UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended March 31, 2015

OR

☐ 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.)

2855 Gazelle Court, Carlsbad, CA 92010
(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 ☒ No ☐

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 ☒ No ☐

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 ☒	Accelerated filer ☐
Non-accelerated filer ☐ (Do not check if a smaller reporting company)	Smaller reporting company ☐

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 ☐ No ☒

The number of shares of voting common stock outstanding as of April 30, 2015 was 119,713,341.

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TRADEMARKS

Isis Pharmaceuticals® is a registered trademark of Isis Pharmaceuticals, Inc.

Akcea Therapeutics™ is a trademark of Isis Pharmaceuticals, Inc.

Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc.

KYNAMRO® is a registered trademark of Genzyme Corporation

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

	March 31, 2015 (Unaudited)	December 31, 2014
ASSETS		
Current assets:		
Cash and cash equivalents	$ 148,348	$ 142,998
Short-term investments	546,706	585,834
Contracts receivable	26,934	3,903
Inventories	6,839	6,290
Investment in Regulus Therapeutics Inc.	93,446	81,881
Other current assets	13,154	15,691
Total current assets	835,427	836,597
Property, plant and equipment, net	89,047	88,958
Licenses, net	2,221	2,690
Patents, net	17,915	17,186
Deposits and other assets	10,823	10,378
Total assets	$ 955,433	$ 955,809
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 16,487	$ 17,984
Accrued compensation	5,411	12,302
Accrued liabilities	23,746	30,451
Current portion of long-term obligations	2,058	2,882
Current portion of deferred contract revenue	52,586	51,713
Total current liabilities	100,288	115,332
Long-term deferred contract revenue	119,083	127,797
1 percent convertible senior notes	332,274	327,486
2¾ percent convertible senior notes	48,579	48,014
Long-term obligations, less current portion	7,510	7,669
Long-term financing liability for leased facility	71,848	71,731
Total liabilities	679,582	698,029
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 119,602,322 and 118,442,726 shares issued and outstanding at March 31, 2015 and December 31, 2014, respectively	120	118
Additional paid-in capital	1,251,928	1,224,509
Accumulated other comprehensive income	47,114	39,747
Accumulated deficit	(1,023,311)	(1,006,594)
Total stockholders' equity	275,851	257,780
Total liabilities and stockholders' equity	$ 955,433	$ 955,809

See accompanying notes.

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

	Three Months Ended March 31,	
	2015	**2014**
Revenue:		
Research and development revenue under collaborative agreements	$ 61,892	$ 19,550
Licensing and royalty revenue	691	8,611
Total revenue	62,583	28,161
Expenses:		
Research, development and patent expenses	64,447	53,448
General and administrative	7,466	4,380
Total operating expenses	71,913	57,828
Loss from operations	(9,330)	(29,667)
Other income (expense):		
Investment income	845	657
Interest expense	(9,021)	(4,943)
Gain on investments, net	—	397
Loss before income tax benefit	(17,506)	(33,556)
Income tax benefit	789	2,276
Net loss	$ (16,717)	$ (31,280)
Basic and diluted net loss per share	$ (0.14)	$ (0.27)
Shares used in computing basic and diluted net loss per share	118,948	117,128

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS
(in thousands)
(Unaudited)

	Three Months Ended March 31,	
	2015	**2014**
Net loss	$ (16,717)	$ (31,280)
Unrealized gains on securities, net of tax	7,367	8,261
Reclassification adjustment for realized gains included in net loss	—	(341)
Comprehensive loss	$ (9,350)	$ (23,360)

See accompanying notes.

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

	Three Months Ended March 31,	
	2015	**2014**
Operating activities:		
Net loss	$ (16,717)	$ (31,280)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	1,571	1,561
Amortization of patents	312	263
Amortization of licenses	469	471
Amortization of premium on investments, net	1,749	1,376
Amortization of debt issuance costs	275	135
Amortization of 2¾ percent convertible senior notes discount	565	1,671
Amortization of 1 percent convertible senior notes discount	4,788	—
Amortization of long-term financing liability for leased facility	1,662	1,652
Stock-based compensation expense	13,305	7,069
Gain on investments, net	—	(397)
Non-cash losses related to patents, licensing and property, plant and equipment	93	108
Tax benefit from other unrealized gains on securities	(798)	(2,276)
Changes in operating assets and liabilities:		
Contracts receivable	(23,031)	1,279
Inventories	(549)	496
Other current and long-term assets	(2,451)	(896)
Accounts payable	(2,695)	(2,646)
Accrued compensation	(6,891)	(7,840)
Deferred rent	62	25
Accrued liabilities	(6,704)	2,643
Deferred contract revenue	(7,841)	(5,742)
Net cash used in operating activities	(42,826)	(32,328)
Investing activities:		
Purchases of short-term investments	(40,213)	(69,185)
Proceeds from the sale of short-term investments	78,460	95,288
Purchases of property, plant and equipment	(878)	(1,403)
Acquisition of licenses and other assets, net	(719)	(333)
Proceeds from the sale of strategic investments	—	454
Net cash provided by investing activities	36,650	24,821
Financing activities:		
Proceeds from equity awards	14,116	12,003
Principal payments on debt and capital lease obligations	(2,590)	(2,691)
Net cash provided by financing activities	11,526	9,312
Net increase in cash and cash equivalents	5,350	1,805
Cash and cash equivalents at beginning of period	142,998	159,973
Cash and cash equivalents at end of period	$ 148,348	$ 161,778
Supplemental disclosures of cash flow information:		
Interest paid	$ 37	$ 83
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 1,198	$ 1,506

See accompanying notes.

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three months ended March 31, 2015 and 2014 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2014. The financial statements include all normal recurring adjustments, which we consider necessary for a fair presentation of our financial position at such dates and our operating results and cash flows for those periods. Results for the interim periods are not necessarily indicative of the results for the entire year. For more complete financial information, these financial statements, and notes thereto, should be read in conjunction with the audited financial statements for the year ended December 31, 2014 included in our Annual Report on Form 10-K filed with the Securities and Exchange Commission, or SEC.

The condensed consolidated financial statements include the accounts of Isis Pharmaceuticals, Inc. ("we", "us" or "our") and our wholly owned subsidiary, Akcea Therapeutics, Inc., which we formed in December 2014.

2. Significant Accounting Policies

Revenue Recognition

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. In the instances in which we have received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on our consolidated balance sheet.

Arrangements with multiple deliverables

Our collaboration agreements typically contain multiple elements, or deliverables, including technology licenses or options to obtain technology licenses, research and development services, and in certain cases manufacturing services, and we allocate the consideration to each unit of accounting based on the relative selling price of each deliverable.

Identifying deliverables and units of accounting

We evaluate the deliverables in our collaboration agreements to determine whether they meet the criteria to be accounted for as separate units of accounting or whether they should be combined with other deliverables and accounted for as a single unit of accounting. When the delivered items in an arrangement have "stand-alone value" to our customer, we account for the deliverables as separate units of accounting. For example, in December 2012, we entered into a global collaboration agreement with AstraZeneca to discover and develop antisense drugs against five cancer targets. As part of the collaboration, we received a $25 million upfront payment in December 2012 and a $6 million payment in June 2013 when AstraZeneca elected to continue the research collaboration. We are also eligible to receive milestone payments, license fees for the research program targets and royalties on any product sales of drugs resulting from this collaboration. In exchange, we granted AstraZeneca an exclusive license to develop and commercialize ISIS-STAT3-2.5$_{Rx}$ and ISIS-AR-2.5$_{Rx}$. We also granted AstraZeneca options to license up to three cancer drugs under the separate research program. We were responsible for completing IND-enabling studies for ISIS-AR-2.5$_{Rx}$, which we completed in early 2014. We were also responsible for completing an ongoing clinical study of ISIS-STAT3-2.5$_{Rx}$, which we substantially completed in the first quarter of 2015. AstraZeneca is responsible for all other global development, regulatory and commercialization activities for ISIS-STAT3-2.5$_{Rx}$ and ISIS-AR-2.5$_{Rx}$. In addition, if AstraZeneca exercises its option for any drugs resulting from the research program, AstraZeneca will assume global development, regulatory and commercialization responsibilities for such drug. Since this agreement has multiple elements, we evaluated the deliverables in this arrangement when we entered into the agreement and determined that certain deliverables, either individually or in combination, have stand-alone value. Below is a list of the four separate units of accounting under our agreement:

- The exclusive license we granted to AstraZeneca to develop and commercialize ISIS-STAT3-2.5$_{Rx}$ for the treatment of cancer;
- The development services we agreed to perform for ISIS-STAT3-2.5$_{Rx}$;
- The exclusive license we granted to AstraZeneca to develop and commercialize ISIS-AR-2.5$_{Rx}$ and the research services we performed for ISIS-AR-2.5$_{Rx}$; and
- The option to license up to three drugs under a research program and the research services we are performing for this program.

Measurement and allocation of arrangement consideration

Our collaborations may provide for various types of payments to us including upfront payments, funding of research and development, milestone payments, licensing fees, profit sharing and royalties on product sales. We initially allocate the amount of consideration that is fixed and determinable at the time the agreement is entered into and exclude contingent consideration. We allocate the consideration to each unit of accounting based on the relative selling price of each deliverable. Delivered items have stand-alone value if they are sold separately by any vendor or the customer could resell the delivered items on a stand-alone basis. We use the following hierarchy of values to estimate the selling price of each deliverable: (i) vendor-specific objective evidence of fair value; (ii) third-party evidence of selling price; and (iii) best estimate of selling price, or BESP. The BESP reflects our best estimate of what the selling price would be if we regularly sold the deliverable on a stand-alone basis. We recognize the revenue allocated to each unit of accounting as we deliver the related goods or services. If we determine that we should treat certain deliverables as a single unit of accounting, then we recognize the revenue ratably over our estimated period of performance.

We determined that the ISIS-STAT3-2.5$_{Rx}$ license had stand-alone value because it is an exclusive license that gives AstraZeneca the right to develop ISIS-STAT3-2.5$_{Rx}$ or to sublicense its rights. In addition, ISIS-STAT3-2.5$_{Rx}$ is currently in development and it is possible that AstraZeneca or another third party could conduct clinical trials without assistance from us. As a result, we considered the ISIS-STAT3-2.5$_{Rx}$ license and the development services for ISIS-STAT3-2.5$_{Rx}$ to be separate units of accounting. We recognized the portion of the consideration allocated to the ISIS-STAT3-2.5$_{Rx}$ license immediately because we delivered the license and earned the revenue. We recognized as revenue the amount allocated to the development services for ISIS-STAT3-2.5$_{Rx}$ over the period of time we performed services. The ISIS-AR-2.5$_{Rx}$ license is also an exclusive license. At the inception of the agreement, ISIS-AR-2.5$_{Rx}$ was in an early stage of research. Therefore, we concluded that our knowledge and expertise with antisense technology was essential for AstraZeneca or another third party to successfully develop ISIS-AR-2.5$_{Rx}$. As a result, we determined that the ISIS-AR-2.5$_{Rx}$ license did not have stand-alone value and we combined the ISIS-AR-2.5$_{Rx}$ license and related research services into one unit of accounting. We recognized revenue for the combined unit of accounting over the period of time we performed services, which ended in the first quarter of 2014. We determined that the options under the research program did not have stand-alone value because AstraZeneca cannot develop or commercialize drugs resulting from the research program until AstraZeneca exercises the respective option or options. As a result, we considered the research options and the related research services as a combined unit of accounting. We are recognizing revenue for the combined unit of accounting over the period of our performance.

We determined that the allocable arrangement consideration was $31 million and we allocated it based on the relative BESP of each unit of accounting. We engaged a third party, independent valuation expert to assist us with determining BESP. We estimated the selling price of the licenses granted for ISIS-STAT3-2.5$_{Rx}$ and ISIS-AR-2.5$_{Rx}$ by using the relief from royalty method. Under this method, we estimated the amount of income, net of taxes, for each drug. We then discounted the projected income for each license to present value. The significant inputs we used to determine the projected income of the licenses included:

- Estimated future product sales;
- Estimated royalties on future product sales;
- Contractual milestone payments;
- Expenses we expect to incur;
- Income taxes; and
- An appropriate discount rate.

We estimated the selling price of the research and development services by using our internal estimates of the cost to perform the specific services, marked up to include a reasonable profit margin, and estimates of expected cash outflows to third parties for services and supplies over the expected period that we will perform research and development. The significant inputs we used to determine the selling price of the research and development services included:

- The number of internal hours we will spend performing these services;
- The estimated number and cost of studies we will perform;
- The estimated number and cost of studies that we will contract with third parties to perform; and
- The estimated cost of drug product we will use in the studies.

Timing of revenue recognition

We recognize revenue over the period of our performance for each deliverable when we determine that it is realized or realizable and earned. Typically, we must estimate our period of performance when the agreements we enter into do not clearly define such information. Our collaborative agreements typically include a research and/or development project plan outlining the activities the agreement requires each party to perform during the collaboration. 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 recognize revenue ratably over such period. We have made estimates of our continuing obligations under numerous agreements and in certain instances the timing of satisfying these obligations may change as the development plans for our drugs progress. Accordingly, our estimates may change in the future. If our estimates and judgments change over the course of these agreements, it may affect the timing and amount of revenue that we recognize in future periods.

Multiple agreements

From time to time, we may enter into separate agreements at or near the same time with the same customer. We evaluate such agreements to determine whether they should be accounted for individually as distinct arrangements or whether the separate agreements are, in substance, a single multiple element arrangement. We evaluate whether the negotiations are conducted jointly as part of a single negotiation, whether the deliverables are interrelated or interdependent, whether fees in one arrangement are tied to performance in another arrangement, and whether elements in one arrangement are essential to another arrangement. Our evaluation involves significant judgment to determine whether a group of agreements might be so closely related that they are, in effect, part of a single arrangement. For example, since early 2012 we have entered into four collaboration agreements with Biogen:

- In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize ISIS-SMN$_{Rx}$ for spinal muscular atrophy, or SMA. As part of the collaboration, we received a $29 million upfront payment and we are responsible for global development of ISIS-SMN$_{Rx}$ through completion of Phase 2/3 clinical trials.

- In June 2012, we entered into a second and separate collaboration agreement with Biogen to develop and commercialize a novel antisense drug targeting DMPK, or dystrophia myotonica-protein kinase. As part of the collaboration, we received a $12 million upfront payment and we are responsible for global development of the drug through the completion of a Phase 2 clinical trial.

- In December 2012, we entered into a third and separate collaboration agreement with Biogen to discover and develop antisense drugs against three targets to treat neurological or neuromuscular disorders. As part of the collaboration, we received $30 million upfront payment and we are responsible for the discovery of a lead antisense drug for each of three targets.

- In September 2013, we entered into a fourth and separate collaboration agreement with Biogen to leverage antisense technology to advance the treatment of neurological diseases. We granted Biogen exclusive rights to the use of our antisense technology to develop therapies for neurological diseases as part of this broad collaboration. We received a $100 million upfront payment and we are responsible for discovery and early development through the completion of a Phase 2 clinical trial for each antisense drug identified during the six year term of this collaboration, while Biogen is responsible for the creation and development of small molecule treatments and biologics.

All four of these collaboration agreements give Biogen the option to license one or more drugs resulting from the specific collaboration. If Biogen exercises an option, it will pay us a license fee and will assume future development, regulatory and commercialization responsibilities for the licensed drug. We are also eligible to receive milestone payments associated with the research and/or development of the drugs prior to licensing, milestone payments if Biogen achieves pre-specified regulatory milestones, and royalties on any product sales of drugs resulting from these collaborations.

We evaluated all four of the Biogen agreements to determine whether we should account for them as separate agreements. We determined that we should account for the agreements separately because we conducted the negotiations independently of one another, each agreement focuses on different drugs, there are no interrelated or interdependent deliverables, there are no provisions in any of these agreements that are essential to the other agreement, and the payment terms and fees under each agreement are independent of each other. We also evaluated the deliverables in each of these agreements to determine whether they met the criteria to be accounted for as separate units of accounting or whether they should be combined with other deliverables and accounted for as a single unit of accounting. For all four of these agreements, we determined that the options did not have stand-alone value because Biogen cannot pursue the development or commercialization of the drugs resulting from these collaborations until it exercises the respective option or options. As such, for each agreement we considered the deliverables to be a single unit of accounting and we are recognizing the upfront payment for each of the agreements over the respective estimated period of our performance.

Milestone payments

Our collaborations often include contractual milestones, which typically relate to the achievement of pre-specified development, regulatory and commercialization events. These three categories of milestone events reflect the three stages of the life-cycle of our drugs, which we describe in more detail in the following paragraph.

Prior to the first stage in the life-cycle of our drugs, we perform a significant amount of work using our proprietary antisense technology to design chemical compounds that interact with specific genes that are good targets for drug discovery. From these research efforts, we hope to identify a development candidate. The designation of a development candidate is the first stage in the life-cycle of our drugs. A development candidate is a chemical compound that has demonstrated the necessary safety and efficacy in preclinical animal studies to warrant further study in humans.

During the first step of the development stage, we or our partners study our drugs in IND-enabling studies, which are animal studies intended to support an Investigational New Drug, or IND, application and/or the foreign equivalent. An approved IND allows us or our partners to study our development candidate in humans. If the regulatory agency approves the IND, we or our partners initiate Phase 1 clinical trials in which we typically enroll a small number of healthy volunteers to ensure the development candidate is safe for use in patients. If we or our partners determine that a development candidate is safe based on the Phase 1 data, we or our partners initiate Phase 2 studies that are generally larger scale studies in patients with the primary intent of determining the efficacy of the development candidate.

The final step in the development stage is Phase 3 studies to gather the necessary safety and efficacy data to request marketing approval from the Food and Drug Administration, or FDA, and/or foreign equivalents. The Phase 3 studies typically involve large numbers of patients and can take up to several years to complete. If the data gathered during the trials demonstrates acceptable safety and efficacy results, we or our partner will submit an application to the FDA and/or its foreign equivalents for marketing approval. This stage of the drug's life-cycle is the regulatory stage.

If a drug achieves marketing approval, it moves into the commercialization stage, during which our partner will market and sell the drug to patients. Although our partner will ultimately be responsible for marketing and selling the partnered drug, our efforts to discover and develop a drug that is safe, effective and reliable contributes significantly to our partner's ability to successfully sell the drug. The FDA and its foreign equivalents have the authority to impose significant restrictions on an approved drug through the product label and on advertising, promotional and distribution activities. Therefore, our efforts designing and executing the necessary animal and human studies are critical to obtaining claims in the product label from the regulatory agencies that would allow us or our partner to successfully commercialize our drug. Further, the patent protection afforded our drugs as a result of our initial patent applications and related prosecution activities in the United States and foreign jurisdictions are critical to our partner's ability to sell our drugs without competition from generic drugs. The potential sales volume of an approved drug is dependent on several factors including the size of the patient population, market penetration of the drug, and the price charged for the drug.

Generally, the milestone events contained in our partnership agreements coincide with the progression of our drugs from development, to regulatory approval and then to commercialization. The process of successfully discovering a new development candidate, having it approved and ultimately sold for a profit is highly uncertain. As such, the milestone payments we may earn from our partners involve a significant degree of risk to achieve. Therefore, as a drug progresses through the stages of its life-cycle, the value of the drug generally increases.

Development milestones in our partnerships may include the following types of events:

- Designation of a development candidate. Following the designation of a development candidate, IND-enabling animal studies for a new development candidate generally take 12 to 18 months to complete;
- Initiation of a Phase 1 clinical trial. Generally, Phase 1 clinical trials take one to two years to complete;
- Initiation or completion of a Phase 2 clinical trial. Generally, Phase 2 clinical trials take one to three years to complete;
- Initiation or completion of a Phase 3 clinical trial. Generally, Phase 3 clinical trials take two to four years to complete.

Regulatory milestones in our partnerships may include the following types of events:

- Filing of regulatory applications for marketing approval such as a New Drug Application, or NDA, in the United States or a Marketing Authorization Application, or MAA, in Europe. Generally, it takes six to twelve months to prepare and submit regulatory filings.
- Marketing approval in a major market, such as the United States, Europe or Japan. Generally it takes one to two years after an application is submitted to obtain approval from the applicable regulatory agency.

Commercialization milestones in our partnerships may include the following types of events

- First commercial sale in a particular market, such as in the United States or Europe.
- Product sales in excess of a pre-specified threshold, such as annual sales exceeding $1 billion. The amount of time to achieve this type of milestone depends on several factors including but not limited to the dollar amount of the threshold, the pricing of the product and the pace at which customers begin using the product.

We assess whether a substantive milestone exists at the inception of our agreements. When a substantive milestone is achieved, we recognize revenue related to the milestone payment immediately. For our existing licensing and collaboration agreements in which we are involved in the discovery and/or development of the related drug or provide the partner with access to new technologies we discover, we have determined that the majority of future development, regulatory and commercialization milestones are substantive. For example, we consider most of the milestones associated with our strategic alliance with Biogen substantive because we are using our antisense drug discovery platform to discover and develop new drugs against targets for neurological diseases. Alternatively, we consider milestones associated with our strategic alliance with Alnylam Pharmaceuticals, Inc. substantive because we provide Alnylam ongoing access to our technology to develop and commercialize RNA interference, or RNAi, therapeutics. In evaluating if a milestone is substantive we consider whether:

- Substantive uncertainty exists as to the achievement of the milestone event at the inception of the arrangement;
- The achievement of the milestone involves substantive effort and can only be achieved based in whole or in part on our performance or the occurrence of a specific outcome resulting from our performance;
- The amount of the milestone payment appears reasonable either in relation to the effort expended or to the enhancement of the value of the delivered items;
- There is no future performance required to earn the milestone; and
- The consideration is reasonable relative to all deliverables and payment terms in the arrangement.

If any of these conditions are not met, we do not consider the milestone to be substantive and we defer recognition of the milestone payment and recognize it as revenue over our estimated period of performance, if any. Further information about our collaborative arrangements can be found in Note 6, *Collaborative Arrangements and Licensing Agreements*.

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 significant future performance obligations and are reasonably assured of collecting the resulting receivable. For example, in the first quarter of 2014, we recognized $7.7 million in revenue from Alnylam related to its license of our technology to one of its partners because we had no performance obligations and collectability was reasonably assured.

Cash, cash equivalents and short-term investments

We consider all liquid investments with maturities of three months or less when we purchase them to be cash equivalents. Our short-term investments have initial maturities of greater than three months from date of purchase. We classify our short-term investments as “available-for-sale” and carry them 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 comprehensive income (loss) and include net realized gains and losses in gain (loss) 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 that we have received as part of a technology license or collaboration agreement. At March 31, 2015 we held ownership interests of less than 20 percent in each of the respective companies.

We account for our equity investments in publicly-held companies at fair value and record unrealized gains and losses related to temporary increases and decreases in the stock of these publicly-held companies as a separate component of comprehensive income (loss). We account for equity investments in privately-held companies under the cost method of accounting because we own less than 20 percent and do not have significant influence over their operations. We hold one cost method investment in Atlantic Pharmaceuticals Limited. Realization of our equity position in this company is uncertain. When realization of our investment is uncertain, we record a full valuation allowance. 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 company, near term prospects of the company and our current need for cash. If we determine that a decline in value in either a public or private investment is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs.

Inventory valuation

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 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 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 for the three months ended March 31, 2015 and 2014. Total inventory, which consisted of raw materials, was $6.8 million and $6.3 million as of March 31, 2015 and December 31, 2014, respectively.

Research, development and patent expenses

Our research and development expenses include wages, benefits, facilities, supplies, external services, clinical trial and manufacturing costs and other expenses that are directly related to our research and development operations. We expense research and development costs as we incur them. When we make payments for research and development services prior to the services being rendered, we record those amounts as prepaid assets on our condensed consolidated balance sheet and we expense them as the services are provided.

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents. We amortize patent costs over the useful life of the patent, beginning with the date the United States Patent and Trademark Office, or foreign equivalent, issues the patent. We review our capitalized patent costs regularly to ensure that they include costs for patents and patent applications that have future value. We evaluate patents and patent applications that we are not actively pursuing and write off any associated costs.

Long-lived assets

We evaluate long-lived assets, which include property, plant and equipment, patent costs, and exclusive licenses acquired from third parties, for impairment on at least a quarterly basis and whenever events or changes in circumstances indicate that we may not be able to recover the carrying amount of such assets.

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.

Basic and diluted net loss per share

We compute basic net loss per share by dividing the net loss by the weighted-average number of common shares outstanding during the period. As we incurred a net loss for the three months ended March 31, 2015 and 2014, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. Common stock from the following would have had an anti-dilutive effect on net loss per share:

- 1 percent convertible senior notes;
- 2¾ percent convertible senior notes;
- Dilutive stock options;
- Unvested restricted stock units; and
- Employee Stock Purchase Plan, or ESPP.

Consolidation of variable interest entities

We identify entities as 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. We perform ongoing qualitative assessments of our variable interest entities to determine whether we have a controlling financial interest in the variable interest entity and therefore are the primary beneficiary. As of March 31, 2015 and December 31, 2014, we had collaborative arrangements with two entities, Regulus and Antisense Therapeutics Limited, that we considered to be variable interest entities. We are not the primary beneficiary for any of these entities as we do not have the power to direct the activities that most significantly impact the economic performance of our variable interest entities, the obligation to absorb losses, or the right to receive benefits from our variable interest entities that could potentially be significant to the variable interest entities. As of March 31, 2015, the total carrying value of our investments in variable interest entities was $93.4 million, and was related to our investment in Regulus. Our maximum exposure to loss related to our variable interest entities is limited to the carrying value of our investments.

Accumulated other comprehensive income

Accumulated other comprehensive income is comprised of unrealized gains and losses on investments, net of taxes, and adjustments we made to reclassify realized gains and losses on investments from other accumulated comprehensive income to our condensed consolidated statement of operations. The following table summarizes changes in accumulated other comprehensive income for the three months ended March 31, 2015 and 2014 (in thousands):

	Three Months Ended March 31,	
	2015	2014
Beginning balance accumulated other comprehensive income	$ 39,747	$ 21,080
Other comprehensive income before reclassifications, net of tax (1)	7,367	8,261
Amounts reclassified from accumulated other comprehensive income (2)	—	(341)
Net current period other comprehensive income	7,367	7,920
Ending balance accumulated other comprehensive income	$ 47,114	$ 29,000

(1) Other comprehensive income from the three months ended March 31, 2015 includes income tax expense of $5.1 million, compared to $5.4 million for the three months ended March 31, 2014.

(2) Included in gain on investments, net on our condensed consolidated statement of operations.

Convertible debt

We account for convertible debt instruments, including our 1 percent and 2¾ percent convertible notes, 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. We determine the carrying amount of the liability component by measuring the fair value of similar debt instruments that do not have the conversion feature. If no similar debt instrument exists, we estimate fair value by using assumptions that market participants would use in pricing a debt instrument, including market interest rates, credit standing, yield curves and volatilities. 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 the associated non-cash interest expense.

We assign a value to the debt component of our convertible notes equal to the estimated fair value of similar debt instruments without the conversion feature, which resulted in us recording our debt at a discount. We are amortizing the debt discount over the life of the convertible notes as additional non-cash interest expense utilizing the effective interest method.

Segment information

In 2015, we began operating as two segments, our Isis Core segment, previously referred to as Drug Discovery and Development, and our new segment, Akcea Therapeutics, which includes the operations of our newly-formed and wholly-owned subsidiary, Akcea Therapeutics, Inc. We formed Akcea to develop and commercialize the drugs from our lipid franchise. We provide segment financial information and results for our Isis Core segment and our Akcea Therapeutics segment based on the segregation of revenues and expenses that our chief decision maker reviews to assess operating performance and to make operating decisions. We use judgments and estimates in determining the allocation of shared expenses to the two segments. Different assumptions or allocation methods could result in materially different results by segment.

Stock-based compensation expense

We measure stock-based compensation expense for equity-classified awards, principally related to stock options, restricted stock units, or RSUs, and stock purchase rights under our ESPP, based on the estimated fair value of the award on the date of grant. We recognize the value of the portion of the award that we ultimately expect to vest as stock-based compensation expense over the requisite service period in our condensed consolidated statements of operations. We reduce stock-based compensation expense for estimated forfeitures at the time of grant and revise in subsequent periods if actual forfeitures differ from those estimates.

We use the Black-Scholes model to estimate the fair value of stock options granted and stock purchase rights under our ESPP. The expected term of stock options granted represents the period of time that we expect them to be outstanding. We estimate the expected term of options granted based on historical exercise patterns. For the three months ended March 31, 2015 and 2014, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Three Months Ended March 31,	
	2015	2014
Risk-free interest rate	1.5%	1.6%
Dividend yield	0.0%	0.0%
Volatility	53.5%	50.5%
Expected life	4.5 years	4.6 years

ESPP:

	Three Months Ended March 31,	
	2015	2014
Risk-free interest rate	0.1%	0.1%
Dividend yield	0.0%	0.0%
Volatility	56.2%	59.0%
Expected life	6 months	6 months

Board of Director Stock Options:

	Three Months Ended March 31, 2014
Risk-free interest rate	2.3%
Dividend yield	0.0%
Volatility	53.3%
Expected life	7.1 years

The fair value of RSUs is based on the market price of our common stock on the date of grant. RSUs vest annually over a four year period. The weighted-average grant date fair value of RSUs granted to employees for the three months ended March 31, 2015 was $68.84 per share.

We did not grant any stock options or RSUs to the Board of Directors for the three months ended March 31, 2015.

The following table summarizes stock-based compensation expense for the three months ended March 31, 2015 and 2014 (in thousands), which was allocated as follows:

	Three Months Ended March 31,	
	2015	2014
Research, development and patent expenses	$ 10,486	$ 5,873
General and administrative	2,819	1,196
Total	$ 13,305	$ 7,069

Non-cash stock-based compensation expense was $13.3 million for the three months ended March 31, 2015, and increased compared to $7.1 million for the same period in 2014 primarily due to the increase in our stock price. As of March 31, 2015, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $60.2 million and $25.0 million, respectively. We will adjust total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize the cost of non-cash, stock-based compensation expense related to non-vested stock options and RSUs over a weighted average amortization period of 1.5 years and 1.8 years, respectively.

Impact of recently issued accounting standards

In May 2014, the FASB issued accounting guidance on the recognition of revenue from customers. Under this guidance, an entity will recognize revenue when it transfers promised goods or services to customers in an amount that reflects what the entity expects in exchange for the goods or services. This guidance also requires more detailed disclosures to enable users of the financial statements to understand the nature, amount, timing and uncertainty of revenue and cash flows arising from contracts with customers. The guidance as currently issued is effective for fiscal years, and interim periods within that year, beginning after December 15, 2016 and will be effective for us in our fiscal year beginning January 1, 2017. On April 1, 2015, the FASB voted to propose deferring the effective date by one year. The FASB would still permit entities to choose to adopt on the original effective date. The proposal is subject to the FASB's due process requirement, which includes a period for public comment. The guidance allows us to select one of two methods of adoption, either the full retrospective approach, meaning the guidance would be applied to all periods presented, or modified retrospective, meaning the cumulative effect of applying the guidance would be recognized as an adjustment to our opening retained earnings balance. We are currently in the process of determining the adoption method and timing as well as the effects the adoption will have on our consolidated financial statements and disclosures.

In August 2014, the FASB issued accounting guidance on how and when to disclose going-concern uncertainties in the financial statements. This guidance will require us to perform interim and annual assessments to determine our ability to continue as a going concern within one year from the date that we issue our financial statements. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2016. We will adopt this guidance in our fiscal year beginning January 1, 2017. We do not expect this guidance to have any effect on our financial statements.

In February 2015, the FASB issued accounting guidance which amends existing consolidation guidance for entities that are required to evaluate whether they should consolidate certain legal entities. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2015. We will adopt this guidance in our fiscal year beginning January 1, 2016. We do not expect this guidance to have any effect on our financial statements.

In April 2015, the FASB issued accounting guidance to simplify the presentation of debt issuance costs. The amended guidance requires us to present debt issuance costs as a direct deduction from the carrying amount of the related debt liability rather than as an asset. The guidance does not require us to change how we recognize and measure our debt issuance costs. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2015. We will adopt this guidance in our fiscal year beginning January 1, 2016. We do not expect this guidance to have a material impact on our financial statements.

In April 2015, the FASB issued accounting guidance to clarify the accounting for fees paid in cloud computing arrangements. The amendment provides guidance to customers about whether a cloud computing arrangement includes a software license element consistent with the acquisition of other software licenses or if the arrangement excludes a software license and should be accounted for as a service contract. The guidance does not change the accounting for service contracts. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2015. We can choose to adopt it either prospectively or retrospectively. We will adopt this guidance in our fiscal year beginning January 1, 2016. We are currently evaluating the impact, if any, of the adoption of this newly issued guidance to our condensed consolidated financial statements.

3. Investments

As of March 31, 2015, we have primarily invested our excess cash in debt instruments of the U.S. Treasury, financial institutions, corporations, and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's, or S&P, or Fitch, respectively. 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 March 31, 2015:

One year or less	58%
After one year but within two years	29%
After two years but within three years	13%
Total	100%

As illustrated above, at March 31, 2015, 87 percent of our available-for-sale securities had a maturity of less than two years.

All of our available-for-sale securities are available to us for use in our current operations. As a result, we categorize all of these securities as current assets even though the stated maturity of some individual securities may be one year or more beyond the balance sheet date.

At March 31, 2015, we had an ownership interest of less than 20 percent in one private company and two public companies with which we conduct business. The privately-held company is Atlantic Pharmaceuticals Limited and the publicly-traded companies are Antisense Therapeutics Limited and Regulus. We account for equity investments in the privately-held company under the cost method of accounting and we account for equity investments in the publicly-traded companies at fair value. We record unrealized gains and losses as a separate component of comprehensive income (loss) and include net realized gains and losses in gain (loss) on investments.

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

March 31, 2015	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Available-for-sale securities:					
Corporate debt securities	$ 190,437	$ 87	$ (31)	$ —	$ 190,493
Debt securities issued by U.S. government agencies	53,006	5	(13)	—	52,998
Debt securities issued by the U.S. Treasury	5,999	4	—	—	6,003
Debt securities issued by states of the United States and political subdivisions of the states (1)	46,571	25	(50)	—	46,546
Total securities with a maturity of one year or less	296,014	121	(94)	—	296,040
Corporate debt securities	137,653	124	(162)	—	137,615
Debt securities issued by U.S. government agencies	62,529	29	(14)	—	62,544
Debt securities issued by states of the United States and political subdivisions of the states	59,667	48	(165)	—	59,550
Total securities with a maturity of more than one year	259,849	201	(341)	—	259,709
Total available-for-sale securities	$ 555,862	$ 322	$ (435)	$ —	$ 555,749

March 31, 2015	Cost Basis	Gross Unrealized Gains	Gross Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Equity securities:					
Regulus Therapeutics Inc.	$ 12,477	$ 80,969	$ —	$ —	$ 93,446
Securities included in other current assets	880	—	—	(880)	—
Total equity securities	$ 13,357	$ 80,969	$ —	$ (880)	$ 93,446
Total available-for-sale and equity securities	$ 569,220	$ 81,291	$ (435)	$ (880)	$ 649,195

December 31, 2014	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Available-for-sale securities:					
Corporate debt securities(1)	$ 219,856	$ 89	$ (89)	$ —	$ 219,856
Debt securities issued by U.S. government agencies	47,496	7	(27)	—	47,476
Debt securities issued by the U.S. Treasury (1)	19,008	9	—	—	19,017
Debt securities issued by states of the United States and political subdivisions of the states (1)	45,196	19	(53)	—	45,162
Total securities with a maturity of one year or less	331,556	124	(169)	—	331,511
Corporate debt securities	152,730	16	(600)	—	152,146
Debt securities issued by U.S. government agencies	62,530	—	(151)	—	62,379
Debt securities issued by states of the United States and political subdivisions of the states	60,073	32	(234)	—	59,871
Total securities with a maturity of more than one year	275,333	48	(985)	—	274,396
Total available-for-sale securities	$ 606,889	$ 172	$ (1,154)	$ —	$ 605,907

December 31, 2014	Cost Basis	Gross Unrealized Gains	Gross Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Equity securities:					
Regulus Therapeutics Inc.	$ 12,477	$ 69,404	$ —	$ —	$ 81,881
Securities included in other current assets	880	—	—	(880)	—
Total equity securities	$ 13,357	$ 69,404	$ —	$ (880)	$ 81,881
Total available-for-sale and equity securities	$ 620,246	$ 69,576	$ (1,154)	$ (880)	$ 687,788

(1) Includes investments classified as cash equivalents on our condensed consolidated balance sheet.

Investments we considered to be temporarily impaired at March 31, 2015 were as follows (in thousands):

	Number of Investments	Less than 12 months of temporary impairment: Estimated Fair Value	Less than 12 months of temporary impairment: Unrealized Losses	More than 12 months of temporary impairment: Estimated Fair Value	More than 12 months of temporary impairment: Unrealized Losses	Total temporary impairment: Estimated Fair Value	Total temporary impairment: Unrealized Losses
Corporate debt securities	132	$ 136,603	$ (193)	$ —	$ —	$ 136,603	$ (193)
Debt securities issued by U.S. government agencies	11	74,094	(27)	—	—	74,094	(27)
Debt securities issued by states of the United States and political subdivisions of the states	24	42,943	(144)	6,231	(71)	49,174	(215)
Total temporarily impaired securities	167	$ 253,640	$ (364)	$ 6,231	$ (71)	$ 259,871	$ (435)

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 believe it is more likely than not that we will be able to hold these securities to maturity. Therefore we anticipate full recovery of their amortized cost basis at maturity.

4. Fair Value Measurements

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes our money market funds and treasury securities classified as available-for-sale securities and our investment in 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 us to develop our own assumptions. Our Level 3 investments include our investments in the equity securities of publicly-held biotechnology companies for which we calculated a lack of marketability discount because there were restrictions on when we could trade the securities. We determine the lack of marketability discount by using a Black-Scholes model to value a hypothetical put option to approximate the cost of hedging the stock until the restriction ends. The majority of our securities have been classified as Level 2. We obtain the fair value of our Level 2 investments from our custodian bank or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian banks or professional pricing service provider and comparing that fair value to the fair value based on observable market prices. During the three months ended March 31, 2015, there were no transfers between our Level 1 and Level 2 investments. We recognize transfers between levels of the fair value hierarchy on the date of the event or change in circumstances that caused the transfer.

We measure the following major security types at fair value on a recurring basis. The following summary breaks down the fair-value hierarchy that we used to value each security at March 31, 2015 and December 31, 2014 (in thousands):

	At March 31, 2015	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 112,777	$ 112,777	$ —	$ —
Corporate debt securities (2)	328,108	—	328,108	—
Debt securities issued by U.S. government agencies (2)	115,542	—	115,542	—
Debt securities issued by the U.S. Treasury (2)	6,003	6,003	—	—
Debt securities issued by states of the United States and political subdivisions of the states (3)	106,096	—	106,096	—
Investment in Regulus Therapeutics Inc.	93,446	93,446	—	—
Total	$ 761,972	$ 212,226	$ 549,746	$ —

	At December 31, 2014	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 104,680	$ 104,680	$ —	$ —
Corporate debt securities (4)	372,002	—	372,002	—
Debt securities issued by U.S. government agencies (2)	109,855	—	109,855	—
Debt securities issued by the U.S. Treasury (5)	19,017	19,017	—	—
Debt securities issued by states of the United States and political subdivisions of the states (6)	105,033	—	105,033	—
Investment in Regulus Therapeutics Inc.	81,881	—	—	81,881
Total	$ 792,468	$ 123,697	$ 586,890	$ 81,881

(1) Included in cash and cash equivalents on our condensed consolidated balance sheet.

(2) Included in short-term investments on our condensed consolidated balance sheet.

(3) $9.0 million included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.

(4) $0.8 million included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.

(5) $10 million included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.

(6) $9.3 million included in cash and cash equivalents on our condensed consolidated balance sheet, with the difference included in short-term investments on our condensed consolidated balance sheet.

In November 2014, Regulus completed a public offering. As part of the offering, we sold shares of Regulus' common stock and became subject to trading restrictions on our remaining shares through January 2015. Therefore, at December 31, 2014, our investment in Regulus included a lack of marketability discount and was classified as a Level 3 investment. At the end of January 2015, we reclassified our investment in Regulus to a Level 1 investment because the contractual trading restrictions on the shares we own ended.

The following is a summary of our investments measured at fair value on a recurring basis using significant unobservable inputs (Level 3) for the three months ended March 31, 2015 (in thousands):

Beginning balance of Level 3 investments	$ 81,881
Total gain included in accumulated other comprehensive income (loss)	22,377
Transfers out of Level 3 investments	(104,258)
Ending balance of Level 3 investments	$ —

Other Fair Value Disclosures

Our 1 percent and 2¾ percent convertible notes had a fair value of $233.7 million and $584.7 million, respectively at March 31, 2015. We determine the fair value of our convertible notes based on quoted market prices for these notes, which are Level 2 measurements.

5. Income Taxes

Intraperiod tax allocation rules require us to allocate our provision for income taxes between continuing operations and other categories of earnings, such as other comprehensive income. In periods in which we have a year-to-date pre-tax loss from continuing operations and pre-tax income in other categories of earnings, such as other comprehensive income, we must allocate the tax provision to the other categories of earnings. We then record a related tax benefit in continuing operations. During the three months ended March 31, 2015 and 2014, we recorded unrealized gains on our investments in available-for-sale securities in other comprehensive income, net of taxes. As a result, for the three months ended March 31, 2015 and 2014, we recorded a $0.8 million and $2.3 million tax benefit, respectively, on our condensed consolidated statements of operations and a $5.1 million and $5.4 million tax expense, respectively, in other comprehensive income.

6. Collaborative Arrangements and Licensing Agreements

Traditional Pharmaceutical Alliances and Licensing

Bayer HealthCare

In May 2015, we entered into an exclusive license agreement with Bayer HealthCare to develop and commercialize ISIS-FXI$_{Rx}$ for the prevention of thrombosis. We are responsible for completing ongoing development activities. Bayer HealthCare is responsible for all other development and commercialization activities for ISIS-FXI$_{Rx}$. This transaction is subject to clearances under the Hart-Scott Rodino Antitrust Improvements Act.

Under the terms of the agreement, we are eligible to receive $155 million in near-term payments, including an immediate $100 million payment and a $55 million milestone payment upon advancement of the program following a Phase 2 study in patients with compromised kidney function. Over the term of the agreement, we are eligible to receive up to $375 million in license fees, milestone payments and other payments, including up to $120 million for the achievement of development milestones and up to $110 million for the achievement of commercialization milestones. In addition, we are eligible to receive tiered royalties in the low to high 20 percent range on gross margins of ISIS-FXI$_{Rx}$. We will earn the next milestone payment of $55 million upon the advancement of the program following a Phase 2 study of ISIS-FXI$_{Rx}$ in patients with compromised kidney function.

Our agreement with Bayer HealthCare will continue until the expiration of all payment obligations under the agreement. In addition, the agreement, or any program under the agreement, may terminate early under the following situations:

- Bayer HealthCare may terminate the agreement or any program at any time by providing written notice to us;
- Either we or Bayer HealthCare may terminate the agreement or any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement, or the entire agreement if the other party becomes insolvent; and
- If Hart-Scott Rodino clearance is not received by December 31, 2015.

Biogen

We have established four strategic collaborations with Biogen that broaden and expand our severe and rare disease franchise for neurological disorders.

ISIS-SMN$_{Rx}$

In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize ISIS-SMN$_{Rx}$ for the treatment of SMA. We are currently conducting a Phase 3 study evaluating ISIS-SMN$_{Rx}$ in infants with SMA and a Phase 3 study evaluating ISIS-SMN$_{Rx}$ in children with SMA. In addition, we are evaluating ISIS-SMN$_{Rx}$ in two Phase 2 open-label, multiple-dose, dose-escalation studies, one in children with SMA and one in infants with SMA. Patients from both of the Phase 2 studies continue to have access to ISIS-SMN$_{Rx}$ through open-label extension dosing. We are responsible for completing the Phase 2 and Phase 3 trials we are currently conducting. If Biogen exercises its option, it will pay us a license fee and will assume all other global development, regulatory and commercialization responsibilities. Biogen has the option to license ISIS-SMN$_{Rx}$. Biogen may exercise this option upon completion of and data review of the first successful Phase 2/3 trial or completion of both Phase 2/3 trials. An amendment in December 2014 provided for additional opt-in scenarios, based on the filing or the acceptance of a new drug application or marketing authorization application with the FDA or EMA.

We received an upfront payment of $29 million, which we are amortizing through February 2017. We are also eligible to receive a license fee, milestone payments and royalties up to the mid-teens on any product sales of ISIS-SMN$_{Rx}$. In 2014, we and Biogen amended our original agreement to reflect changes made to the clinical development plan for ISIS-SMN$_{Rx}$. As a result, we and Biogen agreed to increase the payments that we are eligible to receive under this collaboration by approximately $57 million. Under the terms of the amended agreement, we are eligible to receive up to $327 million in a license fee and payments, including $102 million in substantive milestone and other payments associated with the clinical development of ISIS-SMN$_{Rx}$ prior to licensing and $150 million in substantive milestone payments if Biogen achieves pre-specified regulatory milestones. In the first quarter of 2015, we earned a $9 million milestone payment for advancing the Phase 3 study of ISIS-SMN$_{Rx}$ in infants with SMA and we earned a $7 million milestone payment for advancing the open-label extension study of ISIS-SMN$_{Rx}$ in children with SMA. From inception through March 2015, we have received nearly $110 million in payments for advancing ISIS-SMN$_{Rx}$. We will earn the next milestone payment of $8.5 million if we further advance the Phase 3 study in infants with SMA.

ISIS-DMPK-2.5$_{Rx}$

In June 2012, we and Biogen entered into a second and separate collaboration agreement to develop and commercialize a novel antisense drug, ISIS-DMPK-2.5$_{Rx}$, targeting DMPK for the treatment of myotonic dystrophy type 1, or DM1. We are responsible for global development of the drug through the completion of the first Phase 2 clinical trial. Biogen has the option to license the drug through the completion of the first Phase 2 trial. If Biogen exercises its option, it will assume all other global development, regulatory and commercialization responsibilities. Under the terms of the agreement, we received an upfront payment of $12 million, which we are amortizing through June 2017. Over the term of the collaboration, we are eligible to receive up to $259 million in a license fee and substantive milestone payments, including up to $59 million in development milestone payments and $130 million in milestone payments if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive royalties up to the mid-teens on any product sales of the drug. From inception through March 2015, we have received $36 million in payments for advancing ISIS-DMPK-2.5$_{Rx}$. We will earn the next milestone payment of $35 million if we initiate a Phase 2 study for ISIS-DMPK-2.5$_{Rx}$.

Neurology

In December 2012, we and Biogen entered into a third and separate collaboration agreement to develop and commercialize novel antisense drugs to three targets to treat neurological or neuromuscular diseases. We are responsible for the development of each of the drugs through the completion of the initial Phase 2 clinical study for such drug. Biogen has the option to license a drug from each of the three programs through the completion of the first Phase 2 study for each program. If Biogen exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities for that drug. Under the terms of the agreement, we received an upfront payment of $30 million, which we are amortizing through December 2020. Over the term of the collaboration, we are eligible to receive up to $259 million in a license fee and substantive milestone payments per program. We are eligible to receive up to $59 million in development milestone payments to support research and development of each program, including amounts related to the cost of clinical trials. We are also eligible to receive up to $130 million in milestone payments per program if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive royalties up to the mid-teens on any product sales of drugs resulting from each of the three programs. In February 2015, we earned a $10 million milestone payment when we initiated an IND-enabling toxicology study of ISIS-BIIB4$_{Rx}$, a drug for an undisclosed target designed to treat a neurodegenerative disease. From inception through March 31, 2015, we have received $40 million in payments under this collaboration. We will earn the next milestone payment of up to $14 million if we initiate a Phase 1 study for ISIS-BIIB4$_{Rx}$.

Strategic Neurology

In September 2013, we and Biogen entered into a fourth and separate collaboration agreement, which is a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurological diseases. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license drugs resulting from this collaboration. The exclusivity for neurological diseases will last through September 2019, and may be extended for any drug development programs being pursued under the collaboration. We will usually be responsible for drug discovery and early development of antisense drugs and Biogen will have the option to license antisense drugs after Phase 2 proof of concept. If Biogen exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities for that drug. Biogen will be responsible for all of the drug discovery and development activities for drugs using other modalities.

Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all drugs developed through this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen. If we have a change of control during the first six years of the collaboration, we may be required to refund Biogen a portion of the $100 million upfront payment, with the amount of the potential refund decreasing ratably as we progress through the initial six year term of the collaboration. We are amortizing the $100 million upfront payment through September 2019. Because the amortization period for the upfront payment will never be less than the initial six year term of the collaboration, the amount of revenue we recognize from the upfront payment will never exceed the amount that Biogen could potentially require us to refund.

For each antisense molecule that is chosen for drug discovery and development under this collaboration, we are eligible to receive up to approximately $260 million in a license fee and substantive milestone payments. We are eligible to receive up to approximately $60 million for the achievement of research and development milestones, including amounts related to the cost of clinical trials, and up to $130 million for the achievement of regulatory milestones. In addition, we are eligible to receive royalties up to the mid-teens on any product sales of antisense drugs developed under this collaboration. If other modalities are chosen, such as small molecules or monoclonal antibodies, we are eligible to receive up to $90 million in substantive milestone payments, including up to $35 million for the achievement of research and development milestones and up to $55 million for the achievement of regulatory milestones. In addition, we are eligible to receive single-digit royalties on any product sales of drugs using non-antisense modalities developed under this collaboration. From inception through March 2015, we have received $125 million in payments under this collaboration. In April 2015, we earned a $10 million milestone payment for validating a fourth target under this collaboration. We will earn the next milestone payment of up to $10 million if we choose another target to advance under this collaboration.

Each of our agreements with Biogen will continue until the earlier of the date all of Biogen's options to obtain the exclusive licenses under the applicable agreement expire unexercised or, if Biogen exercises its option, until the expiration of all payment obligations under the applicable agreement. In addition, each agreement, or any program under an agreement, may terminate early under the following situations:

- Biogen may terminate the agreement or any program at any time by providing written notice to us;
- Under specific circumstances, if we are acquired by a third party with a product that directly competes with a compound being developed under the agreement, Biogen may terminate the affected program by providing written notice to us;
- If, within a specified period of time, any required clearance of a transaction contemplated by an agreement under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, is not received, then either we or Biogen may terminate the affected program by providing written notice to the other party; and
- Either we or Biogen may terminate any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement with respect to the affected program, or the entire agreement if the other party becomes insolvent.

During the three months ended March 31, 2015 and 2014, we earned revenue of $39.2 million and $10.2 million, respectively, from our relationship with Biogen, which represented 63 and 36 percent, respectively of our total revenue for those periods. Our condensed consolidated balance sheet at March 31, 2015 included deferred revenue of $110.8 million related to our relationship with Biogen.

GSK

In March 2010, we entered into a strategic alliance with GSK using our antisense drug discovery platform to seek out and develop new drugs against targets for rare and serious diseases, including infectious diseases and some conditions causing blindness. Our strategic alliance currently includes five drugs in development. GSK has the exclusive option to license drugs resulting from this alliance at Phase 2 proof-of-concept for a license fee. If GSK exercises its exclusive option for any drugs resulting from this alliance, it will be responsible for all further global development, regulatory and commercialization activities for such drug. Under the terms of the agreement, we received a $35 million upfront payment and in May 2011 we received a $3 million payment when we and GSK expanded the collaboration.

In October 2012, we and GSK amended the original agreement to reflect an accelerated clinical development plan for ISIS-TTR_{Rx}. From inception through March 2015, we have earned $60 million, primarily in milestone payments, from GSK related to the development of ISIS-TTR_{Rx}. We are also eligible to earn an additional $10 million pre-licensing milestone payment associated with the ISIS-TTR_{Rx} Phase 2/3 study. In addition, under the amended agreement, we and GSK increased the regulatory and commercial milestone payments we can earn should ISIS-TTR_{Rx} receive marketing approval and meet pre-agreed sales targets.

In addition to ISIS-TTR_{Rx}, we have four drugs in development. We are developing ISIS-HBV_{Rx}, an antisense drug designed to reduce the production of viral proteins associated with hepatitis B virus, or HBV infection. We are also developing ISIS-GSK4-L_{Rx} and ISIS-RHO-2.5_{Rx}, which are antisense drugs we designed to treat ocular diseases. In addition, we recently advanced a drug to treat an undisclosed target, ISIS-GSK6-L_{Rx}, into development.

Under our agreement, if GSK successfully develops all five drugs for one or more indications and achieves pre-agreed sales targets, we could receive license fees and substantive milestone payments of more than $1.3 billion, including up to $220.5 million for the achievement of development milestones, up to $483.5 million for the achievement of regulatory milestones and up to $428 million for the achievement of commercialization milestones. Through March 2015, we have received $129.5 million in payments under this strategic alliance with GSK. We will earn the next milestone payment of $5 million if we further advance ISIS-$GSK4_{Rx}$. In addition, we are eligible to receive royalties up to the mid-teens on sales from any product that GSK successfully commercializes under this alliance.

Our alliance with GSK will continue until the earlier of the date that all of GSK's options to obtain the exclusive licenses under the agreement expire unexercised or, if GSK exercises its option, until the expiration of all payment obligations under the agreement. In addition, the agreement, or any program under the agreement, may terminate early under the following situations:

- GSK may terminate any program, other than the ISIS-TTR_{Rx} program, at any time by providing written notice to us;
- GSK may terminate the ISIS-TTR_{Rx} program by providing written notice to us after reviewing specific data from the Phase 3 study for the program; and
- Either we or GSK may terminate any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement with respect to the affected program, or the entire agreement if the other party becomes insolvent.

During the three months ended March 31, 2015 and 2014, we earned revenue of $16.5 million and $3.3 million, respectively, from our relationship with GSK, which represented 26 and 12 percent, respectively of our total revenue for those periods. Our condensed consolidated balance sheet at March 31, 2015 included deferred revenue of $9.2 million related to our relationship with GSK.

7. Segment Information and Concentration of Business Risk

In 2015, we began reporting our financial results in two reportable segments, Isis Core, previously referred to as Drug Discovery and Development and Akcea Therapeutics, our new wholly owned subsidiary. Segment loss from operations includes revenue less operating expenses attributable to each segment.

In our Isis Core segment we are exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class or best-in-class drugs for us and our partners. Our Isis Core segment generates revenue from a multifaceted partnering strategy.

We established Akcea to develop and commercialize the drugs from our lipid franchise. Moving our lipid drugs into a company that we own and control ensures that our core focus at Isis remains on innovation while allowing us to maintain control over and retain more value from our lipid drugs. To date, Akcea has not earned any revenue.

The following is our segment information for the three months ended March 31, 2015 (in thousands).

	Isis Core	Akcea Therapeutics	Total
Revenue:			
Research and development	$ 61,892	$ —	$ 61,892
Licensing and royalty	691	—	691
Total segment revenue	$ 62,583	$ —	$ 62,583
Loss from operations	$ (2,232)	$ (7,098)	$ (9,330)

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 ten percent or more of our total revenue, was as follows:

	Three Months Ended March 31,	
	2015	2014
Partner A	63%	36%
Partner B	26%	12%
Partner C	1%	12%
Partner D	0%	27%

Contract receivables from two significant partners comprised approximately 92 percent of our contract receivables at March 31, 2015. Contract receivables from three significant partners comprised approximately 99 percent of our contract receivables at December 31, 2014.

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 wholly owned subsidiary, Akcea Therapeutics, Inc.

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 drugs, including KYNAMRO, ISIS-$APOCIII_{Rx}$, ISIS-SMN_{Rx} and ISIS-TTR_{Rx}, and other products in development, and the financial position of Isis Pharmaceuticals, Inc. 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 drugs. 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, 2014, which is on file with the U.S. Securities and Exchange Commission and are available from us, and those identified within this Item in the section entitled "Risk Factors" beginning on page 30 of this Report.

Overview

We are the leading company in RNA-targeted drug discovery and development, exploiting a proven novel drug discovery platform we created to generate a broad pipeline of first-in-class or best-in-class antisense drugs. The efficiency and broad applicability of our drug discovery platform allows us to discover and develop antisense drugs to treat a wide range of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. The efficiency of our drug discovery technology allows us to employ a unique business strategy designed to maximize the value of our drugs and technology while maintaining an effective cost structure that limits our cash needs. Our business strategy is supported by our platform technology, our robust pipeline of drugs and our diverse partnering strategies, which have enabled us to focus on doing what we do best – to discover and develop novel antisense drugs.

We have created a mature and broad pipeline of 38 drugs in development that represents the potential for significant commercial opportunities in many therapeutic areas. We have a number of drugs in later-stage development that we believe represent significant near-term commercial opportunities. ISIS-APOCIII$_{Rx}$ is a drug we designed to treat patients with severely high triglyceride levels, including patients with a severe and rare genetic condition called familial chylomicronemia syndrome, or FCS and patients with partial lipodystrophy, another severe and rare genetic condition. We have completed a broad Phase 2 program in which patients treated with ISIS-APOCIII$_{Rx}$ experienced significantly reduced triglyceride and apolipoprotein C-III, or apoC-III, levels when evaluated as a single agent and in combination with fibrates. We initiated a Phase 3 study of ISIS-APOCIII$_{Rx}$ in patients with FCS in the third quarter of 2014 and we plan to initiate a Phase 3 study in patients with partial lipodystrophy in 2015. In addition to ISIS-APOCIII$_{Rx}$, we are also evaluating ISIS-TTR$_{Rx}$ and ISIS-SMN$_{Rx}$ in Phase 3 studies. We designed these drugs to treat patients with severe and rare diseases, such as transthyretin amyloidosis, or TTR amyloidosis, and spinal muscular atrophy, or SMA, who have very limited therapeutic options. The significant unmet medical need and the severity of these diseases could warrant a rapid path to market. We expect Phase 3 data in 2016/2017 for all three of these drugs, which may support regulatory filings for marketing approvals for these drugs. We believe all three of these drugs have the potential to reach the market in the next several years. We also have numerous drugs in our pipeline advancing in mid-stage clinical development that could represent significant near and mid-term licensing opportunities.

Our novel lipid-lowering product, KYNAMRO (mipomersen sodium) injection, is on the market in the United States for patients with HoFH. Patients with HoFH are at high cardiovascular risk and cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies. In January 2013, the FDA approved the marketing application for KYNAMRO for patients with HoFH. Genzyme, a Sanofi Company, has also obtained marketing approval in other countries, including Mexico, Argentina, South Korea and Peru, and is pursuing marketing approval in multiple additional markets. Genzyme is evaluating KYNAMRO in a late-stage clinical study, FOCUS FH, in patients with severe HeFH, and they plan to report data from this study in 2015.

The efficiency and broad utility of our drug discovery technology supports the continued growth of our pipeline of antisense drugs. To maximize the value of our drugs and technologies, we have a multifaceted partnering strategy. Our partnering strategy provides us the flexibility to license each of our drugs at what we believe is the optimal time to maximize the near- and long-term value of our drugs. In this way, we can expand our and our partners' pipelines with antisense drugs that we design to address significant medical needs while remaining small and focused.

One component of our partnering strategy is to form traditional partnering alliances that enable us to discover and conduct early development of new drugs, outlicense our drugs to partners and build a base of license fees, milestone payments and profit share or royalty income. An example of this is our recent exclusive license of ISIS-FXI$_{Rx}$ to Bayer HealthCare to develop and commercialize ISIS-FXI$_{Rx}$ for the prevention of thrombosis. As a leader in the antithrombotic market, Bayer has the expertise, resources and commitment to broadly develop ISIS-FXI$_{Rx}$. They plan to conduct a robust development plan that represents a commitment to make a substantial investment in ISIS-FXI$_{Rx}$. Bayer’s development plan combines short-term indications, which have the potential for early market entrance in patients with limited therapeutic options, with long-term indications in patients who are underserved by current anti-thrombotic treatments. Another example of our traditional partnering strategy was our license of KYNAMRO to Genzyme.

We also form preferred partner transactions that provide us with a vested partner, such as AstraZeneca, Biogen, GSK, Janssen and Roche, early in the development of a drug. Typically, the drugs we partner early in development are in therapeutic areas of high risk, like severe neurological diseases, or in areas where Phase 2 results would likely not provide a significant increase in value, like cancer. These preferred partner transactions allow us to develop select drugs that could have significant commercial potential with a knowledgeable and committed partner with the financial resources to fund later-stage clinical studies and expertise to complement our own development efforts. We benefit from this strategy because it allows us to expand and broaden our drug discovery efforts to new disease targets. For example, through our broad strategic partnership with Biogen, we are capitalizing on Biogen's extensive resources and expertise in neurological diseases to create a franchise of novel treatments for neurological disorders. Additionally, with Janssen we have a global collaboration to discover and develop antisense drugs to treat autoimmune disorders of the GI tract, which brings together our RNA-targeted technology platform and Janssen's expertise in autoimmune disorders and therapeutic formulation. Similar to our other partnerships, with our preferred partner transactions we benefit financially from upfront payments, milestone payments, licensing fees and royalties.

Earlier this year, we established a wholly owned subsidiary, Akcea Therapeutics, Inc., to develop and commercialize the drugs from our lipid franchise. Akcea will focus on the development and commercialization of ISIS-APOCIII$_{Rx}$, ISIS-APO(a)$_{Rx}$ and ISIS-ANGPTL3$_{Rx}$ as well as more potent follow on drugs for these programs. To lead Akcea, we hired a senior business leader with commercialization expertise in severe and rare and cardiovascular diseases to maximize the value of our lipid franchise assets. Our Akcea CEO has already made several key strategic hires. Moving our lipid drugs into a company that we own and control ensures that our core focus at Isis remains on innovation while allowing us to maintain control over and retain more value from our lipid drugs.

We also work with a consortium of companies that can exploit our drugs and technology. We call these companies satellite companies. We benefit from the disease-specific expertise of our satellite company partners, who are advancing drugs in our pipeline in areas that are outside of our core focus. For example, Regulus is a satellite company partner that we co-founded to discover and develop antisense drugs targeting microRNAs. We sold a portion of our Regulus stock in 2014 for more than $20 million of cash, and we remain a significant shareholder in the company. We also maintain our broad RNA technology leadership through collaborations with satellite companies. All of these different types of relationships are part of our partnering strategy, which we designed to maximize the value of our assets, minimize the development risks of a broad pipeline of novel new drugs, and provide us with significant reliable near-term revenue.

The broad applicability of our drug discovery technology and the clinical successes of the drugs in our pipeline continue to create new partnering opportunities. Since January 2012, we have initiated eight new partnerships that involve antisense drugs for the treatment of various disorders, including neurological diseases, autoimmune disorders of the GI tract, thrombosis and cancer. Most recently, we granted an exclusive license to our partner, Bayer HealthCare, to develop and commercialize ISIS-FXI$_{Rx}$ for the prevention of thrombosis. We formed a broad alliance with Janssen to discover and develop antisense drugs to treat autoimmune disorders in the GI tract, four strategic alliances with Biogen to discover and develop antisense drugs to treat neurologic diseases, a strategic alliance with AstraZeneca to discover and develop antisense drugs to treat cancer and a strategic alliance with Roche to discover and develop antisense drugs to treat Huntington's disease. Additionally, we and our partner, GSK, are developing five drugs, including ISIS-TTR$_{Rx}$, which is in Phase 3 development. We have the potential to earn significant revenue from these partnerships and our other partnered programs. Since 2007 we have received more than $1.4 billion in cash from upfront and licensing fees, equity purchase payments, milestone payments and research and development funding from our partnerships. We have the potential to earn over $8.5 billion in future milestone payments and licensing fees from all of our partnerships. We also have the potential to share in the future commercial success of our inventions and drugs resulting from our partnerships through earn out, profit sharing, or royalty arrangements.

As an innovator in RNA-targeting drug discovery and development, we design and execute our patent strategy to provide us with extensive protection for our drugs and our technology. With our ongoing research and development, we continue to add to our substantial patent estate. Our patents not only protect our key assets—our technology and our drugs—they also form the basis for lucrative licensing and partnering arrangements. Through March 2015, we have generated more than $420 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

Recent Events

Drug Development Highlights *(2015 first quarter and subsequent activities)*

- We and our partners reported positive data on six drugs in our pipeline, including:
  - We reported positive results from an ongoing open-label extension study of ISIS-TTR$_{Rx}$ in patients with FAP. In the open-label study after thirteen weeks of treatment with ISIS-TTR$_{Rx}$, TTR protein was reduced up to 92 percent with a median reduction of 78 percent in patients with FAP compared to their baseline TTR levels at entry into the Phase 3 study.
  - AstraZeneca reported clinical and preclinical data on ISIS-STAT3-2.5$_{Rx}$ demonstrating evidence of antitumor activity in patients with cancer including advanced/metastatic hepatocellular carcinoma and diffuse large B cell lymphoma. Additionally, AstraZeneca reported that, in preclinical studies, co-treatment of ISIS-STAT3-2.5$_{Rx}$ and MEDI4736, an immune checkpoint inhibitor, showed significantly greater antitumor activity than when either drug was administered alone. AstraZeneca plans to initiate two clinical studies evaluating ISIS-STAT3-2.5$_{Rx}$ in combination with MEDI4736 this year.
  - We reported top-line Phase 2 data on ISIS-PTP1B$_{Rx}$ demonstrating that patients with type 2 diabetes experienced statistically significant mean reductions in body weight and HbA1c (0.7 percentage point) at 36 weeks.
  - Regulus reported clinical data on RG-101 showing that patients with hepatitis C virus achieved sustained viral suppression after only a single dose of RG-101, and that some patients remained below the level of detection for hepatitis C virus 20 weeks after a single dose.
  - We reported Phase 1 results showing that ISIS-ANGPTL3$_{Rx}$ produced significant reductions of up to 93 percent in ANGPTL3, up to 63 percent in triglycerides and up to 46 percent in total cholesterol in healthy volunteers.
  - We reported Phase 1 results showing that ISIS-PKK$_{Rx}$ produced significant, dose-dependent reductions of PKK of up to 95 percent in healthy volunteers.

Corporate Highlights *(2015 first quarter and subsequent activities*)

- We licensed ISIS-FXI$_{Rx}$ to Bayer HealthCare to develop and commercialize ISIS-FXI$_{Rx}$ for the prevention of thrombosis.
  - We are eligible to receive up to $375 million in payments, including a $100 million upfront payment and a $55 million milestone payment upon advancement of the program following completion of the planned Phase 2 study.
  - We are eligible to receive tiered royalties in the low to high 20 percent range on gross margins of ISIS-FXI$_{Rx}$.
  - This transaction is subject to clearances under the Hart-Scott Rodino Antitrust Improvements Act.
- We formed an alliance with Janssen to discover and develop antisense drugs to treat autoimmune disorders of the GI tract.
  - We received $35 million in upfront payments and are eligible to receive nearly $800 million in development, regulatory and sales milestone payments and license fees for the programs under this alliance.
  - We will also receive tiered royalties in the near teens on sales of drugs successfully commercialized.
- We formed a wholly owned subsidiary, Akcea Therapeutics, to develop and commercialize our lipid drugs, ISIS-APOCIII$_{Rx}$, ISIS-APO(a)$_{Rx}$, ISIS-ANGPTL3$_{Rx}$ and the follow on drugs for these programs.
- We and Alnylam formed a new agreement that includes a cross-license of intellectual property, providing each company rights to certain of each other's technology advances.
  - The new agreement also provides each company with exclusive RNA therapeutic license rights for two programs.
- We generated more than $195 million in payments from partners, including the following:
  - $100 million from Bayer
  - $42 million from Biogen
  - $35 million from Janssen
  - $17 million from GSK

Critical Accounting Policies

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States. As such, we 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 reviews the development, selection and disclosure of such estimates with our audit committee of our board of directors. In the following paragraphs, we describe the specific risks associated with these critical accounting policies and we caution that future events rarely develop exactly as one may expect, and that best estimates may require adjustment.

The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, require the following:

- Assessing the propriety of revenue recognition and associated deferred revenue;
- Determining the proper valuation of investments in marketable securities and other equity investments;
- Assessing the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimating our net deferred income tax asset valuation allowance; and
- Determining the fair value of convertible debt without the conversion feature

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, 2014.

Results of Operations

Revenue

Total revenue for the three months ended March 31, 2015 was $62.6 million compared to $28.2 million for the same period in 2014. Our revenue fluctuates based on the nature and timing of payments under agreements with our partners and consists primarily of revenue from the amortization of upfront fees, milestone payments and license fees. For example, nearly 75% of our revenue in the first quarter of 2015 was from milestone payments we earned from the success of our partnered programs.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the three months ended March 31, 2015 was $61.9 million compared to $19.6 million for the same period in 2014.

We earned $46 million in milestone payments for the three months ended March 31, 2015. The revenue from milestone payments in the first quarter of 2015 was comprised of:

- $31 million from Biogen including the following:
  - $10 million for initiating investigational new drug supporting studies for ISIS-BIIB4$_{Rx}$;
  - $9 million for advancing CHERISH, a Phase 3 study for ISIS-SMN$_{Rx}$ in infants with SMA;
  - $7 million for advancing the open-label extension study for ISIS-SMN$_{Rx}$ in children with SMA; and
  - $5 million for validating an undisclosed target to treat a neurological disorder.
- $15 million from GSK related to advancing the Phase 2/3 study of ISIS-TTR$_{Rx}$.

In April 2015, we earned a $10 million milestone payment from Biogen for advancing a fourth target under our strategic neurology collaboration. In addition, we project that we will recognize between $85 million and $95 million of new revenue in 2015 from our recently completed license agreement with Bayer HealthCare.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the three months ended March 31, 2015 was $0.7 million compared to $8.6 million for the same period in 2014. The decrease was primarily a result of the $7.7 million in sublicensing revenue we earned for the three months ended March 31, 2014 from Alnylam related to its license of our technology to one of its partners.

Operating Expenses

Operating expenses for the three months ended March 31, 2015 were $71.9 million compared to $57.8 million for the same period in 2014 because we are conducting more later-stage clinical trials in 2015 than we did in 2014, including the continuation of our Phase 3 programs for ISIS-TTR$_{Rx}$, ISIS-SMN$_{Rx}$, and ISIS-APOCIII$_{Rx}$ and an increase in stock compensation expense due to the increase in our stock price. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the costs of development increase.

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

	Three Months Ended March 31,	
	2015	2014
Isis Core	$ 52,068	$ 50,759
Akcea Therapeutics	6,540	—
Non-cash compensation expense related to equity awards	13,305	7,069
Total operating expenses	$ 71,913	$ 57,828

In order to analyze and compare our results of operations to other similar companies, we believe it is important to exclude non-cash compensation expense related to equity awards from our operating expenses. 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. Non-cash compensation expense related to equity awards increased significantly in 2015 compared to 2014 primarily due to the increase in our stock price.

Research, Development and Patent Expenses

Our research, development and patent expenses consist of costs for antisense drug discovery, antisense drug development, manufacturing and operations and R&D support costs.

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

	Three Months Ended March 31,	
	2015	2014
Research, development and patent expenses	$ 53,961	$ 47,575
Non-cash compensation expense related to equity awards	10,486	5,873
Total research, development and patent expenses	$ 64,447	$ 53,448

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

	Three Months Ended March 31,	
	2015	2014
Isis Core	$ 48,220	$ 47,575
Akcea Therapeutics	5,741	—
Non-cash compensation expense related to equity awards	10,486	5,873
Total research, development and patent expenses	$ 64,447	$ 53,448

For the three months ended March 31, 2015, our total research, development and patent expenses were $54.0 million compared to $47.6 million for the same period in 2014, and were higher primarily due to the progression of our three drugs we currently have in Phase 3 studies. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Discovery

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 partners. Antisense drug discovery is also the function that is responsible for advancing our antisense core technology.

As we continue to advance our antisense technology, we are investing in our drug discovery programs to expand our and our partners' drug pipelines. We anticipate that our existing relationships and collaborations, as well as prospective new partners, will continue to help fund our research programs and contribute to the advancement of the science by funding core antisense technology research.

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

	Three Months Ended March 31,	
	2015	2014
Antisense drug discovery expenses	$ 10,661	$ 9,097
Non-cash compensation expense related to equity awards	2,918	1,685
Total antisense drug discovery	$ 13,579	$ 10,782

Antisense drug discovery costs for the three months ended March 31, 2015 were $10.7 million and were slightly higher compared to $9.1 million for the same period in 2014 because we were conducting more research activities in 2015 to support our partnerships. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Development

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

	Three Months Ended March 31,	
	2015	2014
KYNAMRO	$ 1,254	$ 1,797
ISIS-TTR$_{Rx}$	3,231	2,381
ISIS-SMN$_{Rx}$	6,120	1,963
ISIS-APOCIII$_{Rx}$	2,371	1,054
Other antisense development products	9,135	10,779
Development overhead costs	8,673	8,424
Total antisense drug development, excluding non-cash compensation expense related to equity awards	30,784	26,398
Non-cash compensation expense related to equity awards	3,714	2,078
Total antisense drug development	$ 34,498	$ 28,476

Antisense drug development expenses were $30.8 million for the three months ended March 31, 2015, compared to $26.4 million for the same period in 2014. Expenses in the first quarter of 2015 were higher compared to the same period in 2014 primarily due to the progression of our three drugs currently in Phase 3 trials. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the costs of development increase. All amounts exclude non-cash compensation expense related to equity awards. In our 2014 Form 10-K, we began presenting salaries and benefits in the development overhead costs line in our antisense drug development table. We have adjusted 2014 to conform to the current year presentation.

Our antisense drug development expenses by segment were as follows (in thousands):

	Three Months Ended March 31,	
	2015	2014
Isis Core	$ 25,613	$ 26,398
Akcea Therapeutics	5,171	—
Non-cash compensation expense related to equity awards	3,714	2,078
Total antisense drug development	$ 34,498	$ 28,476

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 in which we may 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 drugs in preclinical and early stage clinical research, the fluctuations in expenses from drug to drug, 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 costs. As part of our collaboration with Genzyme, we have transitioned development responsibility for KYNAMRO to Genzyme. We and Genzyme share development costs equally until KYNAMRO is profitable.

Manufacturing and Operations

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

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

	Three Months Ended March 31,	
	2015	2014
Manufacturing and operations	$ 5,633	$ 5,766
Non-cash compensation expense related to equity awards	1,171	699
Total manufacturing and operations	$ 6,804	$ 6,465

Manufacturing and operations expenses were $5.6 million for the three months ended March 31, 2015, and were relatively flat compared to $5.8 million for the same period in 2014. All amounts exclude non-cash compensation expense related to equity awards.

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

	Three Months Ended March 31,	
	2015	2014
Isis Core	$ 5,260	$ 5,766
Akcea Therapeutics	373	—
Non-cash compensation expense related to equity awards	1,171	699
Total antisense drug development	$ 6,804	$ 6,465

R&D Support

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

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

	Three Months Ended March 31,	
	2015	2014
Personnel costs	$ 2,676	$ 2,562
Occupancy	1,833	1,735
Patent expenses	597	374
Depreciation and amortization	543	571
Insurance	312	294
Other	922	778
Total R&D support costs, excluding non-cash compensation expense related to equity awards	6,883	6,314
Non-cash compensation expense related to equity awards	2,683	1,411
Total R&D Support costs	$ 9,566	$ 7,725

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

	Three Months Ended March 31,	
	2015	2014
Isis Core	$ 6,686	$ 6,314
Akcea Therapeutics	197	—
Non-cash compensation expense related to equity awards	2,683	1,411
Total R&D Support costs	$ 9,566	$ 7,725

R&D support costs for the three months ended March 31, 2015 were $6.9 million, compared to $6.3 million for the same period in 2014. All amounts exclude non-cash compensation expense related to equity awards.

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, and finance. Additionally, we include in general and administrative expenses such costs as rent, repair and maintenance of buildings and equipment, depreciation and utilities costs that we need to support the corporate functions listed above.

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

	Three Months Ended March 31,	
	2015	2014
General and administrative expenses	$ 4,647	$ 3,184
Non-cash compensation expense related to equity awards	2,819	1,196
Total general and administrative expenses	$ 7,466	$ 4,380

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

	Three Months Ended March 31,	
	2015	2014
Isis Core	$ 3,848	$ 3,184
Akcea Therapeutics	799	—
Non-cash compensation expense related to equity awards	2,819	1,196
Total general and administrative expenses	$ 7,466	$ 4,380

General and administrative expenses were $4.6 million for the three months ended March 31, 2015, and increased compared to $3.2 million for the same period in 2014 primarily due to increased personnel costs and the addition of Akcea. All amounts exclude non-cash compensation expense related to equity awards.

Akcea Therapeutics, Inc.

The following table sets forth information on operating expenses (in thousands) for our Akcea Therapeutics segment for the three months ended March 31, 2015. Akcea had no operations in 2014.:

Development expenses	$ 5,741
General and administrative expenses	799
Total operating expenses, excluding non-cash compensation expense related to equity awards	6,540
Non-cash compensation expense related to equity awards	558
Total Akcea Therapeutics operating expenses	$ 7,098

Expenses for Akcea Therapeutics were $6.5 million for the three months ended March 31, 2015, and were driven by development costs mainly related to Akcea's Phase 3 program for ISIS-APOCIII$_{Rx}$ and other projects including ISIS-APO(a)$_{Rx}$ and ISIS-ANGPTL3$_{Rx}$. Additionally, starting in 2015, Akcea incurred general and administrative costs necessary to operate and we allocated to Akcea a portion of Isis' general and administrative and R&D support costs for work we performed on behalf of Akcea. All amounts exclude non-cash compensation expense related to equity awards.

Investment Income

Investment income for the three months ended March 31, 2015 was $0.8 million, compared to $0.7 million for the same period in 2014. The slight increase in investment income was primarily due to a higher average cash balance and market conditions during the first quarter of 2015.

Interest Expense

Interest expense includes non-cash amortization of the debt discount and debt issuance costs plus interest expense payable in cash for our 1 percent and 2¾ percent convertible notes, non-cash interest expense related to the long-term financing liability for our primary facility and other miscellaneous debt.

The following table sets forth information on interest expense (in thousands):

	Three Months Ended March 31,	
	2015	2014
2¾ percent convertible notes:		
Non-cash amortization of the debt discount and debt issuance costs	$ 612	$ 1,806
Interest expense payable in cash	421	1,384
1 percent convertible notes:		
Non-cash amortization of the debt discount and debt issuance costs	5,016	—
Interest expense payable in cash	1,250	—
Non-cash interest expense for long-term financing liability	1,662	1,652
Other	60	101
Total interest expense	$ 9,021	$ 4,943

Interest expense for the three months ended March 31, 2015 was $9.0 million compared to $4.9 million in 2014. The increase in interest expense was primarily due to the increase in non-cash amortization of the debt discount and debt issuance costs for our 1 percent notes we issued in November 2014. Additionally, we had more debt outstanding and as a result our interest expense payable in cash increased. In November 2014, we completed a $500 million convertible debt offering. The notes mature in 2021 and bear interest at 1 percent. We used a substantial portion of the net proceeds from the issuance of the 1 percent notes to repurchase $140 million in principal of our 2¾ percent notes. The new principal balance of the 2¾ percent notes is $61.2 million. We record non-cash amortization of the debt discount on our convertible notes because we account for our convertible notes by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate. As a result, we assigned a value to the debt component of our convertible notes equal to the estimated fair value of similar debt instruments without the conversion feature. This means we recorded our convertible notes at a discount that we are amortizing over the life of the notes as non-cash interest expense.

Gain on Investments, net

We recorded a gain on investments of $0.4 million for the three months ended March 31, 2014, primarily due to the sale of a portion of our stock in iCo Therapeutics Inc. We did not sell any securities during the three months ended March 31, 2015**.**

Income Tax Benefit

We recorded a tax benefit of $0.8 million for the three months ended March 31, 2015, compared to $2.3 million for the same period in 2014. Accounting rules require us to allocate our provision for income taxes between continuing operations and other categories of earnings, such as other comprehensive income. In periods in which we have a year-to-date pre-tax loss from continuing operations and pre-tax income in other categories of earnings, such as other comprehensive income, we must allocate the tax provision to the other categories of earnings. We then record a related tax benefit in continuing operations. The tax benefit we recorded in the first quarter of 2015 and 2014 was primarily related to the unrealized gains associated with our investments in Regulus.

Net Loss and Net Loss per Share

Net loss for the three months ended March 31, 2015 was $16.7 million, compared to $31.3 million for the same period in 2014. Basic and diluted net loss per share for the three months ended March 31, 2015 was $0.14 per share, compared to $0.27 per share for the same period in 2014. Our net loss decreased in the first quarter of 2015 compared to the first quarter of 2014 primarily due an increase in revenue from milestone payments.

Liquidity and Capital Resources

We have financed our operations with revenue primarily from research and development collaborative agreements. Additionally, we have earned revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through March 31, 2015, we have earned approximately $1.6 billion in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through March 31, 2015, we have raised net proceeds of approximately $1.1 billion from the sale of our equity securities and we have borrowed approximately $1.3 billion under long-term debt arrangements to finance a portion of our operations.

At March 31, 2015, we had cash, cash equivalents and short-term investments of $695.1 million and stockholders' equity of $275.9 million. In comparison, we had cash, cash equivalents and short-term investments of $728.8 million and stockholders' equity of $257.8 million at December 31, 2014. At March 31, 2015, we had consolidated working capital of $735.1 million, compared to $721.3 million at December 31, 2014. The increase in our working capital primarily relates to the increase in value of our investment in Regulus, offset slightly by cash used to fund our operations. Our cash balance at March 31, 2015 did not include approximately $134 million, which is comprised of $24 million in payments we already received from partners in the second quarter plus $110 million in payments we expect to receive primarily from Bayer upon Hart-Scott-Rodino clearance.

As of March 31, 2015, our debt and other obligations totaled $642.7 million compared to $643.5 million at December 31, 2014.

The following table summarizes our contractual obligations as of March 31, 2015. 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**
1 percent Convertible Senior Notes (principal and interest payable)	$ 535.0	$ 5.0	$ 10.0	$ 10.0	$ 510.0
2¾ percent Convertible Senior Notes (principal and interest payable)	$ 69.5	$ 1.5	$ 3.4	$ 64.6	$ —
Facility Rent Payments	$ 130.2	$ 6.3	$ 13.2	$ 14.0	$ 96.7
Equipment Financing Arrangements (principal and interest payable)	$ 2.3	$ 2.0	$ 0.3	$ —	$ —
Other Obligations (principal and interest payable)	$ 1.3	$ 0.1	$ 0.1	$ 0.1	$ 1.0
Capital Lease	$ 0.1	$ 0.1	$ —	$ —	$ —
Operating Leases	$ 24.7	$ 1.6	$ 3.0	$ 3.0	$ 17.1
Total	$ 763.1	$ 16.6	$ 30.0	$ 91.7	$ 624.8

Our contractual obligations consist primarily of our publicly traded convertible debt. In addition, we also have facility leases, equipment financing arrangements and other obligations.

Convertible Debt Summary

In November 2014, we completed a $500 million offering of convertible senior notes, which mature in 2021 and bear interest at 1 percent. We used a substantial portion of the net proceeds from the issuance of these notes to repurchase $140 million in principal of our 2¾ percent convertible senior notes. As a result, the new principal balance of the 2¾ percent notes is $61.2 million.

At March 31, 2015 our outstanding convertible debt was as follows (amounts in millions unless otherwise noted):

	1 Percent Convertible Senior Notes	2¾ Percent Convertible Senior Notes
Outstanding principal balance	$ 500.0	$ 61.2
Issue date	November 2014	August 2012
Maturity date	November 2021	October 2019
Interest rate	1 percent	2¾ percent
Conversion price per share	$ 66.81	$ 16.63
Total shares of common stock subject to conversion	7.5	3.7

Interest is payable semi-annually for both the 1 percent and 2¾ percent notes. The convertible notes are convertible under certain conditions, at the option of the note holders. We will settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both.

1 Percent Convertible Senior Notes

We may not redeem the 1 percent notes prior to maturity, and no sinking fund is provided for them. Holders of the 1 percent notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indenture governing the 1 percent notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest.

2¾ Percent Convertible Senior Notes

We may redeem the 2¾ percent notes at our option, in whole or in part, on or after October 5, 2016 if the last reported sale price of our common stock for at least 20 trading days (whether or not consecutive) during the period of 30 consecutive trading days ending on the trading day immediately preceding the date we provide the redemption notice exceeds 130 percent of the applicable conversion price for the 2¾ percent notes on each such day. The redemption price for the 2¾ percent notes will equal 100 percent of the principal amount being redeemed, plus accrued and unpaid interest, plus $90 per each $1,000 principal amount being redeemed. Holders of the 2¾ percent notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indenture governing the 2¾ percent notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest.

Equipment Financing Arrangement

In October 2008, we entered into an equipment financing loan agreement, and in September 2009 and June 2012, we amended the loan agreement to increase the aggregate maximum amount of principal we could draw under the agreement. Each draw down under the loan agreement has a term of three years, with principal and interest payable monthly. Interest on amounts we borrow under the loan agreement is based upon the three year interest rate swap at the time we make each draw down plus 3.5 or four percent, depending on the date of the draw. We are using the equipment purchased under the loan agreement as collateral. As of March 31, 2015, our outstanding borrowings under this loan agreement were at a weighted average interest rate of 4.18 percent. The carrying balance under this loan agreement at March 31, 2015 and December 31, 2014 was $2.2 million and $3.2 million, respectively. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

Research and Development Facility Lease Obligation

In March 2010, we entered into a lease agreement with an affiliate of BioMed Realty, L.P. Under the lease, BioMed constructed a new facility in Carlsbad, California. The lease has an initial term of 20 years with an option to extend the lease for up to four five-year periods. Our rent under this lease is based on a percentage of the total construction costs spent by BioMed to acquire the land and build the new facility. To gain early access to the facility, we agreed to modify our lease with BioMed to accept additional responsibility. As a result, accounting rules required us to record the cost of the facility as a fixed asset with a corresponding liability. We are depreciating the building over its economic life and we apply our rent payments, which began on January 1, 2012, against the liability over the term of the lease.

In addition to contractual obligations, we had outstanding purchase orders as of March 31, 2015 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 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, cash equivalents and short-term investments 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, 2014.

Risks Associated with our Isis Core and Akcea Therapeutics Businesses

If the market does not accept KYNAMRO and our other drugs, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, we are not likely to generate revenues or become consistently profitable.

Even though KYNAMRO is approved for HoFH in the United States, and if any of our other drugs are approved for marketing, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, our success will depend upon the medical community, patients and third party payors accepting our drugs as medically useful, cost-effective and safe. Even when the FDA or foreign regulatory authorities approve our or our partners' drugs for commercialization, doctors may not prescribe our drugs to treat patients. We and our partners may not successfully commercialize additional drugs.

In particular, even though KYNAMRO is approved for HoFH in the United States, it may not be commercially successful.

Additionally, in many of the markets where we may sell our drugs in the future, if we cannot agree with the government regarding the price we can charge for our drugs, then we may not be able to sell our drugs in that market.

The degree of market acceptance for KYNAMRO, and any of our other drugs, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, depends upon a number of factors, including the:

- receipt and scope of regulatory approvals;
- establishment and demonstration in the medical and patient community of the efficacy and safety of our drugs and their potential advantages over competing products
- cost and effectiveness of our drugs compared to other available therapies
- 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/or use any drugs that we may develop. In addition, cost control initiatives by governments or third party payors could decrease the price received for KYNAMRO or our other drugs or increase patient coinsurance to a level that makes KYNAMRO or our other drugs, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, unaffordable.

If we fail to compete effectively, our drugs, including KYNAMRO, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, will not contribute significant revenues.

Our competitors engage in drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. Other companies engage 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 drugs, including KYNAMRO, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, 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 treat the same diseases our own collaborative programs target. 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, including KYNAMRO, which is approved, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$.

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 studies of new pharmaceutical products and in obtaining FDA and other regulatory approvals of such products. Accordingly, our competitors may succeed in obtaining regulatory approval for products earlier than we do. Marketing and sales capability is another factor relevant to the competitive position of our drugs, and we will rely on our partners or Akcea to provide this capability.

Regarding KYNAMRO, some competitors are pursuing a development or commercialization strategy that competes with our strategy for KYNAMRO. Other companies are currently developing products that could compete with KYNAMRO. Products such as microsomal triglyceride transfer protein inhibitors, or MTP inhibitors, and other lipid lowering drugs other companies are developing or commercializing could potentially compete with KYNAMRO. For example, Aegerion Pharmaceuticals, Inc. received approval from the FDA and the European Medicines Agency to market its MTP inhibitor, lomitapide, as an adjunct to a low-fat diet and other lipid-lowering treatments in patients with HoFH. Our revenues and financial position could suffer if KYNAMRO cannot compete effectively in the marketplace.

There are several pharmaceutical and biotechnology companies engaged in the development or commercialization of products against targets that are also targets of products in our development pipeline. For example, drugs like tafamadis, diflunisal, and patisiran could compete with ISIS-TTR_{Rx}, drugs like Glybera, pradigastat and CAT-2003 could compete with ISIS-$APOCIII_{Rx}$, and RG7800 and olesoxime and the other products that may emerge from early development programs designed to treat patients with SMA could compete with ISIS-SMN_{Rx}.

KYNAMRO is, and, following approval any of our other drugs, including ISIS-$APOCIII_{Rx}$, ISIS-SMN_{Rx} and ISIS-TTR_{Rx}, could be, subject to regulatory limitations.

Following approval of a drug, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of drug products. We or our partners may not obtain the labeling claims necessary or desirable for successfully commercializing our drug products, including our approved drug, KYNAMRO, and our drugs in development including: ISIS-$APOCIII_{Rx}$, ISIS-SMN_{Rx} and ISIS-TTR_{Rx}.

The FDA and foreign regulatory authorities have the authority to impose significant restrictions on an approved drug product through the product label and on advertising, promotional and distribution activities. For example:

- KYNAMRO is approved in the United States as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, and non-high density lipoprotein-cholesterol in patients with HoFH;
- the KYNAMRO label contains a Boxed Warning citing a risk of hepatic toxicity; and
- KYNAMRO is available only through a Risk Evaluation and Mitigation Strategy called the KYNAMRO REMS.

In addition, when approved, the FDA or a foreign regulatory authority may condition approval on the performance of post-approval clinical studies or patient monitoring, which could be time consuming and expensive. If the results of such post-marketing studies are not satisfactory, the FDA or a foreign regulatory authority may withdraw marketing authorization or may condition continued marketing on commitments from us or our partners that may be expensive and/or time consuming to fulfill.

If we or others identify side effects after any of our drug products are on the market, or if manufacturing problems occur subsequent to regulatory approval, we or our partners may lose regulatory approval, or we or our partners may need to conduct additional clinical studies and/or change the labeling of our drug products including KYNAMRO, ISIS-$APOCIII_{Rx}$, ISIS-SMN_{Rx} and ISIS-TTR_{Rx}.

We depend on our collaboration with Genzyme for the development and commercialization of KYNAMRO.

We have entered into a collaborative arrangement with Genzyme to develop and commercialize KYNAMRO.

We entered into this collaboration primarily to:

- fund some of our development activities for KYNAMRO;
- seek and obtain regulatory approvals for KYNAMRO; and
- successfully commercialize KYNAMRO.

In general, we cannot control the amount and timing of resources that Genzyme devotes to our collaboration. If Genzyme fails to further develop and commercialize KYNAMRO, or if Genzyme's efforts are not effective, our business may be negatively affected. We are relying on Genzyme to obtain additional marketing approvals for and successfully commercialize KYNAMRO. Our collaboration with Genzyme may not continue or result in the successful commercialization of KYNAMRO. Genzyme can terminate our collaboration at any time. If Genzyme stopped developing or commercializing KYNAMRO, we would have to seek additional sources for funding and may have to delay or reduce our development and commercialization programs for KYNAMRO. If Genzyme does not successfully commercialize KYNAMRO, we may receive limited or no revenues for KYNAMRO. In addition, Sanofi's acquisition of Genzyme could disrupt Genzyme or distract it from performing its obligations under our collaboration.

If Genzyme cannot manufacture finished drug product for KYNAMRO or the post-launch supply of the active drug substance for KYNAMRO, KYNAMRO may not achieve or maintain commercial success.

We rely on Genzyme to manufacture the finished drug product for KYNAMRO and the long term supply of KYNAMRO drug substance. Genzyme may not be able to reliably manufacture KYNAMRO drug substance and drug product to support the long term commercialization of KYNAMRO. If Genzyme cannot reliably manufacture KYNAMRO drug substance and drug product, KYNAMRO may not achieve or maintain commercial success, which will harm our ability to generate revenue.

If we or our partners fail to obtain regulatory approval for our drugs, including additional approvals for KYNAMRO or initial approvals for ISIS-$APOCIII_{Rx}$, ISIS-SMN_{Rx} and ISIS-TTR_{Rx}, we or our partners cannot sell them in the applicable markets.

We cannot guarantee that any of our drugs, including ISIS-$APOCIII_{Rx}$, ISIS-SMN_{Rx} and ISIS-TTR_{Rx}, will be safe and effective, or will be approved for commercialization. In addition, we cannot guarantee that KYNAMRO will be approved in additional markets outside the United States or for additional indications. We and our partners must conduct time-consuming, extensive and costly clinical studies to show the safety and efficacy of each of our drugs, including KYNAMRO, ISIS-$APOCIII_{Rx}$, ISIS-SMN_{Rx} and ISIS-TTR_{Rx}, before they can be approved for sale. We must conduct these studies in compliance with FDA regulations and with comparable regulations in other countries.

We and our partners may not obtain necessary regulatory approvals on a timely basis, if at all, for any of our drugs. It is possible that other regulatory agencies will not approve KYNAMRO or any of our other drugs including, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$ for marketing. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our drugs, including KYNAMRO, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, the agency will not approve the specific drug or will require additional studies, which can be time consuming and expensive and which will delay or harm commercialization of the drug. For example, in March 2013 the CHMP of the European Medicines Agency maintained a negative opinion for Genzyme's marketing authorization application for KYNAMRO as a treatment for patients with HoFH.

Failure to receive marketing approval for our drugs, including KYNAMRO outside the United States or initial approvals for ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, or delays in these approvals could prevent or delay commercial introduction of the drug, and, as a result, could negatively impact our ability to generate revenue from product sales.

If the results of clinical testing indicate that any of our drugs 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 drugs are a relatively new approach to therapeutics. If we cannot demonstrate that our drugs are safe and effective for human use, we may need to abandon one or more of our drug development programs. There are ongoing clinical studies for KYNAMRO and sales to patients, adverse events from which could negatively impact our pending or planned marketing approval applications and commercialization of KYNAMRO.

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. Similar results could occur in any additional clinical studies for KYNAMRO and in clinical studies for our other drugs, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$. If any of our drugs in clinical studies, including KYNAMRO, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for the drug and our stock price could decline.

Even if our drugs are successful in preclinical and human clinical studies, the drugs may not be successful in late-stage clinical studies.

Successful results in preclinical or initial human clinical studies, including the Phase 3 results for KYNAMRO and the Phase 2 results for some of our other drugs in development, may not predict the results of subsequent clinical studies, including subsequent studies of KYNAMRO and the Phase 3 studies for ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$. There are a number of factors that could cause a clinical study to fail or be delayed, including:

- the clinical study 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 study due to adverse side effects of a drug on subjects in the trial;
- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical studies;
- enrollment in our clinical studies may be slower than we anticipate;
- the cost of our clinical studies may be greater than we anticipate; and
- the supply or quality of our drugs or other materials necessary to conduct our clinical studies may be insufficient, inadequate or delayed.

Any failure or delay in the clinical studies, including any further studies under the development program for KYNAMRO and the Phase 3 studies for ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, could reduce the commercial potential or viability of our drugs.

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

To successfully commercialize any of our drugs, we or our partner would need 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 drug costs. We may not be able to manufacture our drugs 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 and similar regulations in foreign countries, which the applicable regulatory authorities enforce through facilities inspection programs. We and our contract manufacturers may not comply or maintain compliance with Good Manufacturing Practices, or similar foreign regulations. Non-compliance could significantly delay or prevent receipt of marketing approval for our drugs, including additional approvals for KYNAMRO, and initial approvals for ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, or result in enforcement action after approval that could limit the commercial success of our drugs, including KYNAMRO, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$.

We depend on third parties to conduct our clinical studies 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 to conduct our clinical studies for our drugs and expect to continue to do so in the future. For example, we use clinical research organizations, such as Icon Clinical Research Limited, INC Research Toronto, Inc. and Medpace for the clinical studies for our drugs, including KYNAMRO, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$. We rely heavily on these parties for successful execution of our clinical studies, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that these third parties conduct each of our clinical studies in accordance with the general investigational plan and approved protocols for the study. Third parties may not complete activities on schedule, or may not conduct our clinical studies 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 any expanded product label for KYNAMRO and initial approvals for ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$.

Risks Associated with our Businesses as a Whole

We have incurred losses, and our business will suffer if we fail to consistently achieve profitability in the future.*

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of March 31, 2015, we had an accumulated deficit of approximately $1.0 billion and stockholders' equity of approximately $275.9 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 may 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 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 drug 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 unpartnered drugs. However, we may not be able to negotiate favorable collaborative arrangements for these drug programs. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drugs could suffer.

Our corporate partners are developing and/or funding many of the drugs in our development pipeline. If any of these pharmaceutical companies stops developing and/or funding these drugs, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these drugs on our own.

Our collaborators can terminate their relationships with us under certain circumstances, many of which are outside of our control. In the past, based on the disappointing results of Phase 3 clinical studies, we had a partner discontinue its investment in one of our drugs.

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 drug development programs.

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

- conduct clinical studies;
- seek and obtain regulatory approvals; and
- manufacture, market and sell our drugs.

Once we have secured a collaborative arrangement to further develop and commercialize one of our drug development programs, such as our collaborations with AstraZeneca, Biogen, Genzyme, GSK, and Roche these collaborations may not continue or result in commercialized drugs, or may not progress as quickly as we first anticipated.

For example, a collaborator such as AstraZeneca, Biogen, Genzyme, GSK, or Roche, could determine that it is in its financial interest to:

- pursue alternative technologies or develop alternative products that may be competitive with the drug 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.

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, including KYNAMRO, ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$.

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 study, 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 our investors' expectations, including milestones for additional approvals or sales expectations of KYNAMRO or milestones related to the Phase 3 programs for ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, the price of our securities could decrease.

For example, in March 2013 the CHMP of the European Medicines Agency maintained a negative opinion for Genzyme's marketing authorization application for KYNAMRO as a treatment for patients with HoFH.

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

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

From time to time we have to defend our intellectual property rights. In the event of an intellectual property dispute, we sometimes need to litigate to defend our rights or assert them against others. Disputes can 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 November 2013 we filed a patent infringement lawsuit against Gilead Sciences Inc. in the United States District Court of the Northern District of California. Intellectual property lawsuits may be costly and may not be resolved in our favor.

If a third party claims that our drugs 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 patent 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.

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

Many of our drugs are undergoing clinical studies or are in the early stages of research and development. All of our drug programs will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and/or commitment of significant additional resources prior to their successful commercialization. As of March 31, 2015, we had cash, cash equivalents and short-term investments equal to $695.1 million. If we do not meet our goals to successfully commercialize KYNAMRO and our other drugs, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$, 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:

- additional marketing approvals and successful commercial launch of KYNAMRO;
- 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 studies;
- 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, including ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$.

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 the 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 terminated 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 or drugs.

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 studies may make it more challenging to recruit and retain qualified scientific personnel.

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding March 31, 2015, the market price of our common stock ranged from $22.25 to $77.80 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical study results, technological innovations or new products being developed by us or our competitors, governmental regulation, regulatory approval, changes in payors' reimbursement policies, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

We are exposed to potential product liability claims, and insurance against these claims may not be available to us at a reasonable rate in the future or at all.

Our business exposes us to potential product liability risks that are inherent in the testing, manufacturing, marketing and sale of therapeutic products, including potential product liability claims related to KYNAMRO. We have clinical study insurance coverage and commercial product liability insurance coverage. However, this insurance coverage may not be adequate to cover claims against us, or be available to us at an acceptable cost, if at all. Regardless of their merit or eventual outcome, products liability claims may result in decreased demand for our drug products, injury to our reputation, withdrawal of clinical study volunteers and loss of revenues. Thus, whether or not we are insured, a product liability claim or product recall may result in losses that could be material.

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. We store these materials and various wastes resulting from their use 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 types 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. If 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 or otherwise affects our business, it could delay our progress developing and commercializing our drugs.

We manufacture our research and clinical supplies in a 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 if our facilities 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. In addition, our development and commercialization activities could be harmed or delayed by a shutdown of the U.S. government including the FDA.

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 2/3 percent of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15 percent 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 have in the past, and may in the future, implement a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. In addition, our board of directors has the authority to fix the rights and preferences of, and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

The provisions of our convertible senior 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 KYNAMRO provides that if we are acquired, Genzyme may elect to purchase all of our rights to receive payments under the KYNAMRO collaboration agreement for a purchase price to be mutually agreed 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.

These provisions, as well as Delaware law, including Section 203 of the Delaware General Corporation 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.

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 may issue approximately 11.2 million shares of our common stock upon conversion of our convertible senior 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 continue to incur additional expenses and divert our management's time to comply with these regulations. 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, or PCAOB, or The Nasdaq Global Market. Any such action could adversely affect our financial results and the market price of our common stock.

The SEC and other regulators have continued to adopt new rules and regulations and make additional changes to existing regulations that require our compliance. On July 21, 2010, the Dodd-Frank Wall Street Reform and Protection Act, or the Dodd-Frank Act, was enacted. There are significant corporate governance and executive compensation-related provisions in the Dodd-Frank Act that require the SEC to adopt, or where the SEC has adopted, additional rules and regulations in these areas such as "say on pay" and proxy access. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business.

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

The global credit markets, the financial services industry, the U.S. capital markets, and the U.S. economy as a whole have in the past experienced periods 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. It is possible that a crisis in the global credit markets, the U.S. capital markets, the financial services industry or 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.

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 primarily invest our excess cash in highly liquid short-term investments of the U.S. Treasury and reputable financial institutions, corporations, and U.S. government agencies with strong credit ratings. We typically hold our investments 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

We maintain disclosure controls and procedures that are designed to ensure that information we are required to disclose 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. We designed and evaluate our disclosure controls and procedures recognizing that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance and not absolute assurance of achieving the desired control objectives.

As of our most recently completed fiscal year and as of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation 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, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on our evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of March 31, 2015. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 2015.

We also performed an evaluation 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. We conducted this evaluation under the supervision of and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. 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.

PART II — OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

Santaris Litigation

In September 2011, we filed a patent infringement lawsuit against Santaris Pharma A/S and Santaris Pharma A/S Corp. in the United States District Court of the Southern District of California. Our infringement lawsuit alleged that Santaris' activities providing antisense drugs and antisense drug discovery services to several pharmaceutical companies infringed U.S. Patent No. 6,326,199, entitled "Gapped 2' Modified Oligonucleotides" and U.S. Patent No. 6,066,500, entitled "Antisense Modulation of Beta Catenin Expression." In April 2013, we amended our complaint related to the lawsuit to include additional claims alleging that Santaris' activities providing antisense drugs and antisense drug discovery services to a pharmaceutical company infringed U.S. Patent No. 6,440,739 entitled "Antisense Modulation of Glioma-Associated Oncogene-2 Expression"; and that Santaris induced its actual and prospective pharmaceutical partners to infringe U.S. Patent No. 6,326,199. In March 2015, we and Santaris (now Roche), settled the lawsuit.

Gilead Litigation

In August 2013, Gilead Sciences Inc. filed a suit in the United States District Court of the Northern District of California related to United States Patent Nos. 7,105,499 and 8,481,712 that are jointly owned by Merck Sharp & Dohme Corp. and Isis Pharmaceuticals, Inc. In the suit Gilead is asking the court to determine that Gilead's activities do not infringe any valid claim of the named patents and that the patents are not valid. We and Merck Sharp & Dohme Corp. filed our answer denying Gilead's noninfringement and invalidity contentions, contending that Gilead's commercial sale and offer for sale of sofosbuvir prior to the expiration of the '499 and '712 patents will infringe those patents, and requesting monetary damages to compensate for such infringement. Under our agreement with Merck, Merck is responsible for the costs of this suit.

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

Not applicable.

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

ITEM 5. OTHER INFORMATION

Not Applicable.

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Second Amended and Restated Strategic Collaboration and License Agreement between the Registrant and Alnylam Pharmaceuticals, Inc. dated January 8, 2015. Portions of this exhibit have been omitted and separately filed with the SEC.
10.2	Amendment #1 to HTT Research, Development, Option and License Agreement between the Registrant, F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc. dated January 9, 2015. Portions of this exhibit have been omitted and separately filed with the SEC.
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.
101	The following financial statements from the Isis Pharmaceuticals, Inc. Quarterly Report on Form 10-Q for the quarter ended March 31, 2015, formatted in Extensive Business Reporting Language (XBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of comprehensive loss, (iv) condensed consolidated statements of cash flows and (v) notes to condensed consolidated financial statements (detail tagged).

SIGNATURES

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

Signatures	Title	Date
/s/ Stanley T. Crooke Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	May 5, 2015
/s/ Elizabeth L. Hougen Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	May 5, 2015

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

EXHIBIT 10.1

Execution Copy

SECOND AMENDED AND RESTATED
STRATEGIC COLLABORATION AND
LICENSE AGREEMENT

This Second Amended and Restated Strategic Collaboration and License Agreement (the "Agreement") is executed this January 8, 2015 (the "Second Restatement Date"), between Isis Pharmaceuticals, Inc., a Delaware corporation having an address at 2855 Gazelle Court, Carlsbad, CA 92010 ("Isis") and Alnylam Pharmaceuticals, Inc., a Delaware corporation having an address at 300 Third Street, Cambridge, MA 02142 ("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 continue to pursue RNAi therapeutics and the use of Double Stranded RNA. Alnylam has no present plans to pursue Single Stranded Products;

Isis and Alnylam are parties to the Amended and Restated Strategic Collaboration and License Agreement dated April 28, 2009 (as amended to date, the "First Restated Agreement"), which amended and restated the Strategic Collaboration and License Agreement dated March 11, 2004 (as amended through April 28, 2009 (the "First Restatement Date"), the "Original Agreement") to, among other things, provide each Party with certain 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; and

Isis and Alnylam now wish to amend and restate the First Restated Agreement to (i) reflect the termination of the Research Program and certain rights of Alnylam with respect to Single Stranded RNAi Compounds and Single Stranded RNAi Products, (ii) expand the First Restated Agreement by providing each other (x) non-exclusive licenses to certain additional Patents of the respective Parties and (y) exclusive licenses to research, develop and commercialize oligomeric compounds directed to certain RNA Targets in the Field.

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 certain Double Stranded RNA drugs.
§ Provide Isis with a means for participating in the success of RNAi therapeutics.
§ Enhance the potential of Isis to develop Single Stranded Compound drugs.
§ Provide Alnylam with exclusive rights to research, develop and commercialize oligomeric compounds for certain RNA Targets in the Field.
§ Provide Isis with exclusive rights to research, develop and commercialize oligomeric compounds for certain RNA Targets in the Field.

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 Second Restatement Date, this Agreement restates and supersedes the First Restated Agreement as amended through the Second Restatement Date. The terms and conditions of the First Restated Agreement shall apply for the period from the First Restatement Date until the Second 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

MANUFACTURING SERVICES RELATIONSHIP

3.1 [Intentionally Deleted]

ARTICLE 4

COLLABORATIVE RESEARCH EFFORTS; PROTECTED TARGETS

4.1 [Intentionally Deleted]

4.2 [Intentionally Deleted]

4.3 Isis Enabled Targets for Single Stranded RNAi.

(a) Enabled Targets. Isis will have a pool (the "Enabled Target Pool") containing [***] slots for which Isis can designate certain RNA Targets against which Isis intends to research, develop and commercialize a Single-Stranded RNAi Product (each such slot, an "Enabled Target Slot" and any RNA Target occupying such a slot, an "Enabled Target"); provided, however, that, each time Isis designates as a Development Candidate a Single Stranded RNAi Product Designed for one of Isis' Enabled Targets, then (i) such Enabled Target will be considered to have graduated from Isis' Enabled Target Pool (a "Graduated Enabled Target"), (ii) Isis will be permitted to designate a new Enabled Target to fill the open Enabled Target Slot in Isis' Enabled Target Pool, and (iii) so long as Isis 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 Isis hereunder. For purposes of clarity, except as set forth in 6.1(h)(i) and 6.1(l), as applicable, Isis may not practice the Alnylam Patent Rights to research, develop or commercialize a Single Stranded RNAi Product other than a Single Stranded RNAi Product Designed for one of Isis' Enabled Targets.

(b) [Intentionally Deleted]

(c) Designating Enabled Targets. From time to time after the Second Restatement Date Isis may designate an RNA Target as an Enabled Target upon written notice to Alnylam; provided, that there is an open Enabled Target Slot in the Enabled Target Pool. At no time during the period commencing with the Second Restatement Date and ending upon the expiration of the Alnylam Exclusive Target Royalty Term may Isis designate an Alnylam Exclusive Target as an Enabled Target.

(d) Removing Enabled Targets. From time to time after the Second Restatement Date Isis may remove an RNA Target from the Enabled Target Pool upon written notice to Alnylam (which removal will create an open Enabled Target Slot). In addition, on an Enabled Target-by-Enabled Target basis, if Isis 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 Isis added the applicable Enabled Target to the Enabled Target Pool, then such RNA Target will be automatically removed from the Enabled Target Pool. Once Isis removes an RNA Target from its Enabled Target Pool (whether voluntarily or by operation of this Section 4.3(d)), such RNA Target shall no longer be deemed an Enabled Target hereunder and Isis will be prevented from later adding such RNA Target to its Enabled Target Pool until [***] months have passed from the date such RNA Target was removed.

(e) [Intentionally Deleted]

(f) Confidentiality. The fact that Isis has designated or removed a particular RNA Target within the Enabled Target Pool is Confidential Information of Isis, subject to the provisions of Article 12. Alnylam shall not disclose such Confidential Information of Isis to any Third Party, including its Third Party collaborators, or use such Confidential Information to guide its own (or its Third Party collaborators') decisions to pursue particular RNA Targets, but Alnylam can use such Confidential Information to decline a Third Party's request for a license to such RNA Target.

ARTICLE 5

LICENSES GRANTED BY ISIS TO ALNYLAM

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) Subject to the terms of Section 11.8, 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) [Intentionally Deleted].

(c) Subject to the terms of Section 11.8, 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) [Intentionally Deleted].

(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) Subject to the terms of Section 11.8, under Isis Extended Field Patents, a license to research, develop, make, have made, use, import, offer to sell and sell Double Stranded RNA and Double Stranded RNA Products, other than Alnylam Exclusive Target Products in the Field.

(h) Subject to the terms of Section 11.8, under Isis Exclusive Target Patents, a license to research, develop, make, have made, use, import, offer to sell and sell Alnylam Exclusive Target Products in the Field.

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 license from Isis to Alnylam granted in Section 5.1(a) is 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), (e), (f), and (g) are worldwide and nonexclusive; and the license from Isis to Alnylam granted in Section 5.1(h) is 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 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. Alnylam is not permitted to grant sublicenses under the licenses granted in Section 5.1(f). Alnylam is not permitted to grant sublicenses under the license granted in Section 5.1(g) except that Alnylam is permitted to grant sublicenses in connection with a Bona Fide Third Party Collaboration. Alnylam is permitted to grant sublicenses under the license granted in Sections 5.1(h) except only that any such sublicense granted with respect to a Single Stranded Compound, Single Stranded Product, Single Stranded RNAi Compound or Single Stranded RNAi Product is subject to Isis' prior written consent, which consent may be withheld in Isis' sole discretion. Notwithstanding anything to the contrary in the foregoing, Alnylam is permitted to grant sublicenses under its licenses in Section 5.1 to its Affiliates.

(b) [Intentionally deleted]

(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 First 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) subject to the exclusive license grant to Alnylam in Section 5.1(h), Isis may continue to grant licenses to Third Parties under the Isis Patent Rights for the purpose of manufacturing and selling oligonucleotides; provided that, to the extent such licenses cover Double Stranded RNA Isis will restrict such licenses to [***] and will exclude Agricultural Field Products from such licenses granted after August 27, 2012.

5.3 Limitations on Licenses.

(a) The licenses granted under Section 5.1(a) through (g) above do not grant any rights to Alnylam to practice the Isis Excluded Technology. The licenses granted under Section 5.1(h) above do not grant any rights to Alnylam to practice the Isis Exclusive Target Excluded Technology. If Alnylam wishes to license any Isis Excluded Technology or Isis Exclusive Target 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, in the Joint Patents, and in the Isis Extended Field Patents (i) exclusively for the Isis Reserved DS-Targets, (ii) exclusively for the Isis Encumbered Targets, and (iii) exclusively for the Isis Exclusive 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.

(c) Licenses to Isis Patent Rights, Isis Extended Field Patents and Isis Exclusive Target Patents 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 Second Restatement Date are set forth in Exhibit 5.3(c) attached hereto.

(d) Licenses to Isis Patent Rights, Isis Extended Field Patents and Isis Exclusive Target Patents that are subject to contractual obligations between Isis and Third Parties in effect as of the Second Restatement Date are licensed (i) subject to the restrictions and other terms described in the Isis Third Party Agreements, and (ii) with respect to Agricultural Field Products, to the extent Isis has the right under such Third Party Agreements to grant such a license for Agricultural Field Products. Prior to the Second Restatement Date, Isis has provided Alnylam with copies of the Isis Third Party Agreements, provided, that Isis may redact copies of out-licenses Isis has granted Third Parties so long as the redacted terms do not limit Alnylam's rights hereunder or create obligations for Alnylam. Alnylam hereby agrees to comply, and to cause its sublicensees to comply, with such restrictions and other terms.

(e) Notwithstanding the exclusive nature of the license granted by Isis to Alnylam under Section 5.1(h), Isis may grant Permitted Licenses.

(f) The license to Isis Extended Field Patents granted in Section 5.1(g) does not include any rights with respect to Double Stranded RNA or Double Stranded RNA Products that are designed to modulate any Isis Retained Targets. Isis will endeavor in good faith and use commercially reasonable and diligent efforts to take all actions reasonably necessary, without any obligation on the part of Isis to compensate any Person, to enable Isis to grant a license to Alnylam pursuant to Section 5.1(g) with respect to Double Stranded RNA and Double Stranded RNA Products that are designed to modulate each Isis Retained Target other than the Isis Retained Special Target(s), within [***] days after the Second Restatement Date, and will continue to do so until such ability to license Alnylam is obtained with respect to each Isis Retained Target other than the Isis Retained Special Target(s). Isis will promptly notify Alnylam when such ability to license Alnylam is obtained, and effective upon delivery of such notice to Alnylam, the applicable RNA Target will automatically no longer be an Isis Retained Target, and the Parties will update Schedule 1-69 accordingly as promptly as feasible.

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) 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 Diligence on Alnylam Exclusive Targets. For each Alnylam Exclusive Target, Alnylam will use Commercially Reasonable Efforts (either on its own, with an Affiliate or in a Bona Fide Third Party Collaboration) to develop and commercialize [***].

ARTICLE 6

LICENSES GRANTED BY ALNYLAM TO ISIS; AND 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) Subject to the terms of Section 11.8, 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) [Intentionally Deleted].

(c) Subject to the terms of Section 11.8, 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) [Intentionally Deleted].

(e) Subject to the terms of Section 11.8, 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) [Intentionally Deleted].

(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) Subject to the terms of Section 11.8, 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) [Intentionally Deleted].

(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.

(k) Subject to the terms of Section 11.8, a nonexclusive license under Alnylam Extended Field Patents to research, develop, make, have made, use, import, offer to sell and sell Single Stranded Products, other than Isis Exclusive Target Products in the Field.

(l) Subject to the terms of Section 11.8, an exclusive license under Alnylam Exclusive Target Patents to research, develop, make, have made, use, import, offer to sell and sell Isis Exclusive Target Products in the Field.

6.2 License Option. For each RNA 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, subject to the terms of Section 11.8, Alnylam Current Motif and Mechanism Patents, Alnylam Current 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) [***] 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 Isis [***] 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), 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(e), 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). With respect to the licenses granted by Alnylam pursuant to Section 6.1(h), 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 Program) 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 [***] if requested by Isis and approved in writing by Alnylam, such approval not to be unreasonably withheld). Isis is not permitted to grant sublicenses under the license granted in Section 6.1(k), except that Isis is permitted to grant sublicenses in connection with a Bona Fide Third Party Collaboration. Isis is permitted to grant sublicenses under the license granted in Section 6.1(l), except only that any such sublicense granted with respect to a Double Stranded RNA or a Double Stranded RNA Product is subject to Alnylam's prior written consent, which consent may be withheld in Alnylam's sole discretion. Notwithstanding anything to the contrary in the foregoing, Isis is permitted to grant sublicenses under its licenses in Sections 6.1 and 6.2 to its Affiliates.

(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 RNA Targets other than the Alnylam Exclusive Targets solely for Antisense Drug Discovery Programs (each such slot, a "DS-Target Slot" and any RNA 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), Isis may not practice the Alnylam Patent Rights to 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 Second Restatement Date sets forth the Reserved DS-Targets as of the Second Restatement Date.

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

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

(ii) Add a new RNA 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 an RNA 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 an RNA Target from the Isis DS-Target Pool, Isis will be prevented from later adding such RNA Target to the Isis DS-Target Pool until [***] months have passed from the date Isis removed such RNA Target.

(d) New Target Request. When Isis wishes to add a new RNA Target to occupy a vacant DS-Target Slot, it will provide Alnylam with written notice (the "Request Notice") of the RNA 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 [***] days 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, (iii) the subject of Alnylam's good faith negotiations to enter into a contractual obligation within the [***] months 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, or (iv) an Alnylam Exclusive 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 RNA Targets in the absence of a reasonable intent to discover and develop products that modulate such RNA 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 RNA Target within the Isis DS-Target Pool is Confidential Information of Isis, or that Alnylam has rejected a particular RNA Target proposed for a DS-Target Slot or disallowed the redesignation of a particular RNA 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 RNA Targets, but Alnylam can use such Confidential Information of Isis to decline a Third Party's request for a license to such RNA Target.

6.5 Limitations on Licenses.

(a) The licenses granted under Sections 6.1(a) through (k) and 6.2 above do not grant any rights to Isis to practice the Alnylam Excluded Technology. The license granted under Section 6.1(l) above does not grant any rights to Isis to practice the Alnylam Exclusive Target Excluded Technology. The licenses granted under Sections 6.1 and 6.2 above do not grant any rights to Isis to practice the Alnylam Extended Field Patents or the Alnylam Exclusive Target Patents with respect to Agricultural Products in the Agricultural Field. If Isis wishes to license any Alnylam Excluded Technology or Alnylam Exclusive Target 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, Alnylam Extended Field Patents or Alnylam Exclusive Target Patents 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. To Alnylam's knowledge, as of the Second Restatement Date, there are no Alnylam Extended Field Patents or Alnylam Exclusive Target Patents subject to such retained rights.

(c) Licenses to Alnylam Patent Rights, Alnylam Extended Field Patents and Alnylam Exclusive Target Patents that are subject to contractual obligations between Alnylam and Third Parties in effect as of the Second Restatement Date are licensed subject to the restrictions and other terms of the Alnylam Third Party Agreements. Prior to the Second Restatement Date, Alnylam has provided Isis with copies of the Alnylam Third Party Agreements, the Stanford Agreement and the CRT Agreement, provided in each case Alnylam may redact copies of out-licenses Alnylam has granted Third Parties so long as the redacted terms do not limit Isis' rights hereunder or create obligations for Isis. 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:

(i) licensed by Alnylam under the Agreement effective as of September 17, 2003 between The Board of Trustees of the Leland Stanford Junior University ("Stanford University") and Alnylam Pharmaceuticals, Inc. (as amended, the "Stanford Agreement"); provided that with respect to any such licensed Patents that are or become issued Patents, Isis shall have the option of expanding its licenses to Alnylam Patent Rights, Alnylam Extended Field Patents and/or Alnylam Exclusive Target Patents (as applicable) hereunder to include such issued Patents by notifying Alnylam of such election and paying 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 become payable by Alnylam to Stanford University pursuant to the Stanford Agreement as a result of such expansion of Isis' licenses and Isis' (and its Affiliates' and sublicensees') exercise of its rights thereunder. Upon exercise of such option, the Stanford Agreement will be an Alnylam Third Party Agreement and Exhibit 6.5(c) updated accordingly, such Patents will be licensed to Isis subject to the restrictions and other terms of the Stanford Agreement and Isis hereby agrees to comply, and to cause its sublicensees to comply, with such restrictions and other terms;

(ii) licensed by Alnylam under the License Agreement effective July 18, 2003 between Cancer Research Technology Limited ("CRT") and Alnylam Pharmaceuticals, Inc. (as amended, the "CRT Agreement"); provided that with respect to any such licensed Patents that are or become issued Patents, Isis shall have the option of expanding its licenses to Alnylam Patent Rights, Alnylam Extended Field Patents and/or Alnylam Exclusive Target Patents (as applicable) hereunder to include such issued Patents by notifying Alnylam of such election and paying 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 become payable by Alnylam to CRT pursuant to the CRT Agreement as a result of such expansion of Isis' licenses and Isis' (and its Affiliates' and sublicensees') exercise of its rights thereunder. Upon exercise of such option, the CRT Agreement will be an Alnylam Third Party Agreement and Exhibit 6.5(c) updated accordingly, such Patents will be licensed to Isis subject to the restrictions and other terms of the CRT Agreement and Isis hereby agrees to comply, and to cause its sublicensees to comply, with such restrictions and other terms;

(iii) that are Additional Rights (as defined in Section 11.8) Controlled by Alnylam's wholly-owned subsidiary Sirna Therapeutics, Inc. as of the Second Restatement Date. If during the License Term Isis wishes to include such Additional Rights under the licenses granted to it by Alnylam pursuant to Article 6, Isis will notify Alnylam of its desire to do so and will assume all financial and other obligations to the licensors and/or sellers of such Additional Rights to Alnylam arising from the grant to Isis of such licenses. The Parties will negotiate in good faith regarding sharing any upfront payments or similar acquisition costs incurred by Alnylam to acquire such Additional Rights.

(e) Notwithstanding the licenses and other rights granted to Isis under Sections 6.1 and 6.2, Alnylam retains its rights in the Alnylam Patent Rights, the Joint Patents and the Alnylam Extended Field Patents exclusively for Alnylam Exclusive Targets. Notwithstanding the exclusive nature of the license granted by Alnylam to Isis under Section 6.1(l), Alnylam may grant Permitted Licenses.

(f) The license to Alnylam Extended Field Patents granted in Section 6.1(k) does not include any rights with respect to Single Stranded Products that are designed to modulate any Isis Retained Targets.

6.6 Alnylam Covenant to Isis Regarding Exclusivity for Single Stranded RNAi Products. Alnylam hereby covenants to Isis, that, after the Second 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, 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 and/or import Single Stranded RNAi Compounds or Single Stranded RNAi Products that are not Isis Exclusive Target Products for [***]; (ii) and may grant licenses to Third Parties to, research, develop, make, have made, use and/or import Alnylam Exclusive Target Products; and (iii) 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 [***], or (B) granting any Third Party a license under the [***].

6.7 Diligence on Isis Exclusive Targets. For each Isis Exclusive Target, Isis will use Commercially Reasonable Efforts (either on its own, with an Affiliate or in a Bona Fide Third Party Collaboration) [***].

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) In connection with the First Restated Agreement, Alnylam paid Isis an additional, irrevocable, noncreditable and non-refundable license fee of $11,000,000.

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 (other than Agricultural Field Products) by Alnylam, its Affiliates or sublicensees (except Naked Sublicensees) equal to [***]% of Net Sales of such Products. 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 (other than an Agricultural Field Product) that arise from Alnylam acquiring access to new technologies after the Effective Date; provided, however that (x) the royalty due under this section can never be less than a floor of [***]% and (y) additional royalties arising as the result of the addition, pursuant to Section 11.8, of Isis Current Chemistry Patents, Isis Current 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 this Agreement, and during the Alnylam Extended Field Royalty Term, Alnylam will pay to Isis royalties on sales of Alnylam Extended Field Products (other than Agricultural Field Products) by Alnylam, its Affiliates or sublicensees equal to [***]% of Net Sales of such Products.

(c) Subject to the terms and conditions of this Agreement, and during the Alnylam Exclusive Target Royalty Term, Alnylam will pay to Isis royalties on sales of Alnylam Exclusive Target Products (other than Agricultural Field Products) by Alnylam, its Affiliates or sublicensees equal to [***]% of Net Sales of such Products. Upon expiration of the Alnylam Exclusive Target Royalty Term, the license granted under Section 5.1(h) will terminate.

(d) Subject to the terms and conditions of, and during the term of, this Agreement, Alnylam will pay to Isis royalties on sales of Agricultural Field Products by Alnylam, its Affiliates or sublicensees equal to [***]% of Agricultural Field Product Net Sales. Alnylam may not reduce the royalty due under this subsection (d) for any additional royalties that Alnylam owes to Third Parties on such Agricultural Field Products.

(e) The royalties payable to Isis pursuant to Section 7.2(c) are in addition to, and not in lieu of, the royalties payable to Isis pursuant to Section 7.2(a). Specifically, if an Alnylam Exclusive Target Product (other than an Agricultural Field Product) is subject to the payment of royalties to Isis pursuant to Section 7.2(c) during the applicable Alnylam Exclusive Target Royalty Term and is also an Alnylam Double Stranded RNA Product, then the royalty calculated pursuant to Section 7.2(a) above will also be payable to Isis with respect to such Alnylam Exclusive Target Product for so long as such Alnylam Exclusive Target Product is an Alnylam Double Stranded RNA Product. However, if an Alnylam Exclusive Target Product that is subject to the payment of royalties to Isis pursuant to Section 7.2(c) is also an Alnylam Extended Field Product, it will not be subject to additional royalties under Section 7.2(b). Otherwise, only one royalty shall be due under this Section 7.2 with respect to the same unit of Product and if during any period the application of Sections 7.2(a), (b) and/or (c) to such Product in a country would result in different royalty rates being applied in order to calculate the royalty due with respect to Net Sales of such Product in such country in such period, then the greatest applicable royalty rate shall be applied.

7.3 Research and Development Milestones.

(a) [Intentionally Deleted]

(b) [Intentionally Deleted]

(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 [***]days after the first achievement of each of the following events:

Milestone Event	Milestone Payment
Initiation of Phase I Trial	US$375,000
Initiation of Phase III Trial	US$750,000
Filing NDA	US$[***]
Marketing Approval	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 RNA Target to trigger such milestone payment, whether such milestone is achieved by Alnylam or an Affiliate or sublicensee of Alnylam.

Notwithstanding the foregoing, the provisions of this Section 7.3(c) shall not apply to any Agricultural Field Product.

(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 RNA Target within [***] days after such MicroRNA Product reaches the initiation of [***], and not for any other MicroRNA Product that is an Alnylam Product that modulates the particular RNA Target.

7.4 Sublicensing Revenue on Naked Sublicenses. With respect to Sublicense Revenue from each Naked Sublicense granted by Alnylam and its Affiliates under this Agreement, Alnylam will pay Isis within [***] days following receipt by Alnylam of such Sublicense Revenue (a) fifty percent (50%) of all such Sublicense Revenue that does not constitute royalty payments, and (b) [***] 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.

7.5 Technology Access Fees from Certain Collaborations.

(a) Alnylam will pay Isis a percentage of Technology Access Fees received by Alnylam and its Affiliates pursuant to Bona Fide Discovery Collaborations and Development Collaborations entered into between Alnylam and a Third Party. Alnylam shall make such payment to Isis within [***] days 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 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 Discovery Collaboration or Development Collaboration that involves the same Alnylam Double Stranded RNA Product that triggered such milestone payment.

If Alnylam grants a sublicense under the Isis Exclusive Target Patents where the Patents sublicensed thereunder include Patents that are also Isis Patent Rights, then such sublicense will be treated as a Bona Fide Discovery Collaboration for purposes of this Section 7.5(a) and Alnylam will pay Isis a percentage of Technology Access Fees received by Alnylam and its Affiliates in connection with such sublicense. However, if Alnylam grants a sublicense under the Isis Exclusive Target Patents and/or the Isis Extended Field Patents and the Patents sublicensed thereunder do not include Isis Patent Rights (and do not include Isis Exclusive Target Patents that are also Isis Patent Rights), then no payments are due under this Section 7.5(a).

(b) Notwithstanding the foregoing, for any Bona Fide 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 Discovery Collaboration agreement reaching [***] (in which event Alnylam shall pay Isis such minimum fee within [***] days following such initiation of [***]) or within [***] days 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 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 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. Notwithstanding the foregoing, the provisions of this Section 7.5(b) shall not apply to any Bona Fide Discovery Collaboration involving solely Agricultural Field Products.

7.6 Allocation of Sublicense Income. Each time Alnylam enters into a collaboration or license agreement pursuant to which Alnylam grants a sublicense under the Isis Patent Rights to a Third Party that only relates to Double Stranded RNA (an "Isis IP Sublicense"), the CEO of Isis and the CEO of Alnylam will mutually discuss and agree in writing upon a good faith determination as to whether such Isis IP Sublicense is a Naked Sublicense or a Bona Fide Discovery Collaboration or Development Collaboration or Bona Fide Third Party Collaboration. 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, (5) Isis Single Stranded Product, or (6) Alnylam Exclusive Target Products. Alnylam shall make such payment to Isis within [***] days 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 RNA 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 Effective 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 to Section 11.8, of Alnylam Current Chemistry Patents or Alnylam Current 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 to [***] 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 [***]%.

(c) Subject to the terms and conditions of this Agreement, and during the Isis Extended Field Royalty Term, Isis will pay to Alnylam royalties on sales of Isis Extended Field Products by Isis, its Affiliates or sublicensees equal to [***]% of Net Sales of such Products.

(d) Subject to the terms and conditions of this Agreement, and during the Isis Exclusive Target Royalty Term, Isis will pay to Alnylam royalties on sales of Isis Exclusive Target Products by Isis, its Affiliates or sublicensees equal to [***]% of Net Sales of such Products. Upon expiration of the Isis Exclusive Target Royalty Term, the license granted under Section 6.1(l) will terminate.

(e) The royalties payable to Alnylam pursuant to Section 8.2(d) are in addition to, and not in lieu of, the royalties payable to Alnylam pursuant to Sections 8.2(a) and (b), as applicable. Specifically, if an Isis Exclusive Target Product is subject to the payment of royalties to Alnylam pursuant to Section 8.2(d) during the applicable Isis Exclusive Target Royalty Term and is also a Double Stranded RNA Product that is an Isis Product or an Isis Single Stranded RNAi Product, as the case may be, then the royalty calculated pursuant to Section 8.2(a) or (b), as applicable, will also be payable to Alnylam with respect to such Isis Exclusive Target Product for so long as such Isis Exclusive Target Product is a Double Stranded RNA Product that is an Isis Product or an Isis Single Stranded RNAi Product, as the case may be. However, if an Isis Exclusive Target Product that is subject to the payment of royalties to Alnylam pursuant to Section 8.2(d) is also an Isis Extended Field Product, it will not be subject to additional royalties under Section 8.2(c).

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 [***] days 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 RNA 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 RNA Target within [***] days 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 RNA 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 RNA Target within [***] days after such MicroRNA Product reaches the initiation of [***], and not for any other MicroRNA Product that is an Isis Product that modulates the particular RNA 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 Second Restatement Date, Isis will pay Alnylam, within [***]days following receipt by Isis of such Sublicense Revenue, [***]percent ([***]%) of all such Sublicense Revenue that does not constitute royalty payments.

(b) In the event that Isis enters into 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 RNAi 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 [***] 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 [Intentionally Deleted]

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 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 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 [***] days 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 [***] days 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 Article 7 or 8, each Party will make such withholding payments as required and subtract such withholding payments from the payments set forth in 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 [***] days 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 [***] days 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 [***] days 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 RNA 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. The Parties agree that the provisions of this Section 10.2 shall not apply to licenses involving solely Agricultural Field Products.

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 Patent Rights.

(a) [Intentionally Deleted]

(b) Except as set forth in Sections 11.2(f) and 11.2(h) 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, the Isis Extended Field Patents and the Isis Exclusive Target Patents.

(c) Except as set forth in Section 11.2(g) and 11.2(h) 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, the Alnylam Extended Field Patents and the Alnylam Exclusive Target Patents.

(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 Patents that are licensed under this Agreement. Neither Party will initiate or participate in any opposition, reexamination, interference, litigation, inter partes review, post grant review or other proceeding for the purpose of narrowing or invalidating any claim in a Patent of the other Party; provided, however, that either Party may assert invalidity or non-infringement as a defense in any court proceeding bought by the other Party asserting infringement of a granted Patent that is not a Patent then licensed under this Agreement. Notwithstanding the above, if an interference is declared by the Patent and Trademark Office between two or more of the Parties respective Patents, the Parties agree to use good faith diligent efforts to resolve matters of priority and patentability and reach agreement or understanding as to patentable claims enjoying priority. In the event the Parties do not reach such agreement or understanding within [***] months after declaration of the interference by the Patent and Trademark Office (or such shorter period as necessary to comply with the Patent and Trademark Office calendar), then the Parties agree to submit such matter to arbitration under Section 17.6 and that the Party determined not to have priority of invention with request and agree to adverse judgment either by way of concession of priority or unpatentability or by disclaimer or abandonment of the contest according to the rules of interference practice in existence at the time. The Parties agree to file with the Patent and Trademark Office all agreements pertaining to settlement of the interference in accordance with the rules of interference practice in existence at the time.

(e) At the non-prosecuting Party's request, the other Party will keep the requesting Party reasonably informed, and provide documentation, of all material matters relating to the preparation, filing, prosecution and maintenance of any designated Patent licensed to the non-prosecuting Party under this Agreement.

(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 (i) Isis Exclusive Target Patents that (1) claim (x) an oligomeric compound that hybridizes to and modulates an Alnylam Exclusive Target or (y) a method of using such oligomeric compound in the Field and (2) cover the manufacture, sale or use of an Alnylam Exclusive Target Product that is comprised of a Double Stranded RNA or Double Stranded RNA Product ("Isis Special Target Patent") and (ii) 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 or an Isis Special Target 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. If elections with respect to obtaining patent term extension or supplemental protection certificates or their equivalents in any country with respect to Isis Special Target Patents are available, Alnylam shall have the right (but not the obligation), in its sole discretion, to make any such election and make such filing as necessary to effect such election. Alnylam shall, in its sole discretion, seek and maintain all applicable data exclusivity periods (such as those periods listed in the FDA's Orange Book (including any available pediatric extensions) or foreign equivalents) that are available for Alnylam Exclusive Target Products. Alnylam shall have sole authority with respect to the listing of any Isis Special Target Patents with respect to the Alnylam Exclusive Target Products in the Orange Book.

(g) Isis will be responsible for preparing, filing, prosecuting, maintaining and taking such other actions as are reasonably necessary or appropriate with respect to the Patents that (1) claim (x) an oligomeric compound that hybridizes to and modulates an Isis Exclusive Target or (y) a method of using such oligomeric compound in the Field and (2) cover the manufacture, sale or use of an Isis Exclusive Target Product that is comprised of a Single Stranded Compound or Single Stranded Product ("Alnylam Special Target Patent"). If Isis elects not to file for or continue the prosecution (including any interferences, oppositions, reissue proceedings and re-examinations) or maintenance of an Alnylam Special Target Patent in any country, then, Isis will notify Isis promptly in writing of its intention in sufficient time to enable Alnylam 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 Alnylam will have the right, but not the obligation, to file for or continue the prosecution or maintenance of such Patent in such country, and Isis will cooperate with Isis in regard thereto. If elections with respect to obtaining patent term extension or supplemental protection certificates or their equivalents in any country with respect to Alnylam Special Target Patents are available, Isis shall have the right (but not the obligation), in its sole discretion, to make any such election and make such filing as necessary to effect such election. Isis shall, in its sole discretion, seek and maintain all applicable data exclusivity periods (such as those periods listed in the FDA's Orange Book (including any available pediatric extensions) or foreign equivalents) that are available for Isis Exclusive Target Products. Isis shall have sole authority with respect to the listing of any Alnylam Special Target Patents with respect to the Isis Exclusive Target Products in the Orange Book.

(h) 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, in each case that are Controlled by Alnylam but excluding Joint Patents, Alnylam 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 Alnylam decides to discontinue the preparation, filing, prosecution or maintenance of such a Patent, Alnylam will notify Isis at least [***] days prior to any deadline that, if missed, would materially prejudice the Patent, and Isis will have the right, at Isis' own expense, to prepare, file, prosecute and maintain such Patent.

11.3 Filing and Prosecution of Jointly Owned Patents.

(a) The Parties will mutually agree on which of the Parties will be designated as being the responsible Party for preparing, filing, prosecuting, maintaining and taking such other actions as are reasonably necessary or appropriate with respect to each 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) and (d) below, each Party will bear its own costs and expenses in filing, prosecuting, maintaining and extending the Alnylam Patent Rights, Alnylam Extended Field Patents, Alnylam Exclusive Target Patents, Isis Patent Rights, Isis Extended Field Patents and Isis Exclusive Target Patents, respectively.

(b) Except as set forth in Section 11.4(c) and (d) 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 and the Isis Special Target 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 or an Isis Special Target Patent in any country, and Isis assumes the continued prosecution of such Isis Special Patent or Isis Special Target 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 or Isis Special Target Patent for which Isis assumed prosecution.

(d) Isis will bear [***]% of its own costs and expenses in filing, prosecuting, maintaining and extending the Alnylam Special Target Patents. If Isis elects not to file for or continue the prosecution (including any interferences, oppositions, reissue proceedings and re-examinations) or maintenance of an Alnylam Special Target Patent in any country, and Alnylam assumes the continued prosecution of such Alnylam Special Target Patent (as permitted by Section 11.2(g)) in such country, then the Parties will [***] all of Alnylam's costs and expenses in filing, prosecuting, maintaining and extending the Alnylam Special Target Patent for which Alnylam 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, Joint Patents, Alnylam Extended Field Patents, Alnylam Exclusive Target Patents, Isis Extended Field Patents or Isis Exclusive Target Patents by any person that reasonably affects the other Party's business and of which it becomes aware. The notice shall set forth the facts of such infringement or misappropriation in reasonable detail.

(b) Subject to subsections (c)(i) and (h) below, Alnylam will have the sole and exclusive right, in its sole discretion and at its expense, to assert and enforce (i) any Isis Patent Rights, Alnylam Patent Rights, Joint Patents, Alnylam Extended Field Patents, or Alnylam Exclusive Target 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 and (ii) any Isis Exclusive Target Patents against any party engaging in an unlicensed or unauthorized making, having made, using, selling, offering for sale or importing of any allegedly infringing oligomeric compound that hybridizes to and modulates an Alnylam Exclusive Target but only if such Isis Exclusive Target Patent is the only Patent Controlled by Alnylam that covers such allegedly infringing oligomeric compound.

(c)

(i) For any enforcement by Alnylam under subsection (b) above that includes Isis Patent Rights or Isis Exclusive Target Patents 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, Isis Extended Field Patents or Isis Exclusive Target Patents covering a [***] chemical modification is at risk.

(ii) Subject to subsection (b) above and subsection (h) below, Isis will have the sole and exclusive right, in its sole discretion and at its expense, to assert and enforce Alnylam Exclusive Target Patents against any party engaging in an unlicensed or unauthorized making, having made, using, selling, offering for sale or importing of any allegedly infringing oligomeric compound that hybridizes to and modulates an Isis Exclusive Target but only if such Alnylam Exclusive Target Patent is the only Patent Controlled by Isis that covers such allegedly infringing oligomeric compound.

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

(i) Isis will have the sole and exclusive right, in its sole discretion and at its expense, to assert and enforce any (i) Isis Patent Rights, (ii) Isis Extended Field Patents, and (iii) Isis Exclusive Target Patents;

(ii) Alnylam will have the sole and exclusive right, in its sole discretion and at its expense, to assert and enforce any (i) Alnylam Patent Rights, (ii) Alnylam Extended Field Patents, (iii) Alnylam Exclusive Target Patents, and (iv) the Isis Special Patents; and

(iii) The Parties 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 by the terms of the Isis Third Party Agreements. The rights granted hereunder to Isis to enforce certain licensed in or jointly owned Alnylam Patent Rights are further limited as described in the Alnylam Third Party Agreements.

(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 licensed to the nonenforcing Party under this Agreement without prior written authorization of the nonenforcing Party.

(h) If the Party with enforcement rights under subsection (b), (c) or (d) above (the "Primary Party") fails to initiate proceedings against any actual or suspected infringement within [***] days 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 the applicable Products and distributed as such Net Sales would have been distributed.

11.6 If any Person asserts in writing or in any legal proceeding that any of the Isis Exclusive Target Patents or Alnylam Exclusive Target Patents are unenforceable based on any term or condition of this Agreement, the Parties shall amend this Agreement as may reasonably be required to effect the original intent of the Parties, including to preserve the enforceability of such Patents and the intended economic and non-economic effects of this Agreement.

11.7 [Intentionally Deleted]

11.8 Future Licenses. If after the First Restatement Date, a Party (the "Controlling Party") invents or acquires rights or title to an invention claimed by a Patent that (i) would be included in the Isis Current Chemistry Patents, Isis Current Motif and Mechanism Patents, Isis Extended Field Patents or Isis Exclusive Target Patents if such Party is Isis or in the Alnylam Current Chemistry Patents, Alnylam Current Motif and Mechanism Patents, Alnylam Extended Field Patents or Alnylam Exclusive Target 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 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 (as defined in the First Restated Agreement) 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 Discovery Collaboration agreement, or Development Collaboration agreement or Bona Fide Third Party 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, Alnylam Extended Field Products or Alnylam Exclusive Target 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, Isis Extended Field Products or Isis Exclusive Target 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 Second 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 a 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 Product) to the extent such license is necessary to develop, make and have made, sell and import such 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 [Intentionally Deleted]

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 Article 7 or 8. Sections 4.3(f), 6.4(i), and 11.1, and Articles 1, 9, 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) 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, the First Restatement Date and the Second 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 Alnylam Representation and Warranty. Alnylam hereby represents and warrants to Isis that as of the effective date of the Agbio License Agreement, the Agbio License Agreement included a collaboration involving the discovery and/or development of Double Stranded RNA Products, in which Alnylam played 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/or development of such Double Stranded RNA Products.

15.3 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. 2855 Gazelle Court Carlsbad, CA 92010 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: SVP and General Counsel Fax No.: +1 (617) 812-0353
with a copy to:	Faber Daeufer & Itrato PC 950 Winter Street, Suite 4500 Waltham, Massachusetts 02451 Attention: Sumy C. Daeufer, Esq. Fax No.: +1 (781) 795-4747

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) [Intentionally Deleted].

(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 [***] such Acquisition will be permitted to [***] pursuant to Section 6.4(a) shall be limited to [***] per calendar year, and (iii) the royalties payable by Isis with respect to Isis Single Stranded RNAi Products will be adjusted in accordance with Section 8.2(b).

(d) Notwithstanding anything in this Agreement to the contrary, following the closing of an Acquisition of a Party (the "Acquired Party"), the Parties agree that the other Party (the "Non-Acquired Party") shall not obtain rights or access to the Patents controlled by the Acquirer (as defined below) or any of the Affiliates of such Acquirer (other than the Acquired Party and its Affiliates which exist immediately prior to the closing of such Acquisition (such Affiliates, the "Pre-Existing Affiliates")); and the Acquirer and its Affiliates (other than the Acquired Party and its Pre-Existing Affiliates) shall not obtain rights or access to the Patents controlled by the Non-Acquired Party or any of its Affiliates pursuant to this Agreement, or be bound by the restrictions set forth in Section 6.6. For clarity but without limitation, the Non-Acquired Party's rights in all Patents Controlled by the Acquired Party or any of its Pre-Existing Affiliates, which Patents exist as of the date of the closing of such Acquisition and are then licensed hereunder to the Non-Acquired Party, shall remain licensed to such Non-Acquired Party after the date of the closing of such Acquisition in accordance with and subject to the terms and conditions of this Agreement and shall not be affected in any manner by virtue of such Acquisition. "Acquirer" means, with respect to the Acquired Party, the Third Party that acquires such Acquired Party or its direct or indirect controlling Affiliate, or that acquires all or substantially all of the assets of the Acquired Party or its direct or indirect controlling Affiliate, in any case via an Acquisition.

(e) 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. For clarity, however, the letter agreement between the Parties dated January 18, 2012 is not superseded by this Agreement and continues in full force and effect. 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 Second Restatement Date.

Isis Pharmaceuticals, Inc.		**Alnylam Pharmaceuticals, Inc.**	
By:	/s/ *B. Lynne Parshall*	By:	/s/ *John Maraganore*
Name:	B. Lynne Parshall	Name:	John Maraganore
Title:	Chief Operating Officer	Title:	Chief Executive Officer

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 Second 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 an RNA Target and a Party, any ongoing drug discovery, development, or commercialization of a compound directed to such RNA Target being conducted by such Party (whether on its own or through a sublicensee).

3. "Affiliate" with respect to a Person means any other Person controlling, controlled by, or under common control with such Person. 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.

4. "Agbio License Agreement" shall mean that certain License and Collaboration Agreement with Monsanto Company dated as of August 27, 2012, as amended through the Second Restatement Date, and from time to time after the Second Restatement Date; *provided* Isis has approved by prior written consent any such amendment after the Second Restatement Date that would diminish Isis' rights under this Agreement or increase Isis' obligations under this Agreement; and *provided further* in each case Alnylam has provided Isis a copy of such amendment before, or promptly after executing such amendment.

5. "Agricultural Field" shall mean applications in agriculture, horticulture, forestry, aquaculture and/or the residential markets relating to plants, fish, arthropods and/or pests and pathogens thereof (e.g., home, lawn, and/or garden). The Agricultural Field excludes, without limitation, (a) all human and animal (other than fish and arthropods) therapeutic, prophylactic or diagnostic applications; (b) the development, sale and use of research reagent products for any purpose; and (c) modification of any cells, tissues or organisms for the purpose of manufacturing heterologous proteins, peptides or viruses for any purpose other than the modification of plants, plant cells, or plant tissues for the purpose of manufacturing heterologous proteins, peptides or viruses for application to plants, fish, arthropods and/or pests or pathogens thereof.

6. "Agricultural Field Product" meansa product that contains a Double Stranded RNA (including transgenic applications thereof) for application in the Agricultural Field that either (a) modulates the viability and/or biological processes (including expression of genes and/or proteins) of (i) plants, (ii) fish, (iii) arthropods, and/or (iv) pests or pathogens thereof; or (b) modifies plants, plant cells or plant tissues for the purpose of manufacturing heterologous proteins, peptides or viruses for application to (i) plants, (ii) fish, (iii) arthropods, and/or (iv) pests or pathogens thereof.

7. "Agricultural Field Product Net Sales" will mean (a) the gross invoice price of Agricultural Field Products sold by Alnylam, its Affiliates and sublicensees (but with respect to Alnylam does not include Naked Sublicensees) to a Third Party; provided, that such Third Party is an end-user of such Licensed Product or a Third Party which purchases Agricultural Field Product(s) (whether in packaged form or bulk form) from Alnylam, its Affiliate or sublicensee and resells such Agricultural Field Product(s) to third parties in a manner consistent with normal trade practices in the Agricultural Field; less (b) the following items: (i) deductions actually incurred, allowed, paid, accrued or specifically allocated in financial statements in accordance with generally accepted accounting principles, in preparing and utilizing distribution channels for an Agricultural Field Product (including product returns, customer rebates, dealer incentives, volume discounts, seed service fees, cash discounts (pre-pay discounts), (ii) local competitive response, transportation or cargo insurance, taxes, duties or other governmental tariffs (other than income taxes), (iii) government-mandated rebates, and (iv) a reasonable reserve for bad debts, (and some of which items, by way of example, are currently identified as "crop loss and replant" and "seed action pack") in all cases allocated to such Agricultural Field Products in accordance with generally accepted accounting principles and methodologies established by Alnylam, its Affiliates or sublicensee, as the case may be, and that are consistently applied by such party across all of such party's products in the Agricultural Field; provided, that such methodologies may be amended from time to time, upon notice to Isis to reflect general changes to such party's methodologies, which changes are consistently applied by such selling party across such party's products in the Agricultural Field and which changes are made in the ordinary course of such party's business.

Isis and Alnylam agree that any reasonable definition of "*net sales*" customarily used in agricultural industry technology licensing or collaboration contracts that is agreed to under the Agbio License Agreement or subsequently agreed to by Alnylam (or a Third Party acquirer or assignee) and a sublicensee with respect to royalties payable to Alnylam from such sublicensee in an arms-length transaction under a particular sublicense will replace the definition of Agricultural Field Product Net Sales in this Agreement and will be used in calculating the royalty payment to Isis on sales of Agricultural Field Products (including, but not limited to, products that consist of an Agricultural Field Product and other technologies and/or materials (i.e., combination products)) sold pursuant to such sublicense and due under this Agreement.

8. "Alnylam Current Chemistry Patents" means all Chemistry Patents (i) Controlled by Alnylam as of the First Restatement Date or any time thereafter until the Second Restatement Date and (ii) having an earliest priority date of no later than April 30, 2014, provided, however that (a) for any such Chemistry Patents that are acquired, licensed or invented after the First Restatement Date 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 Current Chemistry Patent; and (b) Alnylam Current Chemistry Patents do not include Patents that constitute Alnylam Excluded Technology. Without limitation the Patents listed on Schedule 1-8 attached hereto are Alnylam Current Chemistry Patents, except to the extent such Patents claim Alnylam Excluded Technology.

9. "Alnylam Current Motif and Mechanism Patents" means all Motif and Mechanism Patents (i) Controlled by Alnylam as of the First Restatement Date or any time thereafter until the Second Restatement Date and (ii) having an earliest priority date of no later than April 30, 2014, provided, however that (a) for any such Motif and Mechanism Patents that are acquired, licensed or invented after the First Restatement Date 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 Motif and Mechanism Patent; and (b) Alnylam Motif and Mechanism Patents do not include Patents that constitute Alnylam Excluded Technology. Without limitation the Patents listed on Schedule 1-9 attached hereto are Alnylam Current Motif and Mechanism Patents, except to the extent such Patents claim Alnylam Excluded Technology.

10. "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.

11. "Alnylam Excluded Technology" means (a) inhibitors to specific genes or gene families, (b) Manufacturing Patents, (c) 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, (d) formulation and delivery technologies and (e) the specific technology listed on Schedule 1-11 attached hereto.

12. "Alnylam Exclusive Target" means an RNA Target or protein product of (a) the antithrombin gene (AT, also known as AT3) or (b) the aminolevulinate synthase gene 1 (AS1), which genes are further identified and described on Exhibit B.

13. "Alnylam Exclusive Target Excluded Technology" means (a) Manufacturing Patents, (b) 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, (c) formulation and delivery technologies, and (d) the specific technology listed on Schedule 1-13 attached hereto.

14. "Alnylam Exclusive Target Patents" means all Patents that are Controlled by Alnylam on or prior to the [***] anniversary of the Second Restatement Date that (a) claim (x) an oligomeric compound that hybridizes to and modulates an Isis Exclusive Target or (y) a method of using such oligomeric compound in the Field; or (b) are Chemistry Patents or Motif and Mechanism Patents other than those described in clause (a) above; provided, however that (A) for any such Patents that are acquired, licensed or invented after the First Restatement Date 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 Exclusive Target Patent; and (B) Alnylam Exclusive Target Patents do not include (I) Patents that constitute Alnylam Exclusive Target Excluded Technology, or (II) Patents Controlled by Alnylam that specifically claim an oligomeric compound that hybridizes to and modulates an Alnylam Exclusive Target (or method of using such oligomeric compound in the Field). Alnylam Exclusive Target Patents include, without limitation, the Patents listed on Schedule 1-14 attached hereto.

15. "Alnylam Exclusive Target Product" means an oligomeric compound (a) that hybridizes to and modulates an Alnylam Exclusive Target, and (b) the manufacture, sale or use of which is covered by a Valid Claim within the Isis Exclusive Target Patents. For purposes of determining whether a royalty is payable by Alnylam under Section 7.2(c), an oligomeric compound that hybridizes to and modulates an Alnylam Exclusive Target will continue to be considered an Alnylam Exclusive Target Product during the applicable Alnylam Exclusive Target Royalty Term for such compound in a country if the manufacture, sale or use of such compound in such country is covered by a Valid Claim within the Isis Exclusive Target Patents at the time of First Commercial Sale of such compound in such country.

16. "Alnylam Exclusive Target Royalty Term" means, on a Product-by-Product and country-by-country basis, the period commencing with the First Commercial Sale of an Alnylam Exclusive Target Product and ending on the later of the expiration of (i) the last-to-expire Valid Claim of an Isis Exclusive Target Patent that covers the manufacture, use, or sale of such Alnylam Exclusive Target Product in such country, and (ii) any period of regulatory data protection or market exclusivity or similar regulatory protection afforded by the Regulatory Authorities in such country, including any such periods listed in the FDA's Orange Book, and all international equivalents.

17. "Alnylam Extended Field Patents" means all Chemistry Patents and Motif and Mechanism Patents Controlled by Alnylam on and after the Second Restatement Date and having any earliest priority date between May 1, 2014 and April 30, 2019, inclusive; provided, however that (a) for any such Chemistry Patents or 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 Extended Field Patent; and (b) Alnylam Extended Field Patents do not include Patents that constitute Alnylam Excluded Technology. Alnylam Extended Field Patents include, without limitation, the Patents listed on Schedule 1-17 attached hereto.

18. “Alnylam Extended Field Product” means a Double Stranded RNA Product the manufacture, sale or use of which is covered by a Valid Claim within the Isis Extended Field Patents.

19. “Alnylam Extended Field Royalty Term” means, on a Product-by-Product and country-by-country basis, the period commencing with the First Commercial Sale of an Alnylam Extended Field Product and ending on the expiration of the last-to-expire Valid Claim of an Isis Extended Field Patent that covers the manufacture, use or sale of such Alnylam Extended Field Product in such country.

20. “Alnylam Patent Rights” means Alnylam Current Motif and Mechanism Patents and Alnylam Current 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.

21. “Alnylam Product” means an Alnylam Double Stranded RNA Product or MicroRNA 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.

22. “Alnylam Special Target Patent” has the meaning set forth in Section 11.2(g).

23. “Alnylam Third Party Agreements” means the in-license and other agreements between Alnylam and a Third Party listed on Exhibit 6.5(c).

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

25. “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.

26. "Bona Fide Discovery Collaboration" means (a) with respect to Double Stranded RNA Products that are not Agricultural Field Products, 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 such Double Stranded RNA Products from the point in time at which the relevant RNA Target has been designated through the initiation [***]; and (b) with respect to Agricultural Field Products, a collaboration involving the discovery and/or 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/or development of such Double Stranded RNA Products. A Bona Fide Discovery Collaboration for Double Stranded RNA Products that are not Agricultural Field Products may continue beyond the initiation of such [***]. For Isis Products that are Double Stranded RNA Products, a Bona Fide Discovery Collaboration must be an Antisense Drug Discovery Program. For Alnylam, collaborations that do not include or involve Isis Patent Rights licensed from Isis under Section 5.1(a) (and do not include Isis Exclusive Target Patent Rights that are also Isis Patent Rights), shall not constitute Bona Fide Discovery Collaborations. For Isis, collaborations that do not include or involve Alnylam Patent Rights licensed from Alnylam pursuant to Section 6.2, shall not constitute Bona Fide Discovery Collaborations. A Party's experimentation relating to the discovery and development of Double Stranded RNA Products that modulate a relevant RNA 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 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 Discovery Collaboration agreement will be aggregated to constitute a single Bona Fide Discovery Collaboration. The Agbio License Agreement is deemed a Bona Fide Discovery Collaboration for purposes of this Agreement.

27. "Bona Fide Third Party Collaboration" means, with respect to a Party a collaboration between such Party and a Third Party involving the discovery, development and/or commercialization of, (a) in the case of Alnylam, an Alnylam Extended Field Product or an Alnylam Exclusive Target Product, as the case may be or (b) in the case of Isis, an Isis Extended Field Product or an Isis Exclusive Target Product, as the case may be. For Alnylam, such collaborations that do not include or involve Isis Extended Field Patents or Isis Exclusive Target Patents licensed from Isis hereunder shall not constitute Bona Fide Third Party Collaborations. For Isis, such collaborations that do not include or involve Alnylam Extended Field Patents or Alnylam Exclusive Target Patents licensed from Alnylam hereunder shall not constitute Bona Fide Third Party Collaborations.

28. "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.

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

30. “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

31. “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).

32. “Control” or “Controlled” means, with respect to any Patent or other intellectual property right, possession of the right by a Party or its Affiliates (whether by ownership, license or otherwise, other than pursuant to a license granted under this Agreement), 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.

33. “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.

34. "CRT" has the meaning set forth in Section 6.5(d)(ii).

35. "CRT Agreement" has the meaning set forth in Section 6.5(d)(ii).

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

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

38. "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 Alnylam, collaborations that do not include or involve Isis Patent Rights licensed from Isis under Sections 5.1(a) (and do not include Isis Exclusive Target Patent Rights that are also Isis Patent Rights), shall not constitute Development Collaborations. For Isis, collaborations that do not include or involve Alnylam Patent Rights licensed from Alnylam pursuant to Sections 6.1(a), (h), (i) or Section 6.2, shall not constitute Development Collaborations.

39. "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.

40. "Double Stranded RNA Product" means (a) a pharmaceutical composition that contains a Double Stranded RNA or (b) an Agricultural Field Product.

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

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

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

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

45. "Field" means the treatment and/or prevention of all human or animal diseases.

46. "First Commercial Sale" means, with respect to a country and a Product, the first sale for end use or consumption of such Product in such country after all required Marketing Approvals in such country have been obtained.

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

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

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

50. "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.

51. "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.

52. "Isis Current Chemistry Patents" means all Chemistry Patents (i) Controlled by Isis as of the First Restatement Date or any time thereafter until the Second Restatement Date and (ii) having an earliest priority date of no later than April 30, 2014; provided, however that (a) for any such Chemistry Patents that are acquired, licensed or invented after the First Restatement Date 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 Current Chemistry Patent; and (b) Isis Current Chemistry Patents do not include Patents that constitute Isis Excluded Technology. Without limitation the Patents listed on Schedule 1-52 attached hereto are Isis Current Chemistry Patents, except to the extent such Patents claim Isis Excluded Technology.

53. "Isis Current Motif and Mechanism Patents" means all Motif and Mechanism Patents (i) Controlled by Isis as of the First Restatement Date or any time thereafter until the Second Restatement Date and (ii) having an earliest priority date of no later than April 30, 2014; provided, however that (a) for any such Motif and Mechanism Patents that are acquired, licensed or invented after the First Restatement Date 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 Motif and Mechanism Patent; and (b) Isis Current Motif and Mechanism Patents do not include Patents that constitute Isis Excluded Technology. Without limitation the Patents listed on Schedule 1-53 attached hereto are Isis Current Motif and Mechanism Patents, except to the extent such Patents claim Isis Excluded Technology.

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

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

56. "Isis Encumbered Target" means an RNA Target (a) to which Isis has a contractual obligation to a Third Party existing as of the Second Restatement Date that precludes Isis from granting a license under Section 5 with respect to such RNA 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 an RNA Target will cease to be an Isis Encumbered Target.

57. "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 Patents; (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 1-57 attached hereto.

58. "Isis Exclusive Target" means an RNA Target or protein product of (a) the Factor X1 gene (FX1) or (b) the Apo(a) gene (Apoa1), which genes are further identified and described on Exhibit A.

59. "Isis Exclusive Target Excluded Technology" means (a) Manufacturing Patents, (b) analytical technologies, kits and assays, including without limitation methods, systems and compositions of matter for amplifying, quantifying, detecting, characterizing or identifying nucleic acids or non-oligomeric ligands thereto, (c) formulation and delivery technologies, and (d) the specific technology listed on Schedule 1-59 attached hereto.

60. "Isis Exclusive Target Patents" means all Patents Controlled by Isis on or prior to the [***] anniversary of the Second Restatement Date that (a) claim (x) an oligomeric compound that hybridizes to and modulates an Alnylam Exclusive Target or (y) a method of using such oligomeric compound in the Field; or (b) are Chemistry Patents or Motif and Mechanism Patents other than Patents described in clause (a) above; provided, however that (A) for any such Patents that are acquired, licensed or invented after the Restatement Date 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 Exclusive Target Patent; and (B) Isis Exclusive Target Patents do not include (I) Patents that constitute Isis Exclusive Target Excluded Technology, (II) Patents Controlled by Isis that specifically claim an oligomeric compound that hybridizes to and modulates an Isis Exclusive Target (or method of using such oligomeric compound in the Field). Isis Exclusive Target Patents include, without limitation, the Patents listed on Schedule 1-60 attached hereto, except to the extent such Patents claim Isis Exclusive Target Excluded Technology.

61. “Isis Exclusive Target Product” means an oligomeric compound that (a) hybridizes to and modulates an Isis Exclusive Target, and (b) the manufacture sale or use of which is covered by a Valid Claim within the Alnylam Exclusive Target Patents. For purposes of determining whether a royalty is payable by Isis under Section 8.2(d), an oligomeric compound that hybridizes to and modulates an Isis Exclusive Target will continue to be considered an Isis Exclusive Target Product during the applicable Isis Exclusive Target Royalty Term for such compound in a country if the manufacture, sale or use of such compound in such country is covered by a Valid Claim within the Alnylam Exclusive Target Patents at the time of First Commercial Sale of such compound in such country.

62. “Isis Exclusive Target Royalty Term” means, on a Product-by-Product and country-by-country basis, the period commencing with the First Commercial Sale of an Isis Exclusive Target Product and ending on the later of the expiration of (i) the last-to-expire Valid Claim of an Alnylam Exclusive Target Patent that covers the manufacture, use or sale of such Isis Exclusive Target Product in such country, and (ii) any period of regulatory data protection or market exclusivity or similar regulatory protection afforded by the Regulatory Authorities in such country, including any such periods listed in the FDA’s Orange Book, and all international equivalents.

63. “Isis Extended Field Patents” means all Chemistry Patents and Motif and Mechanism Patents Controlled by Isis on and after the Second Restatement Date and having any earliest priority date between May 1, 2014 and April 30, 2019, inclusive; provided, however that (a) for any such Chemistry Patents or 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 Extended Field Patent; and (b) Isis Extended Field Patents do not include Patents that constitute Isis Excluded Technology. Isis Extended Field Patents include, without limitation, the Patents listed on Schedule 1-63 attached hereto, except to the extent such Patents claim Isis Excluded Technology.

64. “Isis Extended Field Product” means any Single Stranded Product the manufacture sale or use of which is covered by a Valid Claim within the Alnylam Extended Field Patents.

65. “Isis Extended Field Royalty Term” means, on a Product-by-Product and country-by-country basis, the period commencing with the First Commercial Sale of an Isis Extended Field Product and ending on the expiration of the last-to-expire Valid Claim of an Alnylam Extended Field Patent that covers the manufacture, use or sale of such Isis Extended Field Product in such country.

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

67. “Isis Patent Rights” means Isis Current Motif and Mechanism Patents, and Isis Current Chemistry Patents.

68. “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.

69. “Isis Retained Target” means each RNA Target that is subject to certain Third Party obligations of Isis and described on Schedule 1-69 attached hereto, as such schedule is updated from time to time pursuant to Section 5.3(f).

70. “Isis Retained Special Target” means each RNA Target designated as such on Schedule 1-69 attached hereto.

71. “Isis Single Stranded Product” means any single stranded oligomeric compound (a) that hybridizes in whole or in part to, and modulates the amount or activity of, an RNA Target, (b) is not a Double Stranded RNA or Double Stranded RNA Product, (c) is not a Single Stranded RNAi Compound, Single Stranded RNAi Product or Isis Single Stranded RNAi Product, and (d) the manufacture, sale or use of which is covered by a Valid Claim within the Alnylam Patent Rights.

72. “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.

73. “Isis Special Patents” means the Patents specifically listed on Schedule 1-73 attached hereto. The Parties may mutually agree in writing from time to time to add additional Patents to Schedule 1-73 attached hereto.

74. “Isis Special Target Patent” has the meaning set forth in Section 11.2(f).

75. “Isis Third Party Agreements” means the agreements between Isis and a Third Party listed on Exhibit 5.3(d).

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

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

78. “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

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

80. “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 $[***].

81. “Manufacturing Patents” means Patent claims claiming (1) a method of joining together component pieces of an oligomeric compound; (2) an improved method of making a component piece where such component piece is disclosed prior to the first filing of the Patent claiming such improved method; (3) in the case of concurrently-filed Patents claiming a new component piece and disclosing multiple methods of making the new component piece in a separate concurrently-filed Patent, the method(s) most suitable for making the new component piece at large scale (provided at least one method must be treated under this Agreement as claimed under a Chemistry Patent and not under a Manufacturing Patent); or (4) compounds used in such methods of joining together component pieces, other than the component pieces themselves and precursors of such component pieces. Thus, for example, Manufacturing Patents include claims to methods such as deprotection, capping, loading onto a solid support, and cleaving from a solid support, all of which are methods used in the process of assembling oligomeric compounds from component pieces; and reagents, such as solid supports themselves, useful in such methods.

82. “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.

83. “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.

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

85. “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.

86. "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 Discovery Collaboration or (c) a Bona Fide Third Party 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 that are not Isis Products for which Isis has exercised its option under Section 6.2 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 Patent Rights shall not constitute Naked Sublicenses.

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

88. "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.

89. "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).

Notwithstanding anything in this Agreement to the contrary, where the term "Net Sales" is used in this Agreement to apply to Agriculture Field Products, in such context the term "Net Sales" shall be replaced with "Agricultural Field Product Net Sales".

Isis and Alnylam agree that any reasonable definition of "*net sales*" customarily used in drug discovery, development or commercialization licensing or collaboration contracts that is agreed to by a Party (or a Third Party acquirer or assignee) and a sublicensee with respect to royalties payable to such Party from such sublicensee in an arms-length transaction under a particular sublicense will replace the definition of Net Sales in this Agreement and will be used in calculating the royalty payment to the other Party on sales of Products (other than Agricultural Field Products) sold pursuant to such sublicense and due under this Agreement, for so long as the same definition of net sales is used to calculate the royalty payable from the applicable sublicensee to such Party.

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

91. "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.

92. "Permitted Licenses" means (1) licenses granted by Isis or Alnylam (as the case may be) before or after the Second Restatement Date to any Third Party under the Alnylam Exclusive Target Patents (where Alnylam is the granting Party) or the Isis Exclusive Target Patents (where Isis is the granting Party) to (a) use oligonucleotides (or supply oligonucleotides to end users) solely to conduct pre-clinical research, or (b) enable such Third Party to manufacture or formulate oligonucleotides, where (i) such Third Party is primarily engaged in providing contract manufacturing or services and is not primarily engaged in drug discovery, development or commercialization of therapeutics; and (ii) the granting Party does not assist such Third Party to identify, discover or make an Alnylam Exclusive Target Product (where Isis is the granting Party) or an Isis Exclusive Target Product (where Alnylam is the granting Party); and (2) material transfer, collaboration, sponsored research or similar agreements with academic collaborators or non-profit institutions solely to conduct noncommercial Research.

93. “Person” means any person, organization, corporation or other business entity.

94. “Product” means an Alnylam Product, an Isis Product, an Alnylam Extended Field Product, an Isis Extended Field Product, an Alnylam Exclusive Target Product, or an Isis Exclusive Target Product, as the case may be.

95. “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.

96. “Research Program” means the Parties’ research collaboration focused on Single Stranded RNAi Compounds and conducted pursuant to the First Restated Agreement.

97. “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. The Research Program Patents are listed on Schedule 1-97 attached hereto.

98. “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.

99. “Reserved DS-Target” has the meaning set forth in Section 6.4(a).

100. “RNA Target” means a ribonucleic acid transcript with a defined sequence and/or function, including all splice variants and mutant forms of such transcript.

101. “Single Stranded Compound” means a single stranded oligomeric compound (a) that hybridizes in whole or in part to, and modulates the amount or activity of, an RNA Target, and (b) is not a Double Stranded RNA, a Double Stranded RNA Product, a Single Stranded RNAi Compound, or a Single Stranded RNAi Product.

102. “Single Stranded Product” means a pharmaceutical composition that contains a Single Stranded Compound and is not a Double Stranded RNA, a Double Stranded RNA Product, a Single Stranded RNAi Compound, or a Single Stranded RNAi Product.

103. “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.

104. “Single Stranded RNAi Product” means a pharmaceutical composition that contains a Single Stranded RNAi Compound.

105. “Stanford University” has the meaning set forth in Section 6.5(d)(i).

106. “Stanford Agreement” has the meaning set forth in Section 6.5(d)(i).

107. “Sublicense Revenue” means any payments that (1) with respect to Alnylam, Alnylam receives from a sublicensee in consideration of a Naked Sublicense, 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 (other than sublicenses of rights under Sections 6.1(k) or (l)), 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.

108. “Technology Access Fee” means any payments that Alnylam receives from granting a Third Party access (through sublicense or otherwise) to the Isis Patent Rights (including to Isis Exclusive Target Patent Rights that are also Isis Patent Rights) as part of a Bona Fide Discovery 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, and payments received by Alnylam pursuant to the Agbio License Agreement that are specifically committed to reimburse Alnylam for the cost of Patent prosecution, maintenance and/or defense of Patents covering or claiming Agricultural Field Products; *provided, however*, that any payments received by Alnylam but not applied to reimburse Alnylam for such expenses will be Technology Access Fees, (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.

109. “Third Party” means any party other than Isis or Alnylam and their respective Affiliates.

110. “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 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 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. With respect to any joint patents indicated on this schedule, the licenses granted by Isis to Alnylam in the Agreement are limited to the extent of the joint owner's rights in such joint patents.

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

[***]

Exhibit 5.3(c) Part II, Joint Patent Rights

[***]

EXHIBIT 5.3(D)

ISIS THIRD PARTY AGREEMENTS

The following schedule of Isis Third Party Agreements is provided by Isis to Alnylam, in connection with 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.

AGREEMENTS PROVIDING RIGHTS TO THIRD PARTIES IN CERTAIN ISIS PATENT RIGHTS

[***]

AGREEMENTS GRANTING THIRD PARTIES RIGHTS TO CONDUCT TARGET VALIDATION

[***]

RESEARCH LICENSE AGREEMENTS

[***]

AGREEMENTS CONTAINING CROSS-LICENSES TO NEW TECHNOLOGY ARISING FROM PARTNER COLLABORATIONS

[***]

GOVERNMENT RIGHTS IN ISIS IP

1. **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.

EXHIBIT 6.5(c)

ALNYLAM THIRD PARTY AGREEMENTS

In-License Agreements

1. Co-Exclusive License Agreement between Max-Planck-Innovation GmbH (formerly Garching Innovation GmbH) and Alnylam Pharmaceuticals, Inc., dated December 20, 2002, as amended by Amendment dated July 2, 2003, the Requirements Amendment effective June 15, 2005, the Waiver Amendment effective August 9, 2007 and the Amendment to the Alnylam Co-Exclusive License Agreement dated as of March 14, 2011, by and between Alnylam Pharmaceuticals, Inc., on the one hand, and Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology and Max-Planck-Innovation GmbH, on the other hand; and Co-Exclusive License Agreement between Max Planck Innovation GmbH (formerly Garching Innovation GmbH) and Alnylam Europe AG (formerly Ribopharma AG), dated July 30, 2003.

Other Third Party Agreements

1. Amended and Restated License and Collaboration Agreement among Alnylam, Isis and Regulus Therapeutics Inc., dated January 1, 2009, as amended on June 7, 2010, October 25, 2011, and August 2, 2013.

2. License and Collaboration Agreement between Alnylam and Takeda Pharmaceutical Company Limited dated May 27, 2008, as amended by letter agreements dated March 16, 2011 and August 18, 2009.

3. License and Collaboration Agreement between Alnylam and F. Hoffmann-La Roche Ltd. and Hoffmann-La Roche Inc. dated July 8, 2007, as amended by that certain letter amendment dated May 29, 2008. This License and Collaboration Agreement has been assigned to Arrowhead Research Corporation.

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 [***] of any additional running royalties to be paid to such third party up to [***] 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 [***] 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 1-8

Alnylam Current Chemistry Patents

[***]

Schedule 1-9

Alnylam Current Motif and Mechanism Patents

[***]

Schedule 1-11

Alnylam Excluded Technology

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

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

Schedule 1-13

Alnylam Exclusive Target Excluded Technology

[***]

Schedule 1-14

Alnylam Exclusive Target Patents

[***]

Schedule 1-17

Alnylam Extended Field Patents

[***]

Isis Current Chemistry Patents Schedule 1-52

[***]

Isis Current Motif and Mechanism Patents Schedule 1-53

[***]

ISIS EXCLUDED TECHNOLOGY SCHEDULE 1-57

The following schedule of Excluded Technology is provided by Isis Pharmaceuticals, Inc. to Alnylam Pharmaceuticals, Inc., in connection with 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 [***];
- [***] 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 [***] are excluded:

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

3. 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
[***]	[***]	[***]	[***]

4. Walder Patents (B)

The Walder Patents are excluded. "Walder Patents" means and includes [***].

5. 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.

6. 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.

7. 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.

8. Max-Planck-Innovation GmbH.

Isis is not granting Alnylam any sublicense under the Co-Exclusive License Agreement dated April 27, 2009 among Isis, Alnylam and Max-Planck-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.

Isis Exclusive Target Excluded Technology Schedule 1-59

The following schedule of Isis Exclusive Target Excluded Technology is provided by Isis Pharmaceuticals, Inc. to Alnylam Pharmaceuticals, Inc., in connection with 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 Isis Exclusive Target Excluded Technology and any other schedule or terms of the Agreement, this schedule will govern.

9. Intellectual property covering:

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

10. [***]/4'-Thio Chemistry.

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

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

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

11. 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
[***]	[***]	[***]	[***]

12. Walder Patents (B)

The Walder Patents are excluded. "Walder Patents" means and includes [***].

13. 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.

14. 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.

15. 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.

16. Max-Planck-Innovation GmbH.

Isis is not granting Alnylam any sublicense under the Co-Exclusive License Agreement dated April 27, 2009 among Isis, Alnylam and Max-Planck-Innovation GmbH.

(C) Isis cannot sublicense the technologies marked with this footnote.
(D) 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.

Isis Exclusive Target Patents Schedule 1-60

[***]

Isis Extended Field Patents Schedule 1-63

[***]

Isis Manufacturing Patents Schedule 1-66

[***]

Schedule 1-69

Isis Retained Targets

Isis Retained Special Targets:

[***]

Other Isis Retained Targets:

[***]

Isis Special Patents Schedule 1-73

[***]

Research Program Patents Schedule 1-97

[***]

Exhibit A

Isis Exclusive Targets

1. The human Factor XI gene (also known as coagulation factor XI, plasma thromboplastin antecedent, F11, FXI) and its protein product. As of the Second Restatement Date, the gene has NCBI Gene ID 2160, an example of an identifier for the Factor XI gene is NCBI RefSeq code NM_000128 and an example of an identifier for the Factor XI protein product is NCBI RefSeq code NP_000119.

2. The human Apo(a) gene (also known as apolipoprotein(a); LPA; Lipoprotein, Lp(a); Lp(a)) and its protein product. As of the Second Restatement Date, the gene has NCBI Gene ID 4018, an example of an identifier for the Apo(a) gene is NCBI RefSeq code NM_005577 and an example of an identifier for the Apo(a) protein product is NCBI RefSeq code NP_005568.

Exhibit B

Alnylam Exclusive Targets

1. The human antithrombin geneand its protein product, antithrombin (also known as SERPINC1, antithrombin3, AT3 and ATIII). As of the Second Restatement Date, an example of an identifier for the antithrombin gene is NCBI RefSeq code NM_000488 and an example of an identifier for the antithrombin protein product is NCBI RefSeq code NP_000479.

2. The human ALAS-1 gene and its protein product ALAS-1 (also known as ALAS, ALAS3, ALASH, aminolevulinate delta-synthase, Delta-ALA synthase, Delta-Aminolevulinate synthase 1, 5-aminolevulinic acid synthase 1, ALAS-H, 5-aminolevulinate synthase, MIG4, aminolevulinate synthase-1, AS1). As of the Second Restatement Date, an example of an identifier for the ALAS-1 gene is NCBI RefSeq code NM_000688 and an example of an identifier for the ALAS-1 protein product is NCBI RefSeq code NP_000679.

EXHIBIT 10.2

AMENDMENT #1 TO HTT RESEARCH, DEVELOPMENT, OPTION AND LICENSE AGREEMENT

This **AMENDMENT #1 TO THE RESEARCH, DEVELOPMENT, OPTION AND LICENSE AGREEMENT** (this "***Amendment***") is entered into and made effective as of the 9th day of January, 201**5** (the "***Amendment Date***") by and between **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("***Isis***"), and **F. HOFFMANN-LA ROCHE LTD**, a Swiss corporation, having its principal place of business at Grenzacherstrasse 124, 4070 Basel, Switzerland ("***Roche Basel***") and **HOFFMANN-LA ROCHE INC.**, a New Jersey corporation, having its principal place of business at 150 Clove Road, Suite 8, Little Falls, New Jersey 07424 ("***Roche Nutley***"; Roche Basel and Roche Nutley are collectively referred to as "***Roche***"). Isis and Roche are each referred to herein by name or as a "***Party***" or, collectively, as "***Parties***."

RECITALS

WHEREAS, Isis and Roche are parties to the HTT Research, Development, Option and License Agreement dated April 8th, 2013, as amended (the "***Agreement***");

WHEREAS, Isis and Roche desire to amend the Agreement to clarify its rights and obligations thereunder; and

NOW, THEREFORE, in consideration of the premises and mutual covenants herein contained, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties, intending to be legally bound, do hereby agree that Section 7.12 of the Agreement is amended by replaced with the following:

7.12. **No Challenge**. If, during the Agreement Term, solely with respect to rights to the [***] that are included (or, prior to Option exercise, are eligible to be included) in a license granted to Roche under Section 4.1.1, Roche, its Affiliates or Sublicensees, in the United States or any other country, (a) commence or otherwise voluntarily determine to participate in (other than as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order) any action or proceeding, challenging or denying the enforceability or validity of any claim within an issued patent or patent application within such [***], or (b) direct, support or actively assist any other Person (other than as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order) in bringing or prosecuting any action or proceeding challenging or denying the validity of any claim within an issued patent or patent application within such [***], then unless, within thirty (30) days after written notice from Isis, Roche rescinds any actions brought by Roche, its Affiliates, or Sublicensees, Isis may, to the extent permitted under Applicable Law, terminate this Agreement and the provisions of Section 10.4.1 and Section 10.4.2 will apply; [***].

Capitalized terms not otherwise defined herein will have the meanings given in the Agreement.

* - * - * - *

[Signature page follows]

IN WITNESS WHEREOF, the Parties have caused this Amendment to be executed by their duly authorized representatives as of the Amendment Date.

ISIS PHARMACEUTICALS, INC.

By: */s/ B. Lynne Parshall*
Name: B. Lynne Parshall
Title: Chief Operating Officer
Date:

F. HOFFMAN-LA ROCHE LTD

By: */s/ Dr. Christoph Sarry*
Name: Dr. Christoph Sarry
Title: Global Alliance Director
Date: 12 January 2015

By: */s/ Stefan Arnold*
Name: Stefan Arnold
Title: Head Legal Pharma

HOFFMAN-LA ROCHE INC.

By: */s/ John P Parise*
Name: John P Parise
Title: Authorized Signatory
Date: Jan 12, 2015

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: May 5, 2015

/s/ Stanley T. Crooke

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

EXHIBIT 31.2

CERTIFICATION

I, Elizabeth L. Hougen, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: May 5, 2015

/s/ Elizabeth L. Hougen

Elizabeth L. Hougen
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 Elizabeth L. Hougen, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Quarterly Report on Form 10-Q for the period ended March 31, 2015, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: May 5, 2015

/s/ Stanley T. Crooke	/s/ Elizabeth L. Hougen
Stanley T. Crooke, M.D., Ph.D. Chief Executive Officer	Elizabeth L. Hougen 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.