Section 8.2(b) on the Net Sales of Isis Single Stranded RNAi Products following such Acquisition will be [***]%.

8.3 Development Milestones.

(a) Subject to Section 8.4, Isis, its Affiliates or sublicensees will pay to Alnylam the following milestone payments for each Double Stranded RNA Product that is an Isis Product within [***] after the first achievement of each of the following events:

Milestone Event	Milestone Payment
Initiation of Phase I Trial	US$[***]
Initiation of Phase III Trial	US$[***]
Filing NDA	US$[***]
Marketing Approval	US$[***]

Each milestone payment under this Section 8.3(a) will only be due on [***] Double Stranded RNA Product that is an Isis Product that modulates a particular Gene Target to trigger such milestone payment, whether such milestone is achieved by Isis or an Affiliate or sublicensee of Isis.

(b) Isis, its Affiliates or sublicensees will pay to Alnylam a milestone payment of US$[***] for the [***] Isis Single Stranded Product that is an Isis Product that modulates a particular Gene Target within [***] after such Isis Single Stranded Product reaches the initiation of IND-Enabling Studies, and not for any other Isis Single Stranded Product that modulates that particular Gene Target.

(c) Isis, its Affiliates or sublicensees will pay to Alnylam a milestone payment of US$[***] for the [***] MicroRNA Product that is an Isis Product that modulates a particular Gene Target within [***] after such MicroRNA Product reaches the initiation of [***], and not for any other MicroRNA Product that is an Isis Product that modulates the particular Gene Target.

8.4 Sublicense Income on Single Stranded RNAi Sublicenses.

(a) With respect to Sublicense Revenue from each sublicense (or right to obtain a sublicense) related to an Isis Single Stranded RNAi Product granted by Isis and its Affiliates under this Agreement after the Restatement Date, Isis will pay Alnylam, within [***] following receipt by Isis of such Sublicense Revenue, a percentage of all such Sublicense Revenue that does not constitute royalty payments. Such percentage will be calculated based on the year in which Isis executes such sublicense agreement, and whether or not Alnylam has paid Isis the research funding and applicable milestones under Section 4.2(c) and 7.3(a), using the following table:

	Milestone Event	Applicable Percentage
1	Sublicense executed after the Restatement Date but before Alnylam pays Isis the $[***] milestone under Section 7.3(a)	[***]%
2	Sublicense executed after Alnylam pays Isis the $[***] milestone under Section 7.3(a) but before the 3rd milestone event described below	[***]%
3	Sublicense executed after Alnylam pays the first 3 years of research funding under Section 4.2(c) and the $[***] milestone for First *In Vivo* Efficacy in NHP under Section 7.3(a)	[***]%

(b) In the event that Isis enters an Antisense Drug Discovery Program pursuant to which Isis (i) grants a sublicense under the Alnylam Patent Rights to further develop and/or commercialize an Isis Single Stranded RNAi Product, (ii) commits to discover and/or develop Double Stranded RNA Products or single stranded oligonucleotides that are not Single Stranded RNAi Compounds, or (iii) grants a license or sublicense to intellectual property which would not otherwise result in any amounts becoming payable to Alnylam hereunder (an "Other Isis Sublicense"), then in determining the applicable payment due from Isis to Alnylam in connection with such Antisense Drug Discovery Program, the CEO of Isis and the CEO of Alnylam will mutually agree in writing upon a good faith allocation of the consideration received by Isis under such Antisense Drug Discovery Program between and among the consideration attributable to the components of such Antisense Drug Discovery Program that qualify as

(x) a sublicense to further develop and/or commercialize an Isis Single Stranded Product, (y) a collaboration to discover and/or develop Double Stranded RNA Products or single stranded oligonucleotides that are not Single Stranded RNAi Compounds, and (z) an Other Isis Sublicense; and Isis will pay Alnylam Sublicense Income Fees under Section 8.4(a) in accordance with such allocation. Within 30 days following the execution of each such transaction, Isis, through its CEO, will provide Alnylam's CEO a reasonably detailed and accurate description of such transaction for the purpose of enabling Alnylam's CEO to perform the allocation described in this Section 8.4(b).

8.5 Revenue Sharing for Research Program Patents. Isis will pay Alnylam 50% of any payments received by Isis and its Affiliates pursuant to licenses granted by Isis to a Third Party under the Research Program Patents for any and all purposes, except to research, develop, make, have made, use, import, offer to sell or sell any (1) oligonucleotides (or chemically modified oligonucleotide analogs) designed to work via the RNase H 1 or 2 mechanism (including any oligonucleotide which has [***]), (2) Double Stranded RNA Products, (3) MicroRNA Products, (4) Single Stranded RNAi Products, or (5) Isis Single Stranded Product. Isis shall make such payment to Alnylam within [***] following receipt by Isis of such payments.

ARTICLE 9

OTHER PAYMENT TERMS

9.1 Payments. All payments by a Party under this Agreement will be made in United States dollars by bank wire transfer in next day available funds to such bank account in the United States designated in writing by Alnylam or Isis, from time to time. Royalties payable under Sections 7.2 and 8.2 shall be payable on a quarterly basis within 45 days after the end of each calendar quarter. The Party with such royalty obligation (the "Royalty-Paying Party") shall provide the other Party with a report setting forth (i) gross sales of Alnylam Products or Isis Products, as applicable, by the Royalty-Paying Party, its Affiliates and sublicensees, (ii) all deductions from such gross sales taken in calculating Net Sales, (iii) Net Sales of Alnylam Products or Isis Products, as applicable, by the Royalty-Paying Party, its Affiliates and sublicensees, (iv) royalties payable based on such Net Sales and (v) all other information relevant to the calculation of such royalties, on a product-by-product and country-by-country basis, for each calendar quarter within [***] after the end of such calendar quarter.

9.2 Late Payments; Collections. In the event that any payment, including royalty, milestone, Sublicense Revenue or Technology Access Fee payments, due hereunder is not made when due, the payment will bear interest from the date due at the lesser of (i) 1.5% per month, compounded monthly, or (ii) the highest rate permitted by law; provided, however, that in no event will such rate exceed the maximum legal annual interest rate. If a Party disputes in writing the amount of an invoice presented by the other Party within [***] of receipt of such invoice, interest will only be due on the correct amount as later determined or agreed. The payment of such interest will not limit a Party from exercising any other rights it may have as a consequence of the lateness of any payment. In addition, each Party agrees to pay all external costs of collection, including

reasonable attorneys' fees, incurred by the other Party in enforcing the payment obligations after a due date has passed under this Agreement.

9.3 Audit Rights.

(a) Upon the written request of Isis or Alnylam, as the case may be, and not more than once in each calendar year, Isis or Alnylam will permit the other Party's independent certified public accountant to have access upon reasonable advance notice and during normal business hours to its records as may be reasonably necessary to verify the accuracy of the royalty reports hereunder for the current year and the preceding 2 years prior to the date of such request. The accounting firm will disclose to the auditing Party only whether the royalty reports are correct or incorrect, the specific details concerning any discrepancies, and the corrected amount of Net Sales and royalty payments. No other information will be provided to the auditing Party. Once a Party has audited a particular calendar year under this section, the Party will be precluded from subsequently auditing such calendar year. In any sublicense granted by a Party under this Agreement, such Party will endeavor to secure a similar audit right and if reasonably requested by the other Party will enforce such audit right.

(b) If such accounting firm concludes that additional royalties were owed during such period, the delinquent Party will pay the additional royalties within 90 days of the date such Party receives the accounting firm's written report. The fees charged by such accounting firm will be paid by the auditing Party unless the additional royalties, milestones or other payments owed by the audited Party exceed 5% of the royalties, milestones or other payments paid for the time period subject to the audit, in which case the audited Party will pay the reasonable fees and expenses charged by the accounting firm.

(c) Each Party will treat all financial information subject to review under this Section 9.3 or under any sublicense agreement in accordance with the confidentiality provisions of Article 12, and will cause its accounting firm to enter into an acceptable confidentiality agreement obligating such firm to retain all such financial information in confidence pursuant to such confidentiality agreement.

9.4 Taxes. If laws, rules or regulations require withholding of income taxes or other taxes imposed upon payments set forth in Section 4.2(c) or Article 7 or 8, each Party will make such withholding payments as required and subtract such withholding payments from the payments set forth in Section 4.2(c) or Article 7 or 8. Each Party will submit appropriate proof of payment of the withholding taxes to the other Party within a reasonable period of time. The Parties will cooperate to obtain the appropriate tax clearance and/or recover any such withholdings if possible.

ARTICLE 10

ALNYLAM RIGHTS OF FIRST NEGOTIATION; PREFERRED LICENSEE

10.1 Right of First Negotiation. Isis will notify Alnylam in writing once (i) Isis, on its own with no subsequent rights to Third Parties, intends to initiate [***] for an

Isis Product that is a Double Stranded RNA Product or (ii) if a Third Party with which Isis has a Development Collaboration or a collaboration on an [***] an Isis Double Stranded RNA Product before or during clinical development or commercialization with no subsequent rights to Third Parties. Alnylam will have [***] from the receipt of such notice to notify Isis in writing whether or not Alnylam wishes to negotiate with Isis regarding the development and/or commercialization of such Isis Product. If Alnylam fails to respond to Isis' notice within the [***] or if Alnylam declines in writing to exercise its right of first negotiation, then Isis will be free to develop and commercialize (either on its own or with a Third Party) the Isis Product. If Alnylam wishes to negotiate a license or development or commercialization rights in such Isis Product, the Parties will negotiate in good faith the terms of the license or collaboration agreement. If, despite good faith negotiations, Alnylam and Isis do not reach agreement within [***] from Alnylam's exercise of its right of first negotiation, then Isis will be free to develop and commercialize (either on its own or with a Third Party) the Isis Product; provided that during the period prior to the latest of (x) the initiation of [***] the Isis Product, (y) the [***] anniversary of the commencement of [***] for the Isis Product or (z) in the case of an Isis Product [***] after the commencement of [***], the [***] anniversary of Isis' notice to Alnylam [***], Isis shall not enter into a license or collaboration agreement with a Third Party for such Isis Product on terms (the "More Favorable Terms") that are in the aggregate materially more favorable to the Third Party than the terms on which Isis most recently offered in writing to grant such rights to Alnylam without first offering the More Favorable Terms to Alnylam.

10.2 Preferred Licensee. If, after the Effective Date, Alnylam grants to any Third Party that is not a Major Pharmaceutical Company a license under the Alnylam Patent Rights to develop and commercialize Double Stranded RNA Products, then if (a) either (i) the [***] terms of such license are more favorable to the Third Party than the [***] terms hereunder with respect to Isis Products are to Isis or (ii) the [***] covered by such license exceeds the [***] potentially licensed to Isis hereunder for development and commercialization of Double Stranded RNA Products, and (b) the roles to be played by Alnylam and such Third Party in the development and commercialization of Double-Stranded RNA Products under such Third Party license, the nature of the Gene Targets covered by such Third Party license and any other relevant terms of such Third Party license do not collectively justify the conditions described in the preceding clauses (a)(i) and/or (a)(ii), then Alnylam shall modify the terms of its licenses to Isis hereunder with respect to such conditions so that they are reasonably equivalent to those granted to the Third Party.

ARTICLE 11

INTELLECTUAL PROPERTY

11.1 Ownership of Inventions.

(a) Each Party will solely own all inventions, technology, discoveries, or other proprietary property (collectively, "Inventions") that are made (as determined by U.S. rules of inventorship) solely by employees of or consultants to that Party under this Agreement.

(b) Isis and Alnylam will jointly hold title to all Inventions, whether or not patentable, that are made (as determined by the U.S. rules of inventorship) jointly by employees of or consultants to Isis and Alnylam, as well as to Patents filed thereon. Such Inventions will be "Joint Inventions," and Patents claiming such Joint Inventions will be "Joint Patents." Isis and Alnylam will promptly provide each other with notice whenever a Joint Invention is made. The Parties agree and acknowledge that, except insofar as this Agreement provides otherwise, the default rights conferred on joint owners under US

patent law, including the right of each Party to independently practice, license and use a Joint Patent, will apply in relation to the Joint Patents throughout the world as though US patent law applied worldwide.

(c) The Parties agree, upon reasonable request, to execute any documents reasonably necessary to effect and perfect each other's ownership of any Invention.

11.2 Filing and Prosecution of Isis and Alnylam Patent Rights.

(a) Isis and Alnylam will work closely, through their interactions on the RMC to ensure that, to the greatest degree permitted by United States and foreign patent laws, Patents for Inventions relating to all aspects of Double Stranded RNA and/or Single Stranded RNAi Compounds or Single Stranded RNAi Products are obtained and shared.

(b) Except as set forth in Sections 11.2(f) and 11.2(g) below, Isis will be responsible for preparing, filing, prosecuting, maintaining and taking such other actions as are reasonably necessary or appropriate with respect to the Isis Patent Rights.

(c) Except as set forth in Section 11.2(f) and 11.2(g) below, Alnylam will be responsible for preparing, filing, prosecuting, maintaining and taking such other actions as are reasonably necessary or appropriate with respect to the Alnylam Patent Rights.

(d) Each Party will endeavor in good faith to coordinate its efforts with those of the other Party to minimize or avoid interference with the prosecution of the other Party's Patents. Neither Party will initiate or participate in any opposition, reexamination, interference, litigation or other proceeding for the purpose of narrowing or invalidating any claim in a Patent of the other Party.

(e) At either Party's request, the other Party will keep the requesting Party continuously informed of and provide documentation of all significant matters relating to the preparation, filing, prosecution and maintenance of any designated Patent.

(f) Alnylam will be responsible for preparing, filing, prosecuting, maintaining and taking such other actions as are reasonably necessary or appropriate with respect to the Isis Special Patents. If Alnylam elects not to file for or continue the prosecution (including any interferences, oppositions, reissue proceedings and re-examinations) or maintenance of an Isis Special Patent in any country, then, Alnylam will notify Isis promptly in writing of its intention in sufficient time to enable Isis to meet any deadlines by which an action must be taken to establish or preserve any such rights in such Patent in such country and Isis will have the right, but not the obligation, to file for

or continue the prosecution or maintenance of such Patent in such country, and Alnylam will cooperate with Isis in regard thereto.

(g) Solely with respect to (i) Research Program Patents, or (ii) Patents licensed under this Agreement that claim Inventions that primarily relate to Single Stranded RNAi Compounds, but, in each case, excluding Joint Patents, the Party who Controls such Patent (the "Responsible Party") will be responsible for preparing, filing, prosecuting, maintaining and taking such other actions as are reasonably necessary or appropriate with respect to such Patent. If the Responsible Party decides to discontinue the preparation, filing, prosecution or maintenance of such a Patent, the Responsible Party will notify the other Party at least [***] prior to any deadline that, if missed, would materially prejudice the Patent, and the other Party will have the right, at such Party's own expense, to prepare, file, prosecute and maintain such Patent.

11.3 Filing and Prosecution of Jointly Owned Patents.

(a) The Research Management Committee will designate one of the Parties as being the responsible Party for preparing, filing, prosecuting, maintaining and taking such other actions as are reasonably necessary or appropriate with respect to any Joint Patent.

(b) Each Party will keep the other Party continuously informed of all significant matters relating to the preparation, filing, prosecution and maintenance of Joint Patents, and shall provide the other Party with copies of any substantial prosecution papers within thirty days of receipt.

11.4 Costs and Expenses.

(a) Except as set forth in Section 11.4(c) below, each Party will bear its own costs and expenses in filing, prosecuting, maintaining and extending the Alnylam Patent Rights and Isis Patent Rights, respectively.

(b) Except as set forth in Section 11.4(c) below, the Parties will pay equal shares of all costs and expenses in filing, prosecuting, maintaining and extending the Joint Patents.

(c) Alnylam will bear [***]% of its own costs and expenses in filing, prosecuting, maintaining and extending the Isis Special Patents. If Alnylam elects not to file for or continue the prosecution (including any interferences, oppositions, reissue proceedings and re-examinations) or maintenance of an Isis Special Patent in any country, and Isis assumes the continued prosecution of such Isis Special Patent (as permitted by Section 11.2(f)) in such country, then the Parties will [***] all of Isis' costs and expenses in filing, prosecuting, maintaining and extending the Isis Special Patent for which Isis assumed prosecution.

11.5 Enforcement.

(a) Each Party will promptly advise the other of any suspected or actual infringement of the Isis Patent Rights, Alnylam Patent Rights, or Joint Patents by any

person that reasonably affects the other Party's business. The notice shall set forth the facts of such infringement or misappropriation in reasonable detail.

(b) Subject to subsections (c) and (h) below, Alnylam will have the sole and exclusive right, in its sole discretion and at its expense, to assert and enforce any Isis Patent Rights, Alnylam Patent Rights or Joint Patents against any party engaging in an unlicensed or unauthorized making, having made, using, selling, offering for sale or importing of any allegedly infringing Double Stranded RNA.

(c) For any enforcement by Alnylam under subsection (b) above that includes Isis Patent Rights covering a [***] chemical modification, Isis will actively participate in the planning and conduct of such enforcement and will take the lead of such enforcement to the extent that the scope or validity of any such Isis Patent Rights covering a [***] chemical modification is at risk.

(d) Except as set forth in Sections 11.5(b) and (h),

(i) Isis will have the sole and exclusive right, in its sole discretion and at its expense, to assert and enforce any Isis Patent Rights;

(ii) Alnylam will have the sole and exclusive right, in its sole discretion and at its expense, to assert and enforce any Alnylam Patent Rights and the Isis Special Patent Rights; and

(iii) The RMC will agree in advance on the enforcement of any Joint Patent and will apportion enforcement responsibilities and recoveries amongst the parties.

(e) The rights granted hereunder to Alnylam to enforce certain licensed in or jointly owned Isis Patent Rights are further limited as described in Exhibit 5.3(d) attached hereto. The rights granted hereunder to Isis to enforce certain licensed in or jointly owned Alnylam Patent Rights are further limited as described in Exhibit 6.5(c) attached hereto.

(f) The nonenforcing Party will have the right, at its own expense, to participate in the conduct of the enforcement action and to be represented in such action by its own counsel.

(g) The enforcing Party will not enter into any settlement that impacts the validity, scope or interpretation of any claim of any Joint Patent or of any Patent of the nonenforcing Party without prior written authorization of the nonenforcing Party.

(h) If the Party with enforcement rights under section (b) or (d) above (the "Primary Party") fails to initiate proceedings against any actual or suspected infringement within [***] of receipt of written request for enforcement from the other Party (the "Step-in Party") and if the infringer is directly competing with a Product (the "Affected Product") of such Step-in Party, then (i) if the license granted in this Agreement under which the Step-in Party is selling the Affected Product is exclusive or co-exclusive, the Step-in Party will have the right to assert and enforce the patents that are allegedly being

infringed, or (ii) if the license granted in this Agreement under which the Step-in Party is selling the Affected Product is non-exclusive, the Step-in Party will have no obligation to pay royalties during the period for which the Primary Party fails to initiate proceedings or take other action (including without limitation entering into a licensing arrangement) to eliminate such infringement; provided that the provisions of the immediately preceding clause (ii) shall not apply if the Primary Party elects to grant the Step-in Party enforcement rights with respect to such infringement. The Primary Party will not grant a license to any such infringing Third Party with respect to any directly competitive infringing product on terms materially more favorable (milestones and royalties) than the terms of the license granted hereunder to the Step-in Party or, solely with respect to the Affected Product, will adjust the terms of such license so that they are not materially less favorable than the terms of the license granted to the infringing Third Party. In addition, as a condition to the Step-in Party's right (under clause (i) of this Section 11.5(h)) to assert and enforce a Patent Controlled by the Primary Party that is allegedly being infringed, the Step-in Party must also assert and enforce any relevant Patents Controlled by such Step-in Party against the alleged infringer who is competing with the Affected Product.

(i) Except as otherwise agreed to by the Parties as part of a cost-sharing arrangement, any recovery realized as a result of such litigation, after reimbursement of any reasonable litigation expenses of Isis and Alnylam, shall be retained by the Party or Parties that brought and controlled such litigation for purposes of this Agreement, except that any recovery realized as a result of such litigation shall be treated as Net Sales of Isis Products or Net Sales of Alnylam Products and distributed as such Net Sales would have been distributed.

11.6 [Intentionally Deleted]

11.7 Third Party Patents. The Parties will consult about the need to license any patents Controlled by Third Parties that would be useful or necessary for either Party to research, develop, make, have made, use, sell, offer for sale or import Double Stranded RNA Products or Single Stranded RNAi Products. If it is agreed that there is a desire to obtain a license or to acquire any such patent, the Parties will negotiate in good faith regarding (i) the share of the financial obligations relating to the license or acquisition that each Party will bear; (ii) the compensation of any acquisition costs incurred in connection with obtaining the Patent rights; and (iii) an agreement by the Parties to abide by all terms of the agreement under which the patent rights are granted.

11.8 Future Licenses. If after the Effective Date, a Party (the "Controlling Party") later invents or acquires rights or title to an invention claimed by a Patent that (i) would be included in the Isis Future Chemistry Patents or Isis Future Motif and Mechanism Patents if such Party is Isis or in the Alnylam Future Chemistry Patents or Alnylam Future Motif and Mechanism Patents if such Party is Alnylam (the "Additional Rights") and (ii) carry financial or other obligations, then the Controlling Party must promptly notify the non-Controlling Party of such acquisition or invention. If the non-Controlling Party wishes to include such Additional Rights under the licenses granted pursuant to Article 5 or 6, as applicable, the non-Controlling Party will notify the Controlling Party of its desire to do so and will assume all financial and other obligations

to the Controlling Party's licensors or collaborators, if any, arising from the grant to the non-Controlling Party of such license. Any Additional Rights that do not carry financial or other obligations shall be automatically included under the licenses granted pursuant to Article 5 or 6, as applicable. If a Party pays any upfront payments or similar acquisition costs to access Additional Rights, the Parties will negotiate in good faith regarding sharing such acquisition costs and

payments. When acquiring or creating such Additional Rights, each Party will endeavor in good faith to secure the right to sublicense such Additional Rights to the other Party.

ARTICLE 12

CONFIDENTIALITY

12.1 Nondisclosure Obligation. All Confidential Information disclosed by one Party to the other Party hereunder will be maintained in confidence by the receiving Party and will not be disclosed to a Third Party or Affiliate or used for any purpose except as set forth below.

12.2 Permitted Disclosures. Except as otherwise provided herein, a Party may disclose Confidential Information received from the other Party:

(a) to governmental or other regulatory agencies in order to obtain Patents or approval to conduct clinical trials, or to gain Marketing Approval; provided that such disclosure may be made only to the extent reasonably necessary to obtain such Patents or approvals;

(b) to any adjudicative body as required by law, provided that prior to such disclosure, the Party subject to such disclosure obligation (the "Notifying Party") promptly notifies the other Party of such requirement so that such other Party can seek a protective order, confidential treatment or other appropriate remedy; and provided, further, that in the event that no such protective order, confidential treatment or other remedy is obtained, or that such other Party waives compliance with this section, the Notifying Party will furnish only that portion of the other Party's Confidential Information that it is advised by counsel it is legally required to furnish;

(c) to Affiliates, sublicensees, agents, consultants, and/or other Third Parties for the development, manufacturing and/or marketing of Isis Products or Alnylam Products (or for such parties to determine their interest in performing such activities) in accordance with this Agreement on the condition that such Affiliates, sublicensees and Third Parties agree to be bound by the confidentiality obligations contained in this Agreement;

(d) if such disclosure is required by law or regulation (including without limitation by rules or regulations of any securities exchange or NASDAQ), provided that prior to such disclosure, the Notifying Party promptly notifies the other Party of such requirement so that such other Party can seek a protective order, confidential treatment or other appropriate remedy; and provided, further, that in the event that no such protective order, confidential treatment or other remedy is obtained, or

that such other Party waives compliance with this section, the Notifying Party will furnish only that portion of the other Party's Confidential Information that it is advised by counsel it is legally required to furnish; or

(e) as necessary if embodied in products to develop and commercialize such products.

Either Party may disclose (i) a copy of this Agreement on a confidential basis to prospective lenders and investors, (ii) a mutually agreed upon redacted copy of this Agreement on a confidential basis to prospective collaborators and (iii) the terms of this Agreement as required under applicable securities laws or regulations (including without limitation under rules or regulations of any securities exchange or NASDAQ); provided, however, that, subject to Section 6.4(i), Alnylam shall not disclose Isis' past or current Reserved DS-Targets or past or current Isis Protected Targets without the express prior written consent of Isis, and, subject to Section 4.3(f), neither Party shall disclose the other Party's past or current Enabled Targets without the express prior written consent of the other Party.

12.3 Announcements; Publicity.

(a) Each Party understands that this Agreement is likely to be of significant interest to investors, analysts and others, and that either Party therefore may make public announcements with respect to this Agreement. The Parties agree that any such announcement will not contain confidential business or technical information unless disclosure of confidential business or technical information is required by law or regulation, in which case they will make reasonable efforts to minimize such disclosure of confidential business or technical information to that required by law or regulation. Each Party agrees to provide to the other Party a copy of any such public announcement as soon as reasonably practicable under the circumstances prior to its scheduled release. Except under extraordinary circumstances, each Party shall provide the other with an advance copy of any press release at least two (2) business days prior to the scheduled disclosure. The other Party shall have the right to expeditiously review and recommend changes to any announcement regarding this Agreement or the subject matter of this Agreement, provided that 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 (i) is substantially similar to a previously reviewed disclosure and (ii) in the context of the subsequent disclosure, does not carry a substantially different qualitative message than that carried by the previously reviewed disclosure. The Party whose press release has been reviewed shall in good faith consider any changes that are timely recommended by the reviewing Party.

(b) Each Party will (i) use reasonable, good faith efforts to provide the other Party with at least 5 business days' prior notice (which notice may be given orally to a senior executive officer of the other Party) before such Party publicly announces the execution of a Naked Sublicense, Bona Fide Drug Discovery Collaboration agreement or Development Collaboration agreement (or any material amendments thereto) that could reasonably be expected to be of strategic or financial importance to the other Party's

business and (ii) cooperate with the other Party to enable the other Party to develop appropriate mutually beneficial public announcements regarding such transactions.

ARTICLE 13

INDEMNIFICATION

13.1 Indemnification by Alnylam. Alnylam will indemnify, defend and hold Isis and its agents, employees, officers and directors (the "Isis Indemnitees") harmless from and against any and all liability, damage, loss, cost or expense (including reasonable attorneys' fees) arising out of Third Party claims or suits related to (a) Alnylam's performance of its obligations under this Agreement; (b) breach by Alnylam of its representations and warranties set forth in Article 15; or (c) the discovery, development, manufacture, use, importation or commercialization (including marketing and sale) of Alnylam Products.

13.2 Indemnification by Isis. Isis will indemnify, defend and hold Alnylam and its Affiliates and each of their respective agents, employees, officers and directors (the "Alnylam Indemnitees") harmless from and against any and all liability, damage, loss, cost or expense (including reasonable attorneys' fees) arising out of Third Party claims or suits related to (a) Isis' performance of its obligations under this Agreement; (b) breach by Isis of its representations and warranties set forth in Article 15; or (c) the discovery, development, manufacture, use, importation or commercialization (including marketing and sale) of Isis Products.

13.3 Notification of Claims; Conditions to Indemnification Obligations. A Party entitled to indemnification under this Article 13 shall (a) promptly notify the other 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 shall 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 Article 13 with respect to claims or suits settled or compromised without its prior written consent.

ARTICLE 14

TERM AND TERMINATION OF AGREEMENT

14.1 Term and Termination of Agreement. This Agreement will be effective as of the Restatement Date (unless otherwise expressly stated) and unless terminated earlier

pursuant to Sections 14.2 or 14.3 below, the term of this Agreement will continue in effect until expiration of the License Term.

14.2 Termination upon Material Breach. This Agreement may be terminated upon written notice by either Party to the other at any time during the term of this Agreement if the other Party is in material breach of its obligations hereunder and has not cured such breach within 90 days after written notice requesting cure of the breach; provided, however, that (a) in the event of a good faith dispute with respect to the existence of such a material breach, the 90-day cure period will be stayed until such time as the dispute is resolved pursuant to Section 17.6 hereof, (b) so long as the breaching Party takes substantial steps to cure the breach promptly after receiving notice of the breach from the non-breaching Party and thereafter diligently prosecutes the cure to completion as soon as is practicable, the non-breaching Party may not terminate this Agreement, and (c) any license granted under this Agreement with respect to an Isis or Alnylam Product that has at least reached IND-Enabling Studies may not be terminated for a material breach under this Section 14.2 (*except* for an uncured failure to make any undisputed portion of any payment obligation under Article 7 or 8 with respect to such Isis or Alnylam Product) to the extent such license is necessary to develop, make and have made, sell and import such Isis or Alnylam Product.

14.3 Termination upon Bankruptcy; Rights in Bankruptcy.

(a) This Agreement may be terminated with written notice by either Party at any time during the term of this Agreement upon the filing or institution of bankruptcy, reorganization, liquidation or receivership proceedings by or against the other Party or upon an assignment of a substantial portion of its assets for the benefit of creditors by the other Party; provided, however, in the case of any involuntary bankruptcy proceeding such right to terminate will only become effective if the Party consents to the involuntary bankruptcy or such proceeding is not dismissed within 90 days of the filing thereof.

(b) All rights and licenses granted under or pursuant to this Agreement by Isis or Alnylam are, and will otherwise be deemed to be, for purposes of Section 365(n) of the U.S. Bankruptcy Code, licenses of right to "intellectual property" as defined under Section 101 of the U.S. Bankruptcy Code. The Parties agree that the Parties, as licensees of such rights under this Agreement, will retain and may fully exercise all of their rights and elections under the U.S. Bankruptcy Code. The Parties further agree that, in the event of the commencement of a bankruptcy proceeding-by or against either Party under the U.S. Bankruptcy Code, the Party hereto which is not a Party to such proceeding will be entitled to a complete duplicate of (or complete access to, as appropriate) any such intellectual property and all embodiments of such intellectual property, and same, if not already in their possession, will be promptly delivered to them (i) upon any such commencement of a bankruptcy proceeding upon their written request therefore, unless the Party subject to such proceeding elects to continue to perform all of its obligations under this Agreement, or (ii) if not delivered under (i) above, following the rejection of this Agreement by or on behalf of the Party subject to such proceeding upon written request therefore by the non-subject Party.

14.4 Alnylam's Limited Right to Terminate the Research Program. Notwithstanding Section 4.2, Alnylam may unilaterally elect to terminate the Research Program, by providing Isis a written notice of such election (an "Early Termination Notice") on or before 5:00 PM Pacific Time on September 30, 2010. If Alnylam unilaterally terminates the Research Program (the "Early Collaboration Termination") in accordance with this Section 14.4, then, as of the date of the Early Termination Notice (the "Collaboration Termination Date"):

(a) each Party's obligation to perform under the Research Program, and Alnylam's obligation to provide funding under the Research Program that was not payable on or before the Collaboration Termination Date will automatically terminate;

(b) Alnylam's rights and Isis' obligations under the licenses granted by Isis to Alnylam under Section 5.1(g), 5.1(h) and 5.1(i), including any sublicenses granted by Alnylam thereunder, will automatically terminate;

(c) Solely with respect to the license granted to Isis under Section 6.1(i), the definition of Alnylam Future Motif and Mechanism Patents, and Alnylam Future Chemistry Patents, will be fixed as of the Collaboration Termination Date in accordance with Sections 12 and 13, respectively, of Exhibit 1.1;

(d) Alnylam will be relieved of its obligations to pay Isis any milestones, royalties and sublicense income relating to Alnylam Single Stranded RNAi Products under Sections 7.2(b), 7.3(a), 7.3(b), and 7.4(b) that had not accrued by the Collaboration Termination Date, *except* that if the Collaboration Termination Date is before the [***]-month anniversary of the Restatement Date and before the [***] following the date Alnylam obtains the data that demonstrates the first *In Vivo* Efficacy in Rodents, then Alnylam will not be obligated to pay the $[***] research milestone for the first *In Vivo* Efficacy in Rodents set forth in Section 7.3(a); and

(e) Isis will be relieved of its obligations under Sections 5.5 and 8.5, and its obligations as a Responsible Party under Section 11.2(g).

14.5 Accrued Rights and Surviving Obligations.

(a) Expiration or termination of the Agreement will not relieve the Parties of any obligation accruing prior to such expiration or termination, including, but not limited to, financial obligations under Section 4.2(c) or Article 7 or 8. Sections 4.3(f), 6.4(i), 9.2, 9.3 and 11.1, and Articles 1, 12, 13, 14 and 17 will survive expiration or termination of the Agreement. Provisions concerning reporting requirements will continue in effect in accordance with any applicable timetables set forth herein. Any expiration or early termination of this Agreement will be without prejudice to the rights of either Party against the other accrued or accruing under this Agreement prior to termination. No expiration of this Agreement will relieve a Party of its obligation to pay milestones, royalties, or a percentage of Technology Access Fees or Sublicense Revenue to the extent accrued prior to such expiration.

(b) Except as set forth in Section 14.4.(b), the rights of any sublicensee under any permitted sublicense granted in accordance with Section 5.2 or 6.3 will survive the termination of this Agreement.

ARTICLE 15

REPRESENTATIONS AND WARRANTIES; DISCLAIMER

15.1 Representations and Warranties of the Parties. Each Party represents and warrants to the other Party that, as of the Effective Date and the Restatement Date:

(a) Such Party is duly organized and validly existing under the laws of the state of its incorporation and has full corporate power and authority to enter into this Agreement and to carry out the provisions hereof;

(b) Such Party has taken all corporate action necessary to authorize the execution and delivery of this Agreement and the performance of its obligations under this Agreement;

(c) This Agreement is a legal and valid obligation of such Party, binding upon such Party and enforceable against such Party in accordance with the terms of this Agreement. The execution, delivery and performance of this Agreement by such Party does not conflict with any agreement, instrument or understanding, oral or written, to which such Party is a Party or by which such Party may be bound, and does not violate any law or regulation of any court, governmental body or administrative or other agency having authority over such Party. All consents, approvals and authorizations from all governmental authorities or other Third Parties required to be obtained by such Party in connection with this Agreement have been obtained;

(d) Such Party has sufficient right, power and authority to enter into this Agreement, to perform its obligations under this Agreement and to grant the licenses granted hereunder.

15.2 Disclaimers. THE PARTIES EXPRESSLY DISCLAIM ALL WARRANTIES, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, OR NON-INFRINGEMENT OF THIRD PARTY RIGHTS, UNLESS OTHERWISE EXPRESSLY PROVIDED IN THIS AGREEMENT.

ARTICLE 16

NOTICE

16.1 Notice. All notices which are required or permitted hereunder will be in writing and sufficient if delivered personally, sent by facsimile (and confirmed by telephone), sent by nationally-recognized overnight courier or sent by registered or certified mail, postage prepaid, return receipt requested, addressed as follows:

if to Isis, to: Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attention: Chief Operating Officer
Fax No.: +1 (760) 603-4652

with a copy to: Attention: General Counsel

Fax No.: +1 (760) 268-4922

if to Alnylam, to: Alnylam Pharmaceuticals, Inc.
300 Third Street
Cambridge, MA 02142
Attention: VP Legal
Fax No.: +1 (617) 575-7315

with a copy to: WilmerHale
60 State Street
Boston, Massachusetts 02109
Attention: Steven D. Singer, Esq.
Fax No.: +1 (617) 526-5000

or to such other address as the Party to whom notice is to be given may have furnished to the other Party in writing in accordance herewith. Any such notice will be deemed to have been given when delivered if personally delivered or sent by facsimile on a business day, on the business day after dispatch if sent by nationally-recognized overnight courier and on the third business day following the date of mailing if sent by mail.

ARTICLE 17

MISCELLANEOUS PROVISIONS

17.1 Relationship of the Parties. It is expressly agreed that Isis and Alnylam will be independent contractors and that the relationship between the two Parties will not constitute a partnership, joint venture or agency. Neither Isis nor Alnylam will have the authority to make any statements, representations or commitments of any kind, or to take any action, which will be binding on the other, without the prior consent of the other Party.

17.2 Successors and Assigns. Neither this Agreement nor any interest hereunder may be assigned or otherwise transferred (whether by sale of stock, sale of assets or merger), nor, except as expressly provided hereunder, may any right or obligations hereunder be assigned or transferred by either Party without the prior written consent of the other Party; provided, however, that a Party may, without such consent, assign this Agreement and its rights and obligations hereunder to an Affiliate or in connection with an Acquisition. Notwithstanding the provisions of this Section 17.2:

(a) If Alnylam is the subject of an Acquisition and the entity surviving such Acquisition does not maintain [***] that is substantially similar or greater [***] after the time of the Acquisition, then (i) the limit on the [***] that Isis can [***] pursuant to Section 6.4(a) will [***], and (ii) the exclusive right to grant Naked Sublicenses under Section 5.2 will [***].

(b) Additionally, if Alnylam is the subject of an Acquisition, (i) the royalties payable by Alnylam with respect to Alnylam Single Stranded RNAi Products will be adjusted in accordance with Section 7.2(b), (ii) the definition of Alnylam Future Motif and Mechanism Patents, and Alnylam Future Chemistry Patents, will be fixed as of the date of such Acquisition in accordance with Sections 13 and 12, respectively, of Exhibit 1.1, and (iii) [***].

(c) If Isis is the subject of an Acquisition, (i) the entity surviving such Acquisition will no longer [***] under Section 6.4(a), (ii) the number of [***] such Acquisition will be permitted to [***] pursuant to Section 6.4(a) shall be limited to [***] per calendar year, (iii) the royalties payable by Isis with respect to Isis Single Stranded RNAi Products will be adjusted in accordance with Section 8.2(b), and (iv) the definition of Isis Future Motif and Mechanism Patents, and Isis Future Chemistry Patents, will be fixed as of the date of such Acquisition in accordance with Sections 57 and 58, respectively, of Exhibit 1.1.

(d) Any permitted assignee will assume all obligations of its assignor under this Agreement. Any attempted assignment not in accordance with this Section 17.2 will be void.

17.3 Entire Agreement; Amendments. This Agreement contains the entire understanding of the Parties with respect to the license, development and commercialization of Products hereunder. All express or implied agreements and understandings, either oral or written, heretofore made by the Parties on the same subject matter are expressly superseded by this Agreement. This Agreement may be amended, or any term hereof modified, only by a written instrument duly executed by both Parties hereto.

17.4 Force Majeure. Neither Party will be held liable or responsible to the other Party nor be deemed to have defaulted under or breached this Agreement for failure or delay in fulfilling or performing any term of this Agreement when such failure or delay is caused by or results from causes beyond the reasonable control of the affected Party including, 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 Party 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.

17.5 Applicable Law. The Agreement will be governed by and construed in accordance with the laws of the State of Delaware without reference to any rules of conflict of laws.

17.6 Dispute Resolution.

(a) The Parties recognize that disputes may from time to time arise between the Parties during the term of this Agreement. In the event of such a dispute, either Party, by written notice to the other Party, may have such dispute referred to the Parties' respective executive officers designated below or their successors, for attempted resolution by good faith negotiations within 30 days after such notice is received. Said designated officers are as follows:

For Isis:	Chief Operating Officer
For Alnylam:	President and Chief Operating Officer

If the dispute is not resolved as provided above, the CEO of Isis and the CEO of Alnylam will meet for attempted resolution by good faith negotiations within 15 days after the expiration of the preceding 30 day period.

(b) In the event the designated executive officers are not able to resolve such dispute during such 15-day period, then any such dispute shall be resolved through binding arbitration under the Commercial Arbitration Rules of the American Arbitration Association by a panel of three arbitrators appointed in accordance with such rules. The Parties shall be entitled to the same discovery as permitted under the U.S. Federal Rules of Civil Procedure; provided that the panel shall be entitled in its discretion to grant a request from a Party for expanded or more limited discovery. The award of the arbitrators shall be the sole and exclusive remedy between the Parties regarding any such dispute. An award rendered in connection with an arbitration pursuant to this Section 17.6 shall be final and binding upon the Parties and any judgment upon such award may be entered and enforced in any court of competent jurisdiction. Any arbitration pursuant to this Section 17.6 shall be conducted in San Diego, California if Alnylam initiates the arbitration or in Boston, Massachusetts if Isis initiates the arbitration. Nothing in this Section 17.6 shall be construed as limiting in any way the right of a Party to seek an injunction or other equitable relief with respect to any actual or threatened breach of this Agreement or to bring an action in aid of arbitration. Should any Party seek an injunction or other equitable relief, or bring an action in aid of arbitration, then for purposes of determining whether to grant such injunction or other equitable relief, or whether to issue any order in aid of arbitration, the dispute underlying the request for such injunction or other equitable relief, or action in aid of arbitration, may be heard by the court in which such action or proceeding is brought.

17.7 No Consequential Damages. IN NO EVENT WILL EITHER PARTY OR ANY OF ITS RESPECTIVE AFFILIATES BE LIABLE TO THE OTHER PARTY OR ANY OF ITS AFFILIATES FOR SPECIAL, INDIRECT, INCIDENTAL OR CONSEQUENTIAL DAMAGES, WHETHER IN CONTRACT, WARRANTY, TORT, NEGLIGENCE, STRICT LIABILITY OR OTHERWISE, INCLUDING, BUT NOT LIMITED TO, LOSS OF PROFITS OR REVENUE, OR CLAIMS OF CUSTOMERS OF ANY OF THEM OR OTHER THIRD PARTIES FOR SUCH OR OTHER DAMAGES.

17.8 Captions. The captions to the several Articles and Sections hereof are not a part of this Agreement, but are merely a convenience to assist in locating and reading the several Articles and Sections hereof.

17.9 Waiver. The waiver by either Party hereto of any right hereunder, or the failure to perform, or a breach by the other Party will not be deemed a waiver of any other right hereunder or of any other breach or failure by said other Party whether of a similar nature or otherwise.

17.10 Compliance with Law. Nothing in this Agreement will be deemed to permit a Party to export, re-export or otherwise transfer any Product sold under this Agreement without compliance with applicable laws.

17.11 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.

17.12 Waiver of Rule of Construction. Each Party has had the opportunity to consult with counsel in connection with the review, drafting and negotiation of this Agreement. Accordingly, the rule of construction that any ambiguity in this Agreement will be construed against the drafting Party will not apply.

17.13 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.

17.14 Performance by Affiliates. To the extent that this Agreement imposes obligations on Affiliates of a Party, such Party agrees to cause its Affiliates to perform such obligations.

17.15 No Implied License. Except as expressly provided in Sections 5.1, 6.1 and 6.2 of this Agreement, no Party will be deemed by estoppel or implication to have granted the other Party any license or other right with respect to any intellectual property of such Party.

IN WITNESS WHEREOF, the Parties have executed this Agreement as of the Restatement Date.

ISIS PHARMACEUTICALS, INC.		**ALNYLAM PHARMACEUTICALS, INC.**	
By:	*/s/ B. Lynne Parshall*	By:	*/s/ Barry Greene*
Name:	B. Lynne Parshall	Name:	Barry Greene
Title:	Chief Operating Officer	Title:	President & COO

EXHIBIT 1.1

DEFINITIONS

1. "Acquisition" means any of the following events: (a) the acquisition by any Person or group, other than a Person or group controlling such Party as of the Restatement Date, of "beneficial ownership" (as defined in Rule 13d-3 under the United States Securities Exchange Act of 1934, as amended), directly or indirectly, of fifty percent (50%) or more of the shares of such Party's voting stock; (b) the approval by the shareholders of such Party of a merger, share exchange, reorganization, consolidation or similar transaction of such Party (a "Transaction"), other than a Transaction which would result in the voting stock of such Party outstanding immediately prior thereto continuing to represent (either by remaining outstanding or by being converted into voting securities of the surviving entity) more than fifty percent (50%) of the voting stock of such Party or such surviving entity immediately after such Transaction; or (c) approval by the shareholders of such Party of a complete liquidation of such Party or a sale or disposition of all or substantially all of the assets of such Party.

2. "Active Program" means with respect to a Gene Target and a Party, any ongoing drug discovery, development, or commercialization of a compound directed to such Gene Target being conducted by such Party (whether on its own or through a sublicensee).

3. "Actual FTE Costs" has the meaning set forth in Section 4.2(c).

4. "Actual External Costs" has the meaning set forth in Section 4.2(c).

5. "Advancing Party" has the meaning set forth in Section 4.3(a).

6. "Affiliate" with respect to either Party means Person controlling, controlled by, or under common control with such Party. For purposes of this definition, "control" refers to the possession, directly or indirectly, of the power to direct the management or policies of a Person, whether through the ownership of voting securities, by contract or otherwise, of a Person. Notwithstanding the foregoing, Regulus Therapeutics Inc. will not be considered an Affiliate of either Party.

7. "Alnylam Current Chemistry Patents" means all Chemistry Patents Controlled by Alnylam as of the Restatement Date, including without limitation the Patents listed on Schedule 1-7 attached hereto, *except* Patents that constitute Alnylam Excluded Technology, or Co-Exclusive ssRNAi Patents.

8. "Alnylam Current Motif and Mechanism Patents" means all Motif and Mechanism Patents Controlled by Alnylam as of the Restatement Date, including without limitation the Patents listed on Schedule 1-8 attached hereto, *except* Patents that constitute Alnylam Excluded Technology, or Co-Exclusive ssRNAi Patents.

9. "Alnylam Double Stranded RNA Product" means a Double Stranded RNA Product discovered or developed by Alnylam, its Affiliates or sublicensees, the manufacture, sale or use of which is covered by a Valid Claim within the Isis Patent Rights.

10. "Alnylam Enabled Target Pool" has the meaning set forth in Section 4.3(a).

11. "Alnylam Excluded Technology" means inhibitors to specific genes or gene families, manufacturing and analytical technologies, formulation and delivery technologies and the specific technology listed on Schedule 1-10 attached hereto.

12. "Alnylam Future Chemistry Patents" means all Chemistry Patents Controlled by Alnylam after the Restatement Date and having an earliest priority date of no later than [***] or that is necessary to practice a Patent licensed hereunder; provided, however that (a) for any such Chemistry Patents that are acquired, licensed or invented that include financial or other obligations to a Third Party, the provisions of Section 11.8 will govern whether such Patent will be included as an Alnylam Future Chemistry Patent and (b) Alnylam Future Chemistry Patents do not include Patents that constitute Alnylam Excluded Technology, or Co-Exclusive ssRNAi Patents. Notwithstanding the foregoing, (i) in the event an Acquisition involving Isis occurs before [***], the date "[***]" used in this definition will be automatically changed to the date of such Acquisition; and (ii) in the event of an Early Collaboration Termination under Section 14.4, *solely* with respect to the licenses granted to Isis under Section 6.1(i), the date "[***]" used in this definition will be automatically changed to the Collaboration Termination Date.

13. "Alnylam Future Motif and Mechanism Patents" means all Motif and Mechanism Patents Controlled by Alnylam after the Restatement Date and having an earliest priority date of no later than [***] or that is necessary to practice a Patent licensed hereunder; provided, however that (a) for any such Motif and Mechanism Patents that are acquired, licensed or invented that include financial or other obligations to a Third Party, the provisions of Section 11.8 will govern whether such Patent will be included as an Alnylam Future Motif and Mechanism Patent and (b) Alnylam Future Motif and Mechanism Patents do not include Patents that constitute Alnylam Excluded Technology, or Co-Exclusive ssRNAi Patents. Notwithstanding the foregoing, (i) in the event an Acquisition involving Isis occurs before [***], the date "[***]" used in this definition will be automatically changed to the date of such Acquisition, and (ii) in the event of an Early Collaboration Termination under Section 14.4, *solely* with respect to the licenses granted to Isis under Section 6.1(i), the date "[***]" used in this definition will be automatically changed to the Collaboration Termination Date.

14. "Alnylam Patent Rights" means Alnylam Current Motif and Mechanism Patents, Alnylam Future Motif and Mechanism Patents, Alnylam Current Chemistry Patents and Alnylam Future Chemistry Patents. For purposes of determining whether a royalty is payable by Isis under Section 8.2 in connection with the sale of an Isis Single Stranded RNAi Product, any Joint Patent, a Valid Claim of

which covers the manufacture, use or sale of such Isis Single Stranded RNAi Product, will be considered an Alnylam Patent Right.

15. "Alnylam Product" means an Alnylam Double Stranded RNA Product MicroRNA Product, or Alnylam Single Stranded RNAi Product, discovered or developed by Alnylam, its Affiliates or sublicensees, the manufacture, sale or use of which is covered by a Valid Claim within the Isis Patent Rights.

16. "Alnylam Single Stranded RNAi Product" means any Single Stranded RNAi Product Designed for an Alnylam Enabled Target, the manufacture, sale or use of which is covered by a Valid Claim within the Isis Patent Rights.

17. "Antisense Drug Discovery Program" means an antisense drug discovery program that investigates multiple different mechanisms of modulating a Gene Target to identify a drug candidate, with a predominant emphasis on potential drug candidates that are single-stranded.

18. "Applicable Laws" means all laws, statutes, rules, regulations, orders, judgments, or ordinances having the effect of law of any federal, national, multinational, state, provincial, county, city or other political subdivision.

19. "Bona Fide Drug Discovery Collaboration" means a collaboration involving the discovery and development of Double Stranded RNA Products, in which a Party plays an integral role in the experimentation and an important, though not necessarily dominant or co-equal, role in the decision-making, relating to the discovery and development of Double Stranded RNA Products from the point in time at which the relevant Gene Target has been designated through the initiation of [***]. A Bona Fide Drug Discovery Collaboration may continue beyond the initiation of such [***]. For Isis Products that are Double Stranded RNA Products, a Bona Fide Drug Discovery Collaboration must be an Antisense Drug Discovery Program. For each Party, collaborations that do not include or involve Patents licensed from the other Party hereunder shall not constitute Bona Fide Drug Discovery Collaborations. A Party's experimentation relating to the discovery and development of Double Stranded RNA Products that modulate a relevant Gene Target prior to the commencement of a collaboration shall be deemed to have been conducted in the course of the collaboration for purposes of determining whether the collaboration is a Bona Fide Drug Discovery Collaboration. A series of related collaborations and/or license agreements involving the discovery and development of Double Stranded RNA Products with the same sublicensee or related sublicensees that includes a Bona Fide Drug Discovery Collaboration agreement will be aggregated to constitute a single Bona Fide Drug Discovery Collaboration.

20. "Budget" has the meaning set forth in Section 4.2(a).

21. "Business Day" means a weekday on which banking institutions in Boston, Massachusetts are open for business. For purposes of clarity, a Business Day

shall not include any Saturday or Sunday or federal or Commonwealth of Massachusetts holiday.

22. "Calendar Quarter" means the respective periods of three (3) consecutive calendar months ending on March 31, June 30, September 30 and December 31.

23. "Chemistry Patent" means any Patent that covers (a) an oligomeric compound having a chemical composition that differs from a native oligonucleotide composition or (b) any modification to the base, sugar or internucleoside linkage of the oligomeric compound, and specifically, but without limitation, includes covalently linked conjugates and other such moieties

24. "Co-Exclusive ssRNAi Patents" means third party Patents in-licensed by both Alnylam and Isis prior to [***] to the extent that such Patents Cover Single Stranded RNAi Compounds or Single Stranded RNAi Products.

25. "Collaboration Termination Date" has the meaning set forth in Section 14.4.

26. "Commercially Reasonable Efforts" means the diligent efforts, expertise and resources normally used by a Party to develop, manufacture and commercialize a product or compound owned by it or to which it has rights, which is of similar market potential at a similar stage in its development or product life, taking into account issues of safety, and efficacy, product profile, difficulty in developing the product or compound, competitiveness of the marketplace for the product, the proprietary position of the compound or product, the regulatory structure involved, the potential total profitability of the applicable product(s) marketed or to be marketed and other relevant factors affecting the cost, risk and timing of development and the total potential reward to be obtained if a product is commercialized, but not less than reasonably diligent efforts. In determining whether Commercially Reasonable Efforts have been satisfied, the fact that a Party is required to pay the other Party a royalty or milestones shall not be a factor weighed (i.e., a Party may not apply lesser resources or effort to a Product because it must pay a royalty or milestones to the other Party).

27. "Control" or "Controlled" means, with respect to any Patent or other intellectual property right, possession of the right (whether by ownership, license or otherwise), to assign, or grant a license, sublicense or other right to or under, such Patent or right as provided for herein without violating the terms of any agreement or other arrangement with any Third Party.

28. "Confidential Information" means information which is (a) of a confidential and proprietary nature; and (b) not readily available to that Party's competitors and which, if known by a competitor of that Party, might lessen any competitive advantage of that Party or give such competitor a competitive advantage.

Confidential Information includes, without limitation, (x) information that is proprietary or confidential or which is treated by that Party as confidential and which relates either directly or indirectly to the business of that Party regardless

of the form in which that information is constituted, and which is not lawfully in the public domain; and (y) any confidential information in relation to Patents, technology, know-how, or any improvements owned or Controlled by a Party hereto.

Confidential Information will not include any information that the receiving Party can establish by written records:

(i) was known by it prior to the receipt of Confidential Information from the disclosing Party;

(ii) was disclosed to the receiving Party by a Third Party having the right to do so;

(iii) was, or subsequently became, in the public domain through no fault of the receiving Party, its officers, directors, employees or agents; or

(iv) was concurrently or subsequently developed by personnel of the receiving Party without having had access to the disclosing Party's Confidential Information.

29. "Controlled Contractor" means a Third Party contractor, such as a contract research organization, contract employee, contract manufacturer, consultant and the like, who merely conducts activities on behalf of a Party, is subject to such Party's supervision and control, and will not have any rights (other than non-exclusive rights) in any intellectual property created in connection with such activities.

30. "Designed for" means, when used in relation to a specified Gene Target, a Single Stranded RNAi Compound that is [***] to [***] of the specified [***] via [***].

31. "Development Candidate" means a Single Stranded RNAi Product for which [***] have commenced.

32. "Development Collaboration" means a collaboration by either Party with a Third Party whose purpose is the further development and/or commercialization of a Double Stranded RNA Product or Single Stranded RNAi Product, as applicable, and that begins at or after the initiation of IND-Enabling Studies for such Product. For each Party, collaborations that do not include or involve Patents licensed from the other Party hereunder shall not constitute Development Collaborations.

33. "Double Stranded RNA" means a composition designed to act primarily through an RNAi mechanism that is not a MicroRNA Construct and which consists of either (a) two separate oligomers of native or chemically modified RNA that are hybridized to one another along a substantial portion (greater than or equal to [***]%) 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 (greater than or equal to [***]%) of its length to form a hairpin.

34. "Double Stranded RNA Product" means a pharmaceutical composition that contains a Double Stranded RNA.

35. "Early Collaboration Termination" has the meaning set forth in Section 14.4.

36. "Early Termination Notice" has the meaning set forth in Section 14.4.

37. "Effective Date" means March 11, 2004.

38. "Enabled Target" has the meaning set forth in Section 4.3(a).

39. "Enabled Target Pool" has the meaning set forth in Section 4.3(a).

40. "Enabled Target Slot" has the meaning set forth in Section 4.3(a).

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

42. "FTE Rate" means $[***] per FTE per year for the initial calendar year of the Research Term, such FTE rate to be increased by the percentage increase in the Consumer Price Index — Urban Wage Earners and Clerical Workers, US City Average, All Items, 1982-84 = 100, published by the United States Department of Labor, Bureau of Labor Statistics (or its successor equivalent index, the "CPI") over the CPI as of June 30, 2009, starting as of the beginning of the 2nd calendar year of the Research Term (i.e., beginning in 2010) and each calendar year thereafter during the Research Term, provided that any such increase shall not exceed [***]% per annum.

43. "Gene Target" means a transcriptional unit of a gene, including any protein product of such transcriptional unit, and including all splice variants.

44. "Graduated Enabled Target" has the meaning set forth in Section 4.3(a).

45. "*In Vivo* Efficacy in Rodents" means the first achievement by Alnylam or its sublicensees of at least a [***]% nadir reduction of the mRNA of the intended

Gene Target in an internal organ(s), demonstrated in an independent rodent experiment and confirmed by [***], with an unformulated, unconjugated Single Stranded RNAi Compound administered subcutaneously as a [***] not to exceed [***] mg/kg. If not achieved earlier, this milestone will be deemed to have occurred upon *In Vivo* Efficacy in NHP.

46. "*In Vivo* Efficacy in NHP" means the first achievement by Alnylam or its sublicensees of at least a [***]% nadir reduction of the mRNA of the intended Gene Target in an internal organ(s), demonstrated in an independent NHP experiment and confirmed by [***], with an unformulated, unconjugated Single Stranded RNAi Compound administered subcutaneously at a [***] not to exceed [***] mg/kg per week, with the nadir reduction seen and confirmed in [***] consecutive administration cycles.

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

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

49. "Initiation of Phase I Trial" means the dosing of at least ten human subjects in the first human clinical trial conducted and designed to evaluate safety of a product.

50. "Initiation of Phase III Trial" means the dosing of the first patient in the first pivotal human clinical trial the results of which could be used to establish safety and efficacy of a Product as a basis for an application for marketing approval or that would otherwise satisfy the requirements of 21 CFR 3 12.21I or its foreign equivalent.

51. "Isis Current Chemistry Patents" means all Chemistry Patents Controlled by Isis as of the Restatement Date, including without limitation the Patents listed on Schedule 1-51 attached hereto, *except* Patents that constitute Isis Excluded Technology, or Co-Exclusive ssRNAi Patents.

52. "Isis Current Motif and Mechanism Patents" means all Motif and Mechanism Patents Controlled by Isis as of the Restatement Date, including without limitation the Patents listed on Schedule 1-52 attached hereto, *except* Patents that constitute Isis Excluded Technology, or Co-Exclusive ssRNAi Patents.

53. "Isis DS-Target Pool" has the meaning set forth in Section 6.4(a).

54. "Isis Enabled Target Pool" has the meaning set forth in Section 4.3(a).

55. "Isis Encumbered Target" means a Gene Target (a) to which Isis has a contractual obligation to a Third Party existing as of the Restatement Date that precludes Isis from granting a license under Section 5 with respect to such Gene Target and (b) that is identified and described on a [***] (as defined in the letter agreement dated March 9, 2004 between Alnylam and Isis). When and if such restrictions lapse a Gene Target will cease to be an Isis Encumbered Target.

56. "Isis Excluded Technology" means (a) RNase H mechanisms, RNase H motifs and RNase H oligonucleotides when utilized in an RNase H mechanism, assays and methods thereof; (b) modulators of specific genes, gene families or proteins; (c) manufacturing technologies; (d) analytical technologies, kits and assays, including without limitation methods, systems and compositions of matter for amplifying, quantifying, detecting, characterizing or identifying nucleic acids or nonoligomeric ligands thereto; (e) formulation and delivery technologies; and (f) the specific technology listed on Schedule 1-56 attached hereto.

57. "Isis Future Motif and Mechanism Patents" means all Motif and Mechanism Patents Controlled by Isis after the Restatement Date and having an earliest priority date of no later than [***] or that is necessary to practice a Patent licensed hereunder; provided, however that (a) for any such Motif and Mechanism Patents that are acquired, licensed or invented that include financial or other obligations to a Third Party, the provisions of Section 11.8 will govern whether such Patent will be included as an Isis Future Motif Mechanism Patent, and (b) Isis Future Motif and Mechanism Patents do not include Patents that constitute Isis Excluded Technology, or Co-Exclusive ssRNAi Patents. Notwithstanding the foregoing, in the event of an Acquisition involving Alnylam, the date "[***]" used in this definition will be automatically changed to the date of such Acquisition.

58. "Isis Future Chemistry Patents" means the Chemistry Patents Controlled by Isis after the Restatement Date and having an earliest priority date of no later than [***] or that is necessary to practice a Patent licensed hereunder; provided, however that (a) for any such Chemistry Patents that are acquired, licensed or invented that include financial or other obligations to a Third Party, the provisions of Section 11.8 will govern whether such Chemistry Patents will be included as an Isis Future Chemistry Patent, *except* Patents that constitute Isis Excluded Technology and (b) Isis Future Chemistry Patents do not include Patents that constitute Isis Excluded Technology, or Co-Exclusive ssRNAi Patents. Notwithstanding the foregoing, in the event of an Acquisition involving Alnylam, the date "[***]" used in this definition will be automatically changed to the date of such Acquisition.

59. "Isis Manufacturing Patents" means the Patents specifically listed on Schedule 1-59 attached hereto. The Parties may agree in writing from time to time to add additional Patents to Schedule 1-59 attached hereto.

60. "Isis Partnered Excluded Targets" has the meaning set forth in Section 4.3(e)(i).

61. "Isis Patent Rights" means Isis Current Motif and Mechanism Patents, Isis Future Motif and Mechanism Patents, Isis Current Chemistry Patents and Isis Future Chemistry Patents. For purposes of determining whether a royalty is payable by Alnylam under Section 7.2 in connection with the sale of an Alnylam Single Stranded RNAi Product, any Joint Patent, a Valid Claim of which covers the manufacture, use or sale of such Alnylam Single Stranded RNAi Product, will be considered an Isis Patent Right.

62. “Isis Product” means any Isis Single Stranded Product, MicroRNA Product, Double Stranded RNA Product or Isis Single Stranded RNAi Product, discovered or developed by Isis, its Affiliates or sublicensees, the manufacture, sale or use of which is covered by a Valid Claim within the Alnylam Patent Rights.

63. “Isis Protected Targets” has the meaning set forth in Section 4.3(e).

64. “Isis Single Stranded Product” means any single stranded oligomeric compound (a) that hybridizes in whole or in part with a target RNA and modulates the Gene Target, (b) is not a Double Stranded RNA or Double Stranded RNA Product and (c) the manufacture, sale or use of which is covered by a Valid Claim within the Alnylam Patent Rights. For purposes of clarity, an Isis Single Stranded Product shall not include Single Stranded RNAi Compounds, Single Stranded RNAi Products and Isis Single Stranded RNAi Products.

65. “Isis Single Stranded RNAi Product” means any Single Stranded RNAi Product Designed for an Isis Enabled Target, the manufacture, sale or use of which is covered by a Valid Claim within the Alnylam Patent Rights.

66. “Isis Special Patents” means the Patents specifically listed on Schedule 1-66 attached hereto. The Parties may mutually agree in writing from time to time to add additional Patents to Schedule 1-66 attached hereto

67. “Joint Invention” has the meaning set forth in Section 11.1(b).

68. “Joint Patent” has the meaning set forth in Section 11.1(b).

69. “Know-How” means all tangible or intangible know-how, discoveries, processes, formulas, data, clinical and preclinical results, non-Patented Inventions, Inventions for which Patents are in preparation, trade secrets, and any physical, chemical, or biological material or any replication of any such material in whole or in part that are not otherwise covered by the Isis Patent Rights or the Alnylam Patent Rights

70. “License Term” means the period from the Restatement Date until the date of expiry of the last to expire of the Patents licensed hereunder.

71. “Major Pharmaceutical Company” means a Person that, together with all of its affiliated Persons, had annual pharmaceutical product sales during the most recently completed calendar year in excess of $[***].

72. “Marketing Approval” means the act of a Regulatory Authority necessary for the marketing and sale of the Product in a country or regulatory jurisdiction, including, without limitation, the approval of the NDA by the FDA, EC Approval, and Japanese Approval.

73. “MicroRNA Construct” is a construct having the chemical and physical description of a Double Stranded RNA that is either (a) designed to target a precursor microRNA or a microRNA, thereby to inhibit the production or

function of the microRNA, or (b) designed to function by mimicking the translational repressor function of a naturally occurring microRNA, and which, in relation to its target RNA, has been demonstrated in vitro and, to the extent reasonably feasible, in vivo, to function solely as a translational repressor and not via cleavage of such target RNA.

74. “MicroRNA Product” means a pharmaceutical product that contains a MicroRNA Construct.

75. “Motif and Mechanism Patents” means any Patent that covers an oligomeric structure or composition of matter, or any method of using or incorporating such oligomeric structure or composition of matter *in vitro* or *in vivo*, including without limitation for therapeutic use, in which target RNA levels are modulated by any mechanism other than RNase H.

76. “Naked Sublicense” means a license for Double Stranded RNA that includes rights to the Isis Patent Rights that is not a license in connection with (a) a Development Collaboration or (b) a Bona Fide Drug Discovery Collaboration. A series of Naked Sublicenses to the same sublicensee or related sublicensees will be aggregated to constitute a single Naked Sublicense. For the avoidance of doubt, where this Agreement grants Alnylam exclusive rights to grant Naked Sublicenses, such exclusive rights preclude Isis from granting licenses to the Isis Patent Rights to Third Parties for Double Stranded RNA even though such license grants by Isis would technically be license grants and not sublicense grants. Licenses that do not include or involve rights to Isis Patents shall not constitute Naked Sublicenses.

77. “Naked Sublicensee” means a Third Party that obtains a Naked Sublicense from Alnylam in accordance with the terms of this Agreement.

78. “NDA” means 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.

79. “Net Sales” will mean the gross invoice price of Products sold by Alnylam or Isis (as applicable), their respective Affiliates and sublicensees (but with respect to Alnylam does not include Naked Sublicensees) to a Third Party less the following items: (i) trade discounts, credits or allowances, (ii) credits or allowances additionally granted upon returns, rejections or recalls, (iii) freight, shipping and insurance charges, (iv) taxes, duties or other governmental tariffs (other than income taxes) and (v) government-mandated rebates and (vi) a reasonable reserve for bad debts. Except in the cases of Products used to conduct clinical trials, reasonable amounts of Products used as marketing samples and Product provided without charge for compassionate or similar uses, a Party, its Affiliates or sublicensees will be treated as having sold Products for an amount equal to the fair market value of Products if: (a) Products are used by such Party, its Affiliates or sublicensees without charge or provision of invoice, or (b) Products are provided to a Third Party by such Party, its Affiliates or sublicensees without

charge or provision of invoice and used by such third party.

Such amounts shall be determined from the books and records of Alnylam or Isis (as applicable) and their respective Affiliates and sublicensees, maintained in accordance with GAAP, consistently applied.

In the event the 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, shall be determined by multiplying the Net Sales (as determined without reference to this paragraph) of the Combination Product, during the applicable royalty reporting period, by the fraction, A/A+B, where A is the average sale price of the Product when sold separately in finished form and B is the average sale price of the other product(s) included in the Combination Product when sold separately in finished form, in each case during the applicable royalty reporting period or, if sales of both the Product and the other product(s) did not occur in such period, then in the most recent royalty reporting period in which sales of both occurred. In the event that such average sale price cannot be determined for both the Product and all other products(s) included in the Combination Product, Net Sales for the purposes of determining royalty payments shall be calculated by multiplying the Net Sales of the Combination Product by the fraction of C/C+D where C is the fair market value of the Product and D is the fair market value of all other product(s) included in the Combination Product. As used above, the term "Combination Product" means any pharmaceutical product which consists of a Product and other therapeutically active pharmaceutical compound or any delivery technology that embodies substantial intellectual property rights Controlled by the selling Party (e.g., a common syringe would not constitute a delivery technology that embodies substantial intellectual property rights Controlled by the selling Party, but an implantable delivery device such as a stent would constitute such a delivery technology).

80. "Other Alnylam Sublicense" has the meaning set forth in Section 7.6(a).

81. "Other Isis Sublicense" has the meaning set forth in Section 8.4(b).

82. "Patent" or "Patents" means (a) patent applications (including provisional applications and applications 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; (d) any substitutions, extensions (including supplemental protection certificates), registrations, confirmations, reissues, divisionals, continuations, continuations-in-part, re-examinations, renewals and foreign counterparts thereof; and (e) all patents claiming overlapping priority therefrom.

83. "Person" means any person, organization, corporation or other business entity.

84. "Product" means either an Alnylam Product or an Isis Product as the case may be.

85. "Regulatory Authority" means any applicable government regulatory authority involved in granting approvals for the marketing and/or pricing of a Product worldwide including, without limitation, the United States Food and Drug Administration ("FDA") and any successor government authority having substantially the same function, and foreign equivalents thereof.

86. "Research Costs" has the meaning set forth in Section 4.2(c).

87. "Research Plan" has the meaning set forth in Section 4.2(a).

88. "Research Program" has the meaning set forth in Section 4.2.

89. "Research Program Patent" means any Patents that claim Inventions that were discovered by the employees of either Party in the performance of the Research Program. For purposes of clarity, Research Program Patents may also be Isis Future Motif and Mechanism Patents, Isis Future Chemistry Patents, Alnylam Future Motif and Mechanism Patents, or Alnylam Future Chemistry Patents.

90. "Research Term" has the meaning set forth in Section 4.2.

91. "Research Use" means discovering, developing and optimizing an Alnylam Product or an Isis Product, as applicable, up to, but not including, [***], and/or conducting pilot manufacturing studies of an Alnylam Product or an Isis Product, as applicable. Research Use may include small pilot toxicology studies. With respect to Isis, Research Use does not include studies [***] for potential drug targets, but does include studies [***] for development of Double Stranded RNA Products or Single Stranded RNAi Products, as applicable, from among potential targets for which a reasonable scientific basis exists for believing that such potential targets are associated with a particular disease or condition.

92. "Reserved DS-Target" has the meaning set forth in Section 6.4(a).

93. "RMC" has the meaning set forth in Section 4.1(a).

94. "Single Stranded RNAi Compound" means a single stranded chemically modified oligonucleotide and/or analog designed to cause target mRNA cleavage via the RISC or RNAi mechanism. For purposes of clarity, an ssRNAi compound does not include oligonucleotides (or chemically modified oligonucleotide analogs) designed to work via other mechanisms such as (i) RNase H 1 or 2 (including any oligonucleotide which has [***]); (ii) alteration of splicing; (iii) translation arrest (excluding RNAi-mediated repression of translation); (iv) alteration of processing; (v) polyadenylation; (vi) capping; (vii) modulation of pre-mRNA processing of the target mRNA; or (viii) oligonucleotides (or chemically modified oligonucleotide analogs) designed to mimic a known naturally occurring microRNA.

Working via the RISC or RNAi mechanism means that the compound is capable

of, in an in vitro cell culture assay, causing cleavage of the target mRNA at the [***], as evidenced for example by a [***] assay.

95. "Single Stranded RNAi Product" means a pharmaceutical composition that contains a Single Stranded RNAi Compound.

96. "Sublicense Revenue" means any payments that (1) with respect to Alnylam, Alnylam receives from a sublicensee in consideration of a Naked Sublicense or a sublicense granted by Alnylam as permitted by Section 5.2(b), or (2) with respect to Isis, Isis receives from a sublicensee in consideration of a sublicense to further the research, development or commercialization of an Isis Single Stranded RNAi Product, in each case including, but not limited to, license fees, royalties, milestone payments, and license maintenance fees, but excluding: (i) payments made in consideration of equity or debt securities of the applicable Party at fair market value and (ii) payments specifically committed to reimburse the applicable Party for the fully-burdened cost of research and development. If a Party receives any non-cash Sublicense Revenue, such Party will pay the other Party, at the election of the Party who is entitled to receive Sublicense Revenue payment, either (x) a cash payment equal to the fair market value of the appropriate percentage of the Sublicense Revenue or (y) the in-kind portion, if practicable, of the Sublicense Revenue.

97. "Technology Access Fee" means any payments that Alnylam receives from granting a Third Party access (through sublicense or otherwise) to the Isis Patent Rights as part of a Bona Fide Collaboration or Development Collaboration agreement, including, but not limited to, (1) license fees, (2) collaboration fees, (3) option fees, (4) payments made in consideration for the issuance of equity or debt securities above fair market value, (5) payments made for research and development support above Alnylam's fully-burdened cost, *but* excluding the following payments: (i) payments made in consideration for equity or debt securities of Alnylam at fair market value, (ii) payments made in consideration for thirty-five percent (35%) or more of Alnylam's equity securities at fair market value plus a reasonable control premium, (iii) payments specifically committed to reimburse Alnylam for the fully-burdened cost of research and development, including without limitation the fully-burdened cost of products transferred by Alnylam in connection with such research and development, (iv) [***] (v) payments that are not milestones and that are associated with the sale of commercial products, and (vi) payments that count as Sublicense Revenue under a Naked Sublicense subject to Alnylam's payment obligations to Isis under Section 7.4. If Alnylam receives any non-cash Technology Access Fees, Alnylam will pay Isis, at Isis' election, either (x) a cash payment equal to the fair market value of Isis' appropriate portion of the Technology Access Fee or (y) the in-kind portion, if practicable, of the Technology Access Fee.

98. "Third Party" means any party other than Isis or Alnylam and their respective Affiliates.

99. "Valid Claim" means (i) an issued claim of an unexpired Patent that has not been withdrawn, canceled or disclaimed, or held invalid or unenforceable by a court of competent jurisdiction in an unappealed or unappealable decision, or (ii) a claim of a patent application which has been pending for less than [***] years from the earliest priority date for such application.

EXHIBIT 4.3(c)(iv)

Picking Mechanism Examples

Example A

In the initial round of Picking, the following will be the order (with total number of Enabled Targets after Pick in parentheses):

Alnylam(1) — Isis(1) — Isis(2) — Alnylam(2) — Alnylam(3) —Isis(3) — Isis(4) — Alnylam(4) . . .

Example B

If both Parties have an equal number of Enabled Targets (10, for this example) and the previous round ended with an Alnylam Pass followed by an Isis Pass, the following will be the order (with total number of Enabled Targets after Pick in parentheses):

Alnylam(11) — Isis(11) — Isis(12) — Alnylam(12) — Alnylam(13) —Isis(13) — Isis(14) — Alnylam(14) . . .

Example C

If Alnylam has 10 Enabled Targets and Isis has 5 Enable Targets and there have been no Cleared Targets since the previous Selection Section, the following will be the order (with total number of Enabled Targets after Pick in parentheses) regardless of how the previous Round ended:

[***] . . .

Example D

If Alnylam has 10 Enabled Targets and Isis has 5 Enable Targets and there have been one or more Cleared Targets since the previous Selection Section, the following will be the order (with total number of Enabled Targets after Pick in parentheses) but Isis will not be entitled to Pick a Cleared Target until it Picks its [***] Enabled Target (in italics below) regardless of how the previous Round ended:

[***]

Example E1

If Isis has 10 Enabled Targets and Alnylam has 5 Enable Targets and there have been one or more Cleared Targets since the previous Selection Section, the following will be the order (with total number of Enabled Targets after Pick in parentheses) regardless of how the previous Round ended and assuming that Alnylam does not Pick a Cleared Target until it Picks its [***] Enabled Target (in italics below):

[***] . . .

Example E2

If Isis has 10 Enabled Targets and Alnylam has 5 Enable Targets and there have been one or more Cleared Targets since the previous Selection Section, the following will be the order (with total number of Enabled Targets after Pick in parentheses) regardless of how the previous Round ended and assuming that Alnylam Picks a Cleared Target with its [***] Enabled Target (in italics below), and for clarity, Isis may pick a Cleared Target for its [***] Enabled Target (underlined below):

[***]Isis(11)[***]

EXHIBIT 5.3(C) PART I

ISIS THIRD-PARTY JOINT PATENTS RIGHTS

The following schedule is provided by Isis Pharmaceuticals, Inc. to Alnylam Pharmaceuticals, Inc., in connection with the Strategic Collaboration and License Agreement between Alnylam and Isis (the "**Agreement**"). Capitalized terms used but not otherwise defined herein have the meanings given to such terms in the Agreement.

This schedule and the information and disclosures contained in this schedule are intended only to qualify and limit the licenses granted by Isis to Alnylam in the Agreement and do not expand in any way the scope or effect of any such licenses.

Isis has cases with joint inventorship with the [***] following entities:

[***]

[***]

Exhibit 5.3(c) Part II, Joint Patent Rights

Isis Docket Number	Country Name	Status	Patent Number	Grant Date	Title	3rd Party
[***]	[***]	[***]	[***]	[***]	[***]	[***]
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EXHIBIT 5.3(D)

ISIS ENCUMBERED PATENT RIGHTS

The following schedule of encumbered Patents is provided by Isis Pharmaceuticals, Inc. to Alnylam Pharmaceuticals, Inc., in connection with the Strategic Collaboration and License Agreement between Alnylam and Isis (the "**Agreement**"). Capitalized terms used but not otherwise defined herein have the meanings given to such terms in the Agreement.

This schedule and the information and disclosures contained in this schedule are intended only to qualify and limit the licenses granted by Isis to Alnylam in the Agreement and do not expand in any way the scope or effect of any such licenses.

1. Merck

The Patents identified by Isis docket numbers [***] cover the incorporation of certain Merck-proprietary [***].

The licenses from Isis to Alnylam with respect to these Patents are limited to the Isis Field. In addition, Merck has a research license to practice these Patents in the Isis Field.

"Isis Field" means the use of [the Merck [***]] solely for the purposes of developing [***].

Reference is made to the discussion regarding Merck nucleosides on the Excluded Technology schedule.

2. Gilead Sciences, Inc.

Gilead has retained exclusive rights in the Patents identified by a "Gilead" in the Third Party column to make, have made, use, import, export or sell compounds and other subject matter claimed within the scope of the patents which are [***].

In addition, Gilead has a non-exclusive, non-sublicensable, non-assignable license under such Patents to make and use CodeBlocker Compounds and Oligonucleotide Delivery Systems for internal research purposes, but not for any commercial purpose.

"Codeblocker Compound" means an oligonucleotide that binds directly to DNA or RNA within a cell on a selective basis determined by the nucleotide sequence of the target DNA or RNA and exerts its biological activity predominantly through binding to DNA or RNA to inhibit the transcription or replication of the target DNA or RNA or binding to RNA to inhibit the translation, processing, packaging or regulatory activity of the target RNA. A Codeblocker Compound may also have a mechanism of action or biological activity other than one conferred through direct binding to RNA or DNA provided that (i)

the compound originally was designed to bind a target DNA or RNA and (ii) the final compound or any compounds used to derive the final compound were not identified using selective purification and polymerase amplification in any fashion. An oligonucleotide, is [***]. An oligonucleotide includes RNA or DNA fragments, and may be composed of naturally occurring or non-naturally occurring bases, sugars or intersugar linkages. An oligonucleotide may have [***]. Oligonucleotides may be made such that adjacent nucleoside or nucleoside fragments are linked together by [***] linkages to form the [***] in the linkage.

"Oligonucleotide Delivery System" means any [***] which was developed by Gilead on or prior to [***], and which (i) enhances the [***] of a Codeblocker Compound, (ii) selectively delivers a Codeblocker compound to the intended [***], (iii) provides [***], or (iv) otherwise favorably alters the [***] so as to enhance its pharmacological activity of clinical value. "Oligonucleotide Delivery System" includes [***].

Glaxo Smith Kline has retained rights (originally granted from Gilead to GSK) in the Patents identified by a "Gilead" in the Third Party column to (i) conduct research and development within the GSK Field and (ii) make, have made, use, offer for sale, sell, supply and import within the GSK Field any form or dosage of a GSK Codeblocker Compound and any GSK Codeblocker Delivery System used in connection therewith.

GSK may grant sublicenses only (a) to affiliates, for any use within the GSK Field, and (b) to non-affiliates only to the extent necessary to enable such sublicensee to make, have made, use, offer for sale, sell, supply and import a GSK Codeblocker Compound developed by GSK or a research or development collaborator of GSK during the term of such collaboration and for which GSK (alone or in conjunction with a commercialization partner for such compound) has commenced or is prepared to commence human clinical trials.

"GSK Field" means research with respect to, and the development and use of, GSK Codeblocker Compounds for the diagnosis, prevention or treatment of conditions or diseases in humans.

"GSK Codeblocker Compound" means any material which (i) binds directly to DNA or RNA within a cell on a selective basis determined by the nucleotide sequence of the target DNA or RNA and exerts its biological activity predominantly through binding to DNA or RNA to inhibit the transcription or replication of the target DNA or RNA or binding to RNA to inhibit the translation, processing, packaging or regulatory activity of the target RNA, and (ii) is a molecule [***], and (iii) is not a naturally occurring protein that binds to DNA to regulate transcription, or a peptide derived from such a naturally occurring protein, and (iv) is [***], and (v) was not known by GSK prior to [***].

"GSK Codeblocker Delivery System" means any [***] which is developed by GSK or Gilead pursuant to their Collaborative Research Agreement dated March 25, 1996, and which (i) [***] a GSK Codeblocker Compound, (ii) [***] to the intended target [***],

(iii) provides [***] a GSK Codeblocker Compound from [***], or (iv) otherwise [***] a GSK Codeblocker Compound so as to [***].

3. [***], Inc.

Alnylam cannot grant Naked Sublicenses with respect to the Patents identified by a "[***]" in the Third Party column or the Patents listed on Annex 3. In addition, [***] has the first right to defend and enforce such Patents if it is facing the greatest competitive threat from infringement.

Alnylam must notify Isis if it grants a sublicense of any kind to a Third Party with respect to such Patents.

The [***] has the first right to defend and maintain the Patents with a docket number containing "[***]."

Isis also has access to certain other [***] technology to the extent it is useful for Antisense Products and Antisense Technology (both as defined in Annex 3). However, in addition to the restrictions described above, this technology carries certain other use restrictions depending on how the technology is characterized under the in-license agreement. We do not believe that such technology will be useful to Alnylam, but have provided a description of the technology and its related encumbrances on Annex 3 attached hereto.

4. Tullis Patents.

The Patents identified by a "Tullis" in the Third Party column can only be sublicensed in combination with a product that (i) uses such Patents and (ii) employs as a material element other Isis Patent Rights.

5. Amgen, GSK, Chiron and Pfizer.

Amgen, Inc., Glaxo Smith Kline, Chiron Corporation and Pfizer, Inc. each have a license to use some or all of the Patents identified by a "TV" in the Third Party column for their own internal target validation research.

6. Integrated DNA Technologies, Inc.

With respect to the Patents identified by an "IDT" in the Third Party column, Integrated DNA Technologies, Inc. has a nonexclusive license to make, have made, use, import, offer to sell, sell and have sold oligonucleotides and other related research products to the Academic Market.

"Academic Market" means end-users employed by and located at or in academic, university, government, and other 501(c)(3) registered not-for-profit organizations; provided however that specifically excluded from this definition shall be those end-users

at such institutions whose research is directly funded by a for-profit corporation for the purpose of drug discovery, drug development, or target validation/gene functionalization wherein the funding corporation has a specific legal interest or right to the data and information of the funded research

7. TriLink Biotechnologies, Inc.

TriLink Biotechnologies, Inc. has a non-exclusive license to the Patents identified by a "TriLink" in the Third Party column to (i) make, use, distribute and sell Licensed Products to purchasers who have signed a form license agreement and (ii) have [***] in the manufacture of Licensed Products.

"Licensed Product" means [***]

- "Propyne" means any of the following [***]

[***]

8. Government Rights

Inventions claimed in US Patent Applications: [***] were funded in part by a Small Business Innovation Research grant administered by the National Institutes of Health. Accordingly, the U.S. Federal Government retains certain rights to those inventions.

ANNEX 3

If the Patents marked with either a B1 or B2 restriction are [***] prevails in the [***] and [***] for such Patents broadly cover [***], the licenses under such Patents are limited to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Antisense Products and to practice Antisense Technology; provided that the license will only extend to the issued claims corresponding to the [***] and shall not extend to any other claim of such Patents.

The licenses under the Patents marked with an F restriction are limited (i) to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Antisense Products which contain modifications which have [***], (ii) to practice Antisense Technology using oligonucleotides [***] in such oligonucleotides, and (iii) to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Antisense Products which target genes involved in [***].

The licenses under the Patents marked with a C or D restriction are limited to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Antisense Products and practice Antisense Technology, provided that neither such Antisense Products nor such Antisense Technology use, or are used with, [***].

The licenses under the Patents marked with an A restriction are limited to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Antisense Products and practice Antisense Technology, provided that such Antisense Products and Antisense Technology use, or are used with, the technology covered by the claims of such Patents solely for the [***] purposes only.

The licenses under the Patents marked with an M restriction are limited to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Antisense Products and practice Antisense Technology, which Antisense Products and Antisense Technology primarily act [***].

The licenses under the Patents marked with a K restriction are limited to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Antisense Products and practice Antisense Technology; provided, however, that such licenses will not extend to [***].

For purposes of this description:

- Antisense Products means oligonucleotides or oligonucleotide analogs or mimics thereof targeted to a specific sequence of RNA that hybridize to such sequence

and through such hybridization modulate the production of the targeted gene product. The term Antisense Products shall not include Ribozymes."

- Antisense Technology means the use of any oligonucleotide or oligonucleotide analog or mimic thereof targeted to a specific sequence of RNA that hybridizes to such sequence and through such hybridization modulates the production of the targeted gene product. The term Antisense Technology shall not include Ribozyme technology.

- Ribozymes means oligonucleotides or oligonucleotide analogs or mimics containing a catalytic core having a bulge or stem loop and regions flanking the catalytic core that hybridize to a targeted RNA and modulate the targeted RNA by cleavage at a site next to a specific ribonucleotide triplet by an oligonucleotide catalyzed transesterification reaction.

- Ribozyme Technology means the use of any oligonucleotides or oligonucleotide analogs or mimics thereof containing a catalytic core having a bulge or stem loop and regions flanking the catalytic core that hybridize to a targeted RNA and modulate the targeted RNA by cleavage at a site next to a specific ribonucleotide triplet by an oligonucleotide catalyzed transesterification reaction.

Patent #	HYBN #	Title	Patent Group	Inventors	Restriction
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[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]		[***]	[***]	[***]	[***]
[***]		[***]	[***]	[***]	[***]

Exhibit 6.5(c)

RESTRICTIONS IMPOSED BY AGREEMENTS BETWEEN ALNYLAM AND THIRD PARTIES EXECUTED PRIOR TO THE EFFECTIVE DATE

Because of agreements in effect with Third Parties as of the Effective Date, the following restrictions and other terms apply to Alnylam Patent Rights with respect to which Isis is granted a license, or option to obtain a license, under this Agreement.

RIGHTS LICENSED FROM [***]

The rights licensed from [***] ("[***]") relate to the "[***]" and "[***]" patents.

"[***] patent" means the pending patent applications listed in Schedule 1-5 with the following case numbers: [***].

"[***] patent" means the pending patent applications listed in Schedule 1-5 with the following case numbers, excluding claims [***] (case number [***]) and the equivalent claims in any patent applications and patents resulting from this PCT application: [***].

The restrictions on, and other terms relating to, the rights available to Isis under the Agreement are described in the following clauses excerpted from the Co-Exclusive License executed between Alnylam and [***] on December 20, 2002.

"ARTICLE 2 - GRANT OF RIGHTS

2.4 Sublicenses

…. Immediately after the signature of each sublicense granted under this Agreement, COMPANY shall provide [***] with a copy of the signed sublicense agreement, and COMPANY shall confirm in writing to [***] that COMPANY shall be liable for payment of royalties on NET SALES of

the SUBLICENSEE in accordance with Sections 5.2 and 5.3.

ARTICLE 4 - COMPANY DILIGENCE OBLIGATIONS AND REPORTS

4.1 Activity Requirements

COMPANY shall use commercially reasonable efforts, and shall oblige its SUBLICENSEES to use commercially reasonable efforts, to develop and to introduce into the commercial market LICENSED PRODUCTS at the earliest practical date.

4.2 Development Reports

Commencing with the beginning of 2003, COMPANY shall furnish, and shall oblige its SUBLICENSEES to furnish to COMPANY for inclusion in its reports to [***], to [***] in writing, within 30 (thirty) days after the end of each calendar

quarter with COMPANY's standard R&D report, as provided to the investors pursuant to the Amended and Restated Investor's Rights Agreement Series B, on the progress of its efforts during the immediately preceding calendar quarter to develop and commercialize LICENSED PRODUCTS for each indication and sub-indication within the FIELD. The report shall also contain a discussion of intended R&D efforts for the calendar quarter in which the report is submitted.

4.4 Liability for SUBLICENSEES

If SUBLICENSEES of COMPANY develop, manufacture, use and/or sell LICENSED PRODUCTS under the PATENT RIGHTS, COMPANY warrants and is liable towards [***] that the SUBLICENSEES perform their sublicense agreement in accordance with this Agreement, and COMPANY shall be responsible and liable for royalty payments and reports of the SUBLICENSEES.

4.5 Effect of Failure

In the event that [***] determines that COMPANY or any of its SUBLICENSEES has failed to fulfill any of its obligations under this Section 4, then [***] may treat such failure as a material breach in accordance with Section 11.7.

ARTICLE 5 - SHARES, Royalties and Payment Terms

5.2 Running Royalties

COMPANY shall pay to [***] the following running royalties on NET SALES of therapeutic and prophylactic LICENSED PRODUCTS by COMPANY and its SUBLICENSEES:

[[***]% ([***] percent) to [***]% ([***]%) of NET SALES depending on level of NET SALES].

In the event that COMPANY or a SUBLICENSEE develops [***] LICENSED PRODUCTS, COMPANY shall initiate negotiations with [***] at least 3 (three) months prior to the intended first commercial sale of each [***] LICENSED PRODUCT. COMPANY and [***] shall negotiate in good faith royalties on reasonable market terms for such [***] LICENSED PRODUCT.

…. Non-cash consideration shall not be accepted by COMPANY or any SUBLICENSEE for LICENSED PRODUCTS without the prior written consent of [***].

5.3 Royalty Stacking

(a) Third Party Licenses

In the event COMPANY or a SUBLICENSEE takes, for objective commercial and/or legal reasons, a license from any third party under any patent applications or patents that dominate the PATENT RIGHTS or is dominated by the PATENT RIGHTS in order to develop, make, use, sell or import any LICENSED

PRODUCT [***], then COMPANY is allowed to deduct [***]% ([***] percent) of any additional running royalties to be paid to such third party up to [***]% ([***] percent) of the running royalties stated in Section 5.2, from the date COMPANY has to pay running royalties to such third party. However, the running royalties stated in Section 5.2 shall not be reduced to less than a minimum of [***]% ([***] percent) of NET SALES in any case.
For avoidance of doubt, if COMPANY or a SUBLICENSEE takes a license [***], COMPANY is in no event allowed to deduct any license fees [***] from running royalties due to [***] under this Agreement.

(b) PATENT RIGHTS Coverage

In the event that (i) COMPANY or its SUBLICENSEES sell a LICENSED PRODUCT in a country where no PATENT RIGHTS are issued and no patent applications that are part of the PATENT RIGHTS are pending that have not been pending for less than [***] years after filing national patent applications in the country in question, and (ii) such LICENSED PRODUCT is manufactured in a country where PATENT RIGHTS are issued or patent applications that are part of the PATENT RIGHTS are pending that have not been pending for more than [***] years after filing national patent applications in the country in question, the royalties stated in Section 5.2 will be reduced by [***]% ([***] percent) for such LICENSED

PRODUCT, until the expiration or abandonment of all issued patents and filed patent applications within the PATENT RIGHTS in the country in which the LICENSED PRODUCT is manufactured.

5.4 Reports

Within 30 (thirty) days of the end of each calendar half year, COMPANY shall deliver a detailed report to [***] for the immediately preceding calendar half year showing at least (i) the number of LICENSED PRODUCTS sold by COMPANY and its SUBLICENSEES in each country, (ii) the gross price charged by COMPANY and its SUBLICENSEES for each LICENSED PRODUCTS in each country, (iii) the calculation of NET SALES, and (iv) the resulting running royalties due to [***] according to those figures. If no running royalties are due to [***], the report shall so state.

5.6 Bookkeeping and Auditing

COMPANY is obliged to keep, and shall oblige its SUBLICENSEES to keep, complete and accurate books on any reports and payments due to [***] under this Agreement, which books shall contain sufficient information to permit [***] to confirm the accuracy of any reports and payments made to [***]. [***], or [***] appointed agents, is authorized to check the books of COMPANY, and, upon [***] request, COMPANY, or agents appointed by [***] for COMPANY, shall check the books of its SUBLICENSEES for [***]. The charges for such a check shall be borne by [***]. In the event that such check reveals an underpayment in excess of 5% (five percent), COMPANY shall bear the full cost of such check and shall remit any amounts due to [***] within thirty days of receiving notice thereof from [***].

The right of auditing by [***] under this Section shall expire five years after each report or payment has been made. Sublicenses granted by COMPANY shall provide that COMPANY shall have the right to check the books of its SUBLICENSEES according to this Section 5.6.

5.7 No Refund

All payments made by COMPANY or its SUBLICENSEES under this Agreement are nonrefundable and noncreditable against each other.

ARTICLE 6 - Patent Prosecution AND Infringement

6.3 Infringement

COMPANY shall inform [***] promptly in writing of any alleged infringement of the PATENT RIGHTS by a third party and of any available evidence thereof.

Subject to COMPANY's right to join in the prosecution of infringements set forth below, the OWNERS shall have the right, but not the obligation, to prosecute in their own discretion and at their own expense, all infringements of the PATENT RIGHTS. The total cost of any such sole infringement action shall be borne by the OWNERS, and the OWNERS shall keep any recovery or damages derived therefrom. In any such infringement suits, COMPANY shall, at the OWNERS' expense, cooperate in all respects.

COMPANY shall have the right to join the OWNERS' prosecution of any infringements of the PATENT RIGHTS: In any such joint infringement suits, the OWNERS and COMPANY will cooperate in all respects. The OWNERS and COMPANY 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.

In the event that the OWNERS decide not to prosecute infringements of the PATENT RIGHTS, neither solely nor jointly with COMPANY, [***] shall offer to COMPANY to prosecute any such infringement in its own discretion and at its own expense. …. The OWNERS shall, at COMPANY'S expense, cooperate. The total cost of any such sole infringement action shall be borne by COMPANY, and COMPANY shall keep any recovery or damages derived therefrom.

In the event that COMPANY intends to make any arrangements with the infringer to settle the infringement (such as sublicenses), and solely the OWNERS or the OWNERS jointly with COMPANY have prosecuted the infringement, any such settlement needs the prior written approval of [***], which shall not unreasonably be withheld; reasons to withheld include, without limitation, that the settlement is financially disadvantageous for the OWNERS or [***]. Any infringer to which COMPANY grants such sublicenses shall be a SUBLICENSEE under this Agreement.

ARTICLE 8 - CONFIDENTIALITY

8.2 Obligation for [***]

The content of this Agreement and any information marked confidential which is disclosed to [***] under this Agreement by COMPANY or its SUBLICENSEES shall be treated confidential by [***] during the TERM and for [***] years thereafter. [***] shall not use such information for any purposes other than those necessary to directly further the purpose of this Agreement. [***] may disclose such information to the OWNERS, provided however, that the OWNERS are obliged to confidentiality to the same extent as [***].
The confidentiality obligation shall not apply to information which is (i) publicly available or becomes publicly available through no fault of [***], or (ii) obtained by [***] from another source without a duty of confidentiality, or (iii) demonstrably independently developed or possessed by [***], or (iv) is required by law, regulation, accounting principles or an order of a court or government agency to be disclosed.

ARTICLE 10 - General Compliance with Laws

10.2 Non-Use of OWNERS Names

Neither COMPANY nor its SUBLICENSEES shall use the name of [***] 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 OWNERS, in any promotional material or other public announcement or disclosure without the prior written consent of the OWNERS or in the case of an individual, the consent of that individual. The foregoing notwithstanding, without the consent of the OWNERS, COMPANY may state generally that it is co-exclusively licensed by the OWNERS under the PATENT RIGHTS.

ARTICLE 11 - EFFECTIVENESS AND TERMINATION

11.5 Attack on PATENT RIGHTS

[***] shall have the right to terminate this Agreement immediately upon written notice to COMPANY, if COMPANY attacks, or has attacked or supports an attack through a third party, the validity of any of the PATENT RIGHTS. To the extent legally enforcable, sublicenses granted by COMPANY shall provide that in the event the SUBLICENSEE attacks, or has attacked or supports an attack through a third party, the validity of any of the PATENT RIGHTS, COMPANY shall have the right to terminate the sublicense agreement immediately; upon request of [***], COMPANY shall have the obligation to terminate such sublicense agreement.

11.8 Effect of Termination

…. In no event shall termination of this Agreement release COMPANY or its SUBLICENSEES from the obligation to pay any amounts that became due on or before the effective date of termination.

In the event that any license granted to COMPANY under this Agreement is terminated, any sublicense under such license granted prior to termination of said license shall remain in full fore and effect, provided that:
(a) the SUBLICENSEE is not then in breach of its sublicense agreement, and
(b) the SUBLICENSEE agrees to be bound to [***] as licensor under the terms and conditions of the sublicense agreement, provided that [***] shall have no other obligation than to leave the sublicense granted by COMPANY in place."

RIGHTS LICENSED FROM [***]

The rights licensed from [***] relate to the pending patent applications listed in Schedule 1-5 with the following case numbers: [***].

The restrictions on, and other terms relating to, the rights available to Isis under the Agreement are described in the following clauses excerpted from the agreement executed between Alnylam and [***] on [***]. Articles 7, 8 and 9 of such agreement are included in these excerpts because clause 13.4 of such agreement states that "Any sublicense will expressly include the provisions of Articles 7, 8, and 9 for the benefit of [***]."

"7 ROYALTY REPORTS, PAYMENTS, AND ACCOUNTING

7.1 Quarterly Earned Royalty Payment and Report. Beginning with the first sale of a Licensed Product, Alnylam will make written reports (even if there are no sales) and earned royalty payments to [***] within thirty days after the end of each calendar quarter. This report will be in the form of the report of Appendix B and will state the number, description, and aggregate Net Sales of Licensed Product during the completed calendar quarter, and resulting calculation pursuant to Section 6.3 of earned royalty payment due [***] for the completed calendar quarter. With each report, Alnylam will include payment due [***] of royalties for the completed calendar quarter."

7.2 Termination Report. Alnylam will make a written report to [***] within ninety days after the license expires under Section 3.2. Alnylam will continue to make reports after the license has expired, until all Licensed Product produced under the license have been sold or destroyed. Concurrent with the submittal of each post-termination report, Alnylam will pay [***] all applicable royalties.

7.3 Accounting. Alnylam will keep and maintain records for a period of three years showing the manufacture, sale, use, and other disposition of products sold or otherwise disposed of under the license. Records will include general-ledger records showing cash receipts and expenses, and records that include production records, customers, serial numbers, and related information in sufficient detail to enable Alnylam to determine the royalties payable under this Agreement.

7.4 Audit by [***]. Alnylam will permit an independent certified public accountant selected by [***] and acceptable to Alnylam to examine Alnylam's

books and records from time to time (but no more than one time a year) to the extent necessary to verify reports provided for in Sections 7.1 and 7.2. [***] will pay for the cost of such audit, unless the results of the audit reveal an underreporting of royalties due [***] of five percent or more, in which case, Alnylam will pay the audit costs.

8 NEGATION OF WARRANTIES

8.1 To the best of [***] OTL knowledge, [***] is the sole owner of Licensed Patent and has the right to enter into this Agreement and to grant the rights and licenses set forth herein.

8.2 Negation of Warranties. Nothing in this Agreement is construed as:

(A) [***] warranty or representation as to the validity or scope of any Licensed Patent;

(B) A warranty or representation that anything made, used, sold, or otherwise disposed of under any license granted in this Agreement is or will be free from infringement of patents, copyrights, and other rights of third parties;

(C) An obligation to bring suit against third parties for infringement, except as described in Article 12;

(D) Granting by implication, estoppel, or otherwise any licenses or rights under patents or other rights of [***] or other persons other than Licensed Patent, regardless of whether the patents or other rights are dominant or subordinate to any Licensed Patent; or

(E) An obligation to furnish any technology or technological information.

8.3 No warranties. Except as expressly set forth in this Agreement, [***] makes no representations and extends no warranties of any kind, either express or implied. There are no express or implied warranties of merchantability or fitness for a particular purpose, or that Licensed Product will not infringe any patent, copyright, trademark, or other rights, or any other express or implied warranties.

8.4 Specific Exclusion. Nothing in this Agreement grants Alnylam any express or implied license or right under or to [***] entitled [***] or any patent application corresponding thereto.

9 INDEMNITY

9.1 Indemnification. Alnylam will indemnify, hold harmless, and defend [***] and [***] Hospitals and Clinics, and their respective trustees, officers, employees, students, and agents against all claims for death, illness, personal injury, property damage, and improper business practices arising out of the manufacture, use, sale, or other disposition of Invention, Licensed Patent, Licensed Product, by Alnylam or any sublicensee, or their customers except to the extent such claims are due to the gross negligence or willful misconduct of [***]. [***] agreed to promptly notify Alnylam in writing of any such claim and Alnylam shall manage and control, at its own expense, the defense of such claim and its settlement. Alnylam agrees not to settle any such claim against [***] without [***] written consent where such settlement would include any admission of liability on the part of [***], where the settlement would impose any restriction on the conduct by [***] of any of its activities, or where the settlement would not include an unconditional release of [***] from all liability for claims that are the subject matter of such claim.

9.2 No Liability. Subject to Section 9.1, neither party will be liable to each other for any loss profit, expectation, punitive or other indirect, special, consequential, or other damages whatsoever, in connection with any claim arising out of or related to this Agreement whether grounded in tort (including negligence), strict liability, contract, or otherwise.

9.3 Workers' Compensation. Alnylam will at all times comply, through insurance or self-insurance, with all statutory workers' compensation and employers' liability requirements covering all employees with respect to activities performed under this Agreement.

9.4 Insurance. Alnylam will maintain, during the term of this Agreement, Comprehensive General Liability Insurance, including Product Liability Insurance prior to commercialization, with a reputable and financially secure insurance carrier to cover the activities of Alnylam and its sublicensees. Upon initiation of human clinical trials of Licensed Product, such insurance will provide minimum limits of liability of Five Million Dollars and will include [***] and [***] Hospitals and Clinics, and their respective trustees, directors, officers, employees, students, and agents as additional insureds. Insurance will be written to cover claims incurred, discovered, manifested, or made during or after the expiration of this Agreement and must be placed with carriers with ratings of at least A- as rated by A.M. Best. Alnylam will furnish a Certificate of Insurance evidencing primary coverage and additional insured requirements and requiring thirty (30) days prior written notice of cancellation or material change to [***]. Alnylam will advise [***], in writing, that it maintains excess liability coverage (following form) over primary insurance for at least the minimum limits set forth above. All insurance of Alnylam will be primary coverage; insurance of [***] and [***] Hospitals and Clinics will be excess and noncontributory.

12 INFRINGEMENT BY OTHERS: PROTECTION OF PATENTS

12.1 Infringement Action.

(A) The parties will promptly inform each other of any suspected infringement of any Licensed Patent by a third party.

(B) [***], Licensee and the other Co-Exclusive licensee will meet to discuss the matter during the Co-Exclusive period of this Agreement.

(C) If the Field-of-Use becomes Exclusive for Licensee, [***] and Licensee will meet to discuss the matter during the Exclusive period of this Agreement.

(D) If [***] does not choose to institute suit against said third party within sixty days of notification, then the suit may be brought in both Licensee's and the other Co-Exclusive licensee's names, and [***] name if necessary and the out-of-pocket costs thereof shall be borne equally by Licensee and the other Co-Exclusive licensee and any recovery or settlement shall be shared equally between Licensee and the other Co-Exclusive licensee. In such situation, Licensee and the other Co-Exclusive licensee shall agree to the manner in which they exercise control over such action and if either party desires to also be represented by separate counsel of its own selection, the fees for such counsel shall be paid by such party.

(E) If both [***] and the other Co-Exclusive licensee, or [***] if there is no other Co-Exclusive Licensee, choose not to institute suit against said third party within sixty days of notification, then Licensee shall have the right to institute suit in its own name or if

necessary, in [***] name, to enjoin such infringement. Licensee shall bear the entire cost of such litigation and shall be entitled to retain the entire amount of any recovery or settlement. However, any recovery in excess of litigation/settlement costs will be considered Net Sales and Licensee will pay [***] royalties as indicated in Article 6 hereof. [***] shall provide reasonable assistance to Licensee in the prosecution of any such suit brought by Licensee, at Licensee's expense.

13 SUBLICENSING

13.1 **Permitted Sublicensing for Licensed Co-Exclusive Field of Use**. Alnylam may grant sublicenses in the Co-exclusive Licensed Field of Use during the Co-Exclusive period:

(A) only in conjunction with intellectual property under Alnylam's control; and

(B) only if Alnylam is developing or selling Licensed Products in the Co-Exclusive Licensed Field of Use.

13.2 **Required Sublicensing for Licensed Co-Exclusive Field of Use**.

(A) If Alnylam or its sublicensee(s) is unable or unwilling to serve or develop a potential market or market territory for which there is a willing sublicensee, Alnylam will, at [***] request, negotiate in good faith a sublicense under the Licensed Patents, provided that the same request has been made of the other Co-Exclusive licensee.

(B) Bona fide business concerns of Alnylam will be considered in any good faith negotiations for a sublicense under this Agreement and Alnylam shall not be required to license/sublicense any other intellectual property to such sublicensee.

(C) If the other Co-Exclusive licensee itself or through its sublicensees is already developing a product in the market or market territory for which there is a willing sublicensee, Alnylam will not be required to sublicense to such party.

(D) In case that any other issue arises in the context of Required Sublicensing, [***] will discuss and try to resolve such issue with Alnylam in good faith.

13.3 **Sublicense Requirements**. Any sublicense granted by Alnylam under this Agreement will be subject and subordinate to terms and conditions of this Agreement, except:

(A) Sublicense terms and conditions will reflect that any sublicensee will not further sublicense, with the exception that sublicensee may further sublicense rights under Licensed Patents only as needed or implied in the course of distribution or performance of service as required for the sale to an end user of Licensed Products; and

(B) The earned royalty rate specified in the sublicense [***] in this Agreement.

13.4 **Sublicenses Revert to [***]**. Any sublicense will expressly include the provisions of Articles 7, 8, and 9 for the benefit of [***]. If a sublicensee desires that its sublicense survive the termination of this agreement, [***] agrees that the sublicense will revert to [***] subject to the transfer of all

obligations, including the payment of royalties specified in the sublicense, to [***] or its designee, if this Agreement is terminated.

13.5 **Copy of Sublicenses**. Alnylam will provide [***] in confidence a copy of all relevant portions of any sublicenses granted pursuant to this Article 13.

13.6 **Sharing of Sublicensing Income**. In addition to the earned royalties defined in Article 6, Alnylam will pay [***] percent ([***]%) of the amount received by Alnylam, that is specifically attributable to the Licensed Patents, from a sublicensee in

(A) [***], and

(B) [***] as defined in [***].

13.7 **Royalty-free Sublicenses**. Alnylam may grant royalty-free or noncash sublicenses or cross-licenses if Alnylam pays all royalties due [***] from sublicensee's Net Sales."

EXHIBIT 6.5(d)

DESCRIPTION OF POTENTIAL PASS-THROUGH AMOUNTS PAYABLE TO STANFORD UNIVERSITY

The passages shown below are excerpted from the License Agreement between THE BOARD OF TRUSTEES OF THE LELAND Stanford JUNIOR UNIVERSITY ("Stanford") and Alnylam Pharmaceuticals, Inc. dated September 17, 2003. These passages were selected to provide Isis with sufficient information to understand its potential obligation to Stanford pursuant to Section 6.5(d) of the Agreement.

DEFINITIONS

2.5 "Licensed Field of Use" means delivery of ex-vivo synthesized siRNA Molecules for research, development and therapeutic uses (including a diagnostic necessary for development, sale or reimbursement of a therapeutic Licensed Product). The Licensed Field of Use specifically excludes delivery of any system producing in vivo expressed siRNAs for therapeutic use, including but not limited to episomal and integrated vectors, and recombinant viruses.

2.7 "Co-Exclusive" means that, subject to Article 4, Stanford will only grant one further license in the Licensed Territory in the Licensed Field of Use.

GRANT

3.2 **Co-Exclusivity.** The license is Co-Exclusive, including the right to sublicense pursuant to Article 13, in the Licensed Field of Use for a term beginning on the Effective Date, and ending, on a country-by-country basis, on the expiration of the last to expire of Licensed Patents.

3.4 **Exclusivity.**

(A) If the other Co-Licensee discontinues licensing this Field of Use, then the Field of Use will become exclusive for Alnylam.

(B) If the other Co-Licensee discontinues any other therapeutic license under the Licensed Patents, Stanford shall so inform Alnylam and Alnylam shall have the option to obtain an exclusive, worldwide sublicensable license to such therapeutic field. The terms of any such license shall be negotiated in good faith by Stanford and Alnylam. This option may be exercised by Alnylam by written notice to Stanford at any time during a period of ninety (90) days after notification by Stanford.

ROYALTIES

6.3 **Earned Royalty.** In addition, Alnylam will pay Stanford earned royalties on Net Sales as follows:

(A) [***]% of Net Sales for a Licensed Product subject to the following;

(B) Such royalty payments shall be reduced up to [***]% (from [***]% of Net Sales down to [***]% of Net Sales) by the amount of royalty paid to access additional intellectual property necessary in order to sell Licensed Products ("Additional Earned Royalties").

(C) Such royalty payments shall be reduced as follows:

(1) [***]% if Additional Earned Royalties are [***]% or less.
(2) [***]% if Additional Earned Royalties are greater than [***]% but less than [***]%.
(3) [***]% if Additional Earned Royalties are equal to or greater than [***]% but less than [***]%.
(4) [***]% if Additional Earned Royalties are equal to or greater than [***]% but less than [***]%.
(5) [***]% if Additional Earned Royalties are equal to or higher than [***]%.

(D) Only one royalty is due on each Licensed Product sold by Alnylam or its sublicensees regardless of whether its manufacture, use, importation or sale are or shall be covered by more than one patent or patent application included in Licensed Patents under this Agreement, and no further royalties will be due for use of such Licensed Product by Alnylam or its sublicensee's customers.

6.4 **Creditable Payments.** Creditable payments under this Agreement will be an offset to Alnylam against each earned royalty payment which Alnylam would be required to pay under Section 0 until the entire credit is exhausted.

6.5 **Milestone Payments.**

(A) For the first Licensed Product, Alnylam will make the following payments for the filing of an IND, intitiation of Phase II trial, initiation of Phase III trial, and approval of New Drug Application or equivalent in the U.S. ("Milestone Payments"):

(1) $[***] for filing of the first IND.

(2) $[***] for initiation of the first Phase II trial.

(3) $[***] for initiation of the first Phase III trial.

(4) $[***] for approval of the first New Drug Application or equivalent regulatory approval in the U.S..

(B) For the second Licensed Product, Alnylam will make the following Milestone Payments:

(1) $[***] for filing of the first IND.

(2) $[***] for initiation of the first Phase II trial.

(3) $[***] for initiation of the first Phase III trial.

(4) $[***] for approval of the first New Drug Application or equivalent regulatory approval in the U.S..

(C) For the third and every subsequent Licensed Product, Alnylam will make the following Milestone Payments:

(1) $[***] for filing of the first IND.

(2) $[***] for initiation of the first Phase II trial.

(3) $[***] for initiation of the first Phase III trial.

(4) $[***] for approval of the first New Drug Application or equivalent regulatory approval in the U.S..

(D) Notwithstanding the above, at the time that Stanford receives a Milestone Payment from Alnylam on behalf of a sublicensee under 13.6, the corresponding Milestone Payment under this Section 6.5 will not be due.

6.6 **Obligation to Pay Royalties.** If this Agreement is not terminated in accordance with other provisions, Alnylam will be obligated to pay royalties on all Licensed Product that is either sold or produced under the license granted in Article 3, whether or not the Licensed Product is produced before the Effective Date of this Agreement or sold after the Licensed Patent has expired.

13 **SUBLICENSING**

13.1 **Permitted Sublicensing for Licensed Co-Exclusive Field of Use.** Alnylam may grant sublicenses in the Co-exclusive Licensed Field of Use during the Co-Exclusive period:

(A) only in conjunction with intellectual property under Alnylam's control; and

(B) only if Alnylam is developing or selling Licensed Products in the Co-Exclusive Licensed Field of Use.

13.3 **Sublicense Requirements.** Any sublicense granted by Alnylam under this Agreement will be subject and subordinate to terms and conditions of this Agreement, except:

(A) Sublicense terms and conditions will reflect that any sublicensee will not further sublicense, with the exception that sublicensee may further sublicense rights under Licensed Patents only as needed or implied in the course of distribution or performance of service as required for the sale to an end user of Licensed Products; and

(B) The earned royalty rate specified in the sublicense may be at different rates than the rates in this Agreement.

13.4 **Sublicenses Revert to Stanford.** Any sublicense will expressly include the provisions of Articles 7, 8, and 9 for the benefit of Stanford [Note: these provisions are detailed in Exhibit 6.5(c)]. If a sublicensee desires that its sublicense survive the termination of this agreement, Stanford agrees that the sublicense will revert to Stanford subject to the transfer of all obligations, including the payment of royalties specified in the sublicense, to Stanford or its designee, if this Agreement is terminated.

13.5 **Copy of Sublicenses.** Alnylam will provide Stanford in confidence a copy of all relevant portions of any sublicenses granted pursuant to this Article 13.

13.6 **Sharing of Sublicensing Income.** In addition to the earned royalties defined in Article 6, Alnylam will pay Stanford [***] percent ([***]%) of the amount received by Alnylam, that is specifically attributable to the Licensed Patents, from a sublicensee in
(A) up-front license fees, and
(B) clinical Milestone Payments as defined in Article 6.5.

13.7 **Royalty-free Sublicenses.** Alnylam may grant royalty-free or noncash sublicenses or cross-licenses if Alnylam pays all royalties due Stanford from sublicensee's Net Sales.

EXHIBIT 8.2(c)

DESCRIPTION OF ALNYLAM ROYALTY OBLIGATIONS TO [***] EXISTING AS OF THE EFFECTIVE DATE

As of the Effective Date, Alnylam has the following royalty obligations to [***] ("[***]"):

Alnylam is obligated to pay [***] running royalties on NET SALES (as defined in Alnylam's agreements with [***]) of therapeutic and prophylactic LICENSED PRODUCTS (as defined in Alnylam's agreements with [***]) by Alnylam and its SUBLICENSEES (as defined in Alnylam's agreements with [***]) that range from [***]% ([***] percent) to [***]% ([***] percent) of NET SALES, depending on the level of NET SALES. Royalties payable by Alnylam to [***] are subject to the following Royalty Stacking provision:

“5.3 Royalty Stacking

(a) Third Party Licenses

In the event COMPANY or a SUBLICENSEE takes, for objective commercial and/or legal reasons, a license from any third party under any patent applications or patents that dominate the PATENT RIGHTS or is dominated by the PATENT RIGHTS in order to develop, make, use, sell or import any LICENSED PRODUCT (explicitly excluding, without limitation, any third party patents and patent applications for formulation, stabilization and delivery), then COMPANY is allowed to deduct [***]% ([***] percent) of any additional running royalties to be paid to such third party up to [***]% ([***] percent) of the running royalties stated in Section 5.2, from the date COMPANY has to pay running royalties to such third party. However, the running royalties stated in Section 5.2 shall not be reduced to less than a minimum of [***]% ([***] percent) of NET SALES in any case.

For avoidance of doubt, if COMPANY or a SUBLICENSEE takes a license to a third party target, COMPANY is in no event allowed to deduct any license fees for such target from running royalties due to [***] under this Agreement.”

Because Alnylam’s right to reduce its royalty obligations to [***] pursuant to the foregoing royalty stacking provision is not co-extensive with Isis’ right to reduce its royalty obligations to Alnylam pursuant to Section 8.2 of this Agreement, Isis’ right to reduce its royalty obligations to Alnylam pursuant to Section 8.2 of this Agreement is limited, pursuant to Section 8.2(c) of this Agreement, to the extent necessary to ensure that Isis’ royalty obligations to Alnylam are never less than Alnylam’s royalty obligations to [***] with respect to sales by Isis, its Affiliates and its sublicensees of any Isis Product.

SCHEDULE 1-7
ALNYLAM CURRENT CHEMISTRY PATENTS

Alnylam Current Chemistry Patents include all claims of the patents and patent applications listed below that do not claim inhibitors to specific genes or gene families.

Case No.	Filing Date	Country	Serial No.	Status	Title
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]		[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]

SCHEDULE 1-8
ALNYLAM CURRENT MOTIF AND MECHANISM PATENTS

Alnylam Current Motif and Mechanism Patents include all claims of the patents and patent applications listed below that do not claim inhibitors to specific genes or gene families.

Case No.	Filing Date	Country	Serial No.	Status	Title
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]		[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	
[***]	[***]	[***]	[***]	[***]	
[***]	[***]	[***]	[***]	[***]	
[***]	[***]	[***]	[***]		
[***]	[***]	[***]	[***]		
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[***]			[***]	[***]	
[***]	[***]	[***]		[***]	
[***]	[***]	[***]	[***]	[***]	

[***]† Note that Alnylam's license to this series of patent applications specifically excludes claims [***] and the equivalent claims in any patent applications and patents resulting from this PCT application. The application contains claims relating to [***]. The claims excluded from Alnylam's license are those that [***].

***** Subject to the provisions of section 6.5(d).

Schedule 1-10
ALNYLAM EXCLUDED TECHNOLOGY

1. All Patent rights licensed to Alnylam under the license agreements between [***] dated [***], and between [***]and Alnylam dated [***].

2. All Patent rights licensed to Alnylam under the license agreement between [***] and Alnylam dated [***].

3. All Patent rights licensed to Alnylam under the license agreement between [***] and Alnylam dated [***].

Schedule 1-51 (Updated April 28, 2009)
Isis Current Chemistry Patents

[***]

Schedule 1-52 (Updated April 28, 2009)
Isis Current Motif and Mechanism Patents

[***]

Schedule 1-56
EXCLUDED TECHNOLOGY

The following schedule of Excluded Technology is provided by Isis Pharmaceuticals, Inc. to Alnylam Pharmaceuticals, Inc., in connection with the Strategic Collaboration and License Agreement between Alnylam and Isis (the "**Agreement**"). Capitalized terms used but not otherwise defined herein have the meanings given to such terms in the Agreement.

This schedule and the information and disclosures contained in this schedule are intended only to qualify and limit the licenses granted by Isis to Alnylam in the Agreement and do not expand in any way the scope or effect of any such licenses.

In the event of a conflict between this schedule of Excluded Technology and any other schedule or terms of the Agreement, this schedule will govern.

1. INTELLECTUAL PROPERTY COVERING:

- RNA processing, including modulation of [***]
- PNA chemistry licensed or acquired from (i) [***];
- [***] chemistry licensed or acquired from [***];
- [***] a Gene Target.

2. [***]/4'-THIO CHEMISTRY.

4'-thio chemistries including patents licensed in from [***]

In addition, the following Patents in-licensed from the [***] are excluded:

Isis Docket Number	Country	Status	Patent Number	Granted Date	Title
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]

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

3. GEN-PROBE AND NIH. (A)

The following Patents in-licensed from Gen-Probe Inc. and the National Institute of Health are excluded:

U.S. Patent No. [***] entitled: [***];
U.S. Patent No. [***] entitled: [***]; and
U.S. Patent No. [***] entitled: [***]

4. MCGILL UNIVERSITY (B)

In addition to certain manufacturing technology excluded by definition, the following Patents in-licensed from McGill University are excluded:

Isis Docket Number	Country	Status	Title
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]

5. [***] (B)

The following Patents in-licensed from the [***] are excluded:

[***] Patent No. [***] entitled [***];
[***] Patent Application [***] entitled "[***];
[***] Patent Application [***] entitled [***]; and
[***] Patent No. [***] entitled [***].

6. WALDER PATENTS (B)

The Walder Patents are excluded. "Walder Patents" means and includes [***]. Patent Nos. [***]; [***] Patent No. [***], and [***] Patent Application No. [***] (allowed).

7. MERCK NUCLEOSIDE

Single nucleosides, nucleotides or monomers claimed in Patents filed as of the Effective Date which are prosecuted by Merck and Co. are excluded. However if such Patents are necessary for Alnylam to practice the licenses granted under Section 5.1 with respect to a specific Alnylam Product, then Isis will include such necessary Patents in the licenses granted under Section 5.1.

[***]
Isis believes the agreement under which Isis received a license to the [***] Patents listed below [***].

Isis Docket Number	Country	Status	Patent Number	Grant Date	Title
	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]	[***]

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

8. CARNEGIE INSTITUTION OF WASHINGTON.

Isis is not granting Alnylam any sublicense under the License Agreement dated January 28, 2005 between Isis and Carnegie Institution of Washington.

9. GARCHING INNOVATION GMBH.

Isis is not granting Alnylam any sublicense under the Co-Exclusive License Agreement dated October 18, 2004 among Isis, Alnylam and Garching Innovation GmbH.

(A) Isis cannot sublicense the technologies marked with this footnote.
(B) Although, Isis can sublicense the technologies marked with this footnote, such a sublicense carries additional financial and other obligations. Isis is willing to negotiate a separate sublicense agreement for these technologies.

Schedule 1-59
ISIS MANUFACTURING PATENTS

The Parties have not yet agreed to a specific list of Manufacturing Patents as of the date of the Addendum Transmittal. However, the Parties agree to work together to develop a list of Manufacturing Patents by [***].

Schedule 1-66
ISIS SPECIAL PATENTS

Docket Number	Country	Status	Serial Number	Filing Date	Title
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]

[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
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Docket Number	Country	Status	Serial Number	Filing Date	Title
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]	[***]

Docket Number	Country	Status	Serial Number	Filing Date	Title
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]	[***]
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Docket Number	Country	Status	Serial Number	Filing Date	Title
[***]	[***]	[***]	[***]	[***]	[***]

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: August 6, 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: August 6, 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 June 30, 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: August 6 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.