UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended June 30, 2014

OR

o TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF SECURITIES EXCHANGE ACT OF 1934

For the transition period from to

Commission file number 0-19125

Isis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

Delaware	**33-0336973**
(State or other jurisdiction of incorporation or organization)	(IRS Employer Identification No.)

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 x No o

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

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

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

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

The number of shares of voting common stock outstanding as of August 1, 2014 was 117,735,360.

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TRADEMARKS

Isis Pharmaceuticals® is a registered 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)

	June 30, 2014 (Unaudited)	December 31, 2013
ASSETS		
Current assets:		
Cash and cash equivalents	$ 94,081	$ 159,973
Short-term investments	496,754	496,788
Contracts receivable	41,941	11,102
Inventories	7,776	8,033
Investment in Regulus Therapeutics Inc.	56,678	52,096
Other current assets	8,567	7,518
Total current assets	705,797	735,510
Property, plant and equipment, net	86,321	86,198
Licenses, net	3,631	4,572
Patents, net	16,729	15,517
Deposits and other assets	5,299	5,359
Total assets	$ 817,777	$ 847,156
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 13,453	$ 11,009
Accrued compensation	6,430	12,168
Accrued liabilities	25,166	22,092
Current portion of long-term obligations	4,207	4,408
Current portion of deferred contract revenue	51,560	48,135
Total current liabilities	100,816	97,812
Long-term deferred contract revenue	120,387	142,790
23/4 percent convertible senior notes	153,700	150,334
Long-term obligations, less current portion	4,510	6,542
Long-term financing liability for leased facility	71,504	71,288
Total liabilities	450,917	468,766
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 117,669,618 and 116,471,371 shares issued and outstanding at June 30, 2014 and December 31, 2013, respectively	118	116
Additional paid-in capital	1,352,994	1,324,804
Accumulated other comprehensive income	24,719	21,080
Accumulated deficit	(1,010,971)	(967,610)
Total stockholders' equity	366,860	378,390
Total liabilities and stockholders' equity	$ 817,777	$ 847,156

See accompanying notes.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2014	**2013**	**2014**	**2013**
Revenue:				
Research and development revenue under collaborative agreements	$ 56,628	$ 37,615	$ 76,177	$ 79,285
Licensing and royalty revenue	448	477	9,060	2,166
Total revenue	57,076	38,092	85,237	81,451
Expenses:				
Research, development and patent expenses	59,264	42,631	112,712	80,944
General and administrative	4,462	3,389	8,842	6,811
Total operating expenses	63,726	46,020	121,554	87,755
Loss from operations	(6,650)	(7,928)	(36,317)	(6,304)
Other income (expense):				
Investment income	671	589	1,328	967
Interest expense	(4,961)	(4,808)	(9,904)	(9,603)
(Loss) gain on investments, net	(260)	840	137	1,898
Loss before income tax expense	(11,200)	(11,307)	(44,756)	(13,042)
Income tax (expense) benefit	(881)	1,181	1,395	1,244
Net loss	$ (12,081)	$ (10,126)	$ (43,361)	$ (11,798)
Basic and diluted net loss per share	$ (0.10)	$ (0.09)	$ (0.37)	$ (0.11)
Shares used in computing basic and diluted net loss per share	117,588	108,539	117,359	105,225

See accompanying notes.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2014	2013	2014	2013
Net loss	$ (12,081)	$ (10,126)	$ (43,361)	$ (11,798)
Unrealized (losses) gains on securities, net of tax	(4,456)	9,202	3,806	15,669
Reclassification adjustment for realized losses (gains) included in net loss	175	—	(167)	(1,163)
Comprehensive (loss) income	$ (16,362)	$ (924)	$ (39,722)	$ 2,708

See accompanying notes.

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

	Six Months Ended June 30,	
	2014	**2013**
Operating activities:		
Net loss	$ (43,361)	$ (11,798)
Adjustments to reconcile net loss to net cash (used in) provided by operating activities:		
Depreciation	3,141	3,375
Amortization of patents	543	584
Amortization of licenses	941	1,051
Amortization of premium on investments, net	3,847	2,382
Amortization of debt issuance costs	272	202
Amortization of 2¾ percent convertible senior notes discount	3,366	3,109
Amortization of long-term financing liability for leased facility	3,306	3,276
Stock-based compensation expense	14,776	5,505
Gain on investments, net	(137)	(1,898)
Non-cash losses related to patents, licensing and property, plant and equipment	325	263
Tax benefit from other unrealized gains on securities	(1,395)	-
Changes in operating assets and liabilities:		
Contracts receivable	(30,839)	(1,502)
Inventories	257	(2,188)
Other current and long-term assets	(694)	(492)
Accounts payable	1,991	(1,833)
Accrued compensation	(5,738)	(847)
Deferred rent	69	98
Accrued liabilities	1,965	(135)
Deferred contract revenue	(18,978)	13,012
Net cash (used in) provided by operating activities	(66,343)	12,164
Investing activities:		
Purchases of short-term investments	(179,196)	(144,250)
Proceeds from the sale of short-term investments	175,777	96,926
Purchases of property, plant and equipment	(3,100)	(591)
Acquisition of licenses and other assets, net	(1,791)	(1,171)
Proceeds from the sale of strategic investments	737	1,938
Net cash used in investing activities	(7,573)	(47,148)
Financing activities:		
Proceeds from equity awards	13,416	36,879
Net proceeds from public common stock offering	-	173,223
Proceeds from equipment financing arrangement	-	2,513
Principal payments on debt and capital lease obligations	(5,392)	(5,573)
Net cash provided by financing activities	8,024	207,042
Net (decrease) increase in cash and cash equivalents	(65,892)	172,058
Cash and cash equivalents at beginning of period	159,973	124,482
Cash and cash equivalents at end of period	$ 94,081	$ 296,540
Supplemental disclosures of cash flow information:		
Interest paid	$ 2,920	$ 2,977
Income taxes paid	$ -	$ 2
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 453	$ 1,055

See accompanying notes.

NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
June 30, 2014
(Unaudited)

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three and six months ended June 30, 2014 and 2013 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2013. 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, 2013 included in our Annual Report on Form 10-K filed with the Securities and Exchange Commission ("SEC").

The condensed consolidated financial statements include the accounts of Isis Pharmaceuticals, Inc. ("we", "us" or "our") and our wholly owned subsidiary, Symphony GenIsis, Inc., which is currently inactive.

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 condensed consolidated balance sheet.

Research and development revenue under collaborative agreements

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. 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 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 and 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.

In December 2012, we entered into a collaboration agreement with AstraZeneca to discover and develop antisense therapeutics against five cancer targets. As part of the collaboration, we received a $25 million upfront payment in December 2012 and a $6 million payment in June 2013 when AstraZeneca elected to continue the research collaboration. We are also eligible to receive milestone payments, license fees for the research program targets and royalties on any product sales of drugs resulting from this collaboration. In exchange, we granted AstraZeneca an exclusive license to develop and commercialize ISIS-STAT3$_{Rx}$ and ISIS-AR$_{Rx}$. 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$_{Rx}$, which we completed earlier this year. We are also responsible for completing an ongoing clinical study of ISIS-STAT3$_{Rx}$. AstraZeneca is responsible for all other global development, regulatory and commercialization activities for ISIS-STAT3$_{Rx}$ and ISIS-AR$_{Rx}$. 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$_{Rx}$ for the treatment of cancer;
- The development services we are performing for ISIS-STAT3$_{Rx}$;
- The exclusive license we granted to AstraZeneca to develop and commercialize ISIS-AR$_{Rx}$ and the research services we performed for ISIS-AR$_{Rx}$; and
- The option to license up to three drugs under a research program and the research services we will perform for this program.

We determined that the ISIS-STAT3$_{Rx}$ license had stand-alone value because it is an exclusive license that gives AstraZeneca the right to develop ISIS-STAT3$_{Rx}$ or to sublicense its rights. In addition, ISIS-STAT3$_{Rx}$ 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$_{Rx}$ license and the development services for ISIS-STAT3$_{Rx}$ to be separate units of accounting. We recognized the portion of the consideration allocated to the ISIS-STAT3$_{Rx}$ license immediately because we delivered the license and earned the revenue. We are recognizing as revenue the amount allocated to the development services for ISIS-STAT3$_{Rx}$ over the period of time we perform services. The ISIS-AR$_{Rx}$ license is also an exclusive license. At the inception of the agreement, ISIS-AR$_{Rx}$ 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$_{Rx}$. As a result, we determined that the ISIS-AR$_{Rx}$ license did not have stand-alone value and we combined the ISIS-AR$_{Rx}$ 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 initial allocable arrangement consideration was the $25 million upfront payment because it was the only payment that was fixed and determinable when we entered into the agreement. In June 2013, we increased the allocable consideration to $31 million when we received the $6 million payment. There was considerable uncertainty at the date of the agreement as to whether we would earn the milestone payments, royalty payments, payments for manufacturing clinical trial materials or payments for finished drug product. As such, we did not include those payments in the allocable consideration.

We allocated the allocable consideration 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$_{Rx}$ and ISIS-AR$_{Rx}$ 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.

As a result of the allocation, we recognized $9.3 million of the $25 million upfront payment for the ISIS-STAT3$_{Rx}$ license in December 2012 and we recognized $2.2 million of the $6 million payment for the ISIS-STAT3$_{Rx}$ license in June 2013. We are recognizing the remaining $19.5 million of the $31 million over the estimated period of our performance. Assuming a constant selling price for the other elements in the arrangement, if there was an assumed ten percent increase or decrease in the estimated selling price of the ISIS-STAT3$_{Rx}$ license, we determined that the revenue we would have allocated to the ISIS-STAT3$_{Rx}$ license would change by approximately seven percent, or $750,000, from the amount we recorded.

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 amortize revenue over such period. We have made estimates of our continuing obligations under numerous agreements and in certain instances the timing of satisfying these obligations is difficult to estimate. 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. For example, we adjusted the period of performance on our collaboration with GlaxoSmithKline, or GSK, and our ISIS-SMN$_{Rx}$ collaboration with Biogen Idec. As a result of adding two new development candidates, ISIS-HBV$_{Rx}$ and ISIS-GSK4$_{Rx}$, to our collaboration with GSK, our period of performance was extended beyond our initial estimate. Therefore, we extended the amortization period to correspond to the new extended period of performance. Similarly, with our ISIS-SMN$_{Rx}$ collaboration, we extended the amortization period to correspond to the expansion of the Phase 3 study in infants with Spinal Muscular Atrophy, or SMA. Since we extended the amortization period for our GSK collaboration and our ISIS-SMN$_{Rx}$ collaboration, revenue from the amortization of upfront payments for these collaborations will be $3.3 million less in 2014 compared to 2013.

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 Idec:

- In January 2012, we entered into a collaboration agreement with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ for 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 Idec 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 Idec to discover and develop antisense drugs against three targets to treat neurological or neuromuscular disorders. As part of the collaboration, we received a $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 Idec to leverage antisense technology to advance the treatment of neurological diseases. We granted Biogen Idec 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 Idec is responsible for the creation and development of small molecule treatments and biologics.

All four of these collaboration agreements give Biogen Idec the option or options to license one or more drugs resulting from the specific collaboration. If Biogen Idec 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 Idec achieves pre-specified regulatory milestones, and royalties on any product sales of drugs resulting from these collaborations.

We evaluated all four of the Biogen Idec 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 Idec 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.

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 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. 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 all future development, regulatory and commercialization milestones are substantive. For example, we consider milestones associated with our strategic alliance with Biogen Idec substantive because we are using our antisense drug discovery platform to discover and develop new drugs against targets for neurological diseases. Alternatively, we considered milestones associated with our strategic alliance with Alnylam Pharmaceuticals, Inc. substantive because we provided 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 the estimated period of performance, if any. We consider milestone payments related to progression of a drug through the development and regulatory stages of its life cycle to be substantive milestones because the level of effort and inherent risk associated with these events is high. Further information about our collaborative arrangements can be found in Note 7, *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 sublicensing revenue from Alnylam related to its collaboration with Genzyme because we have no performance obligations related to Alnylam's relationship with Genzyme 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 June 30, 2014 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. The cost method investments we hold are in small companies, which we call satellite companies, and realization of our equity position in those companies is uncertain. In those circumstances 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 six months ended June 30, 2014 and 2013. Total inventory, which consisted of raw materials, was $7.8 million and $8.0 million as of June 30, 2014 and December 31, 2013, 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.

Reclassifications

We have reclassified certain immaterial prior period amounts to conform to the current period presentation. Certain amounts previously reported as research and development revenue have been reclassified to licensing and royalty revenue to conform to the current period presentation.

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 and six months ended June 30, 2014 and 2013, 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:

- 2¾ percent convertible senior notes;
- Dilutive stock options; and
- Restricted stock units.

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 June 30, 2014 and December 31, 2013, we had collaborative arrangements with five entities that we considered to be variable interest entities. We are not the primary beneficiary for any of these entities because 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 June 30, 2014, the total carrying value of our investments in variable interest entities was $59.0 million, and was primarily related to our investment in Regulus. Our maximum exposure to loss related to these 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 securities, net of taxes, and adjustments we made to reclassify realized gains and losses on securities 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 and six months ended June 30, 2014 and 2013 (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2014	2013	2014	2013
Beginning balance accumulated other comprehensive income	$ 29,000	$ 17,784	$ 21,080	$ 12,480
Unrealized (losses) gains on securities, net of tax (1)	(4,456)	9,202	3,806	15,669
Amounts reclassified from accumulated other comprehensive income (2)	175	-	(167)	(1,163)
Net current period other comprehensive income (loss)	(4,281)	9,202	3,639	14,506
Ending balance accumulated other comprehensive income	$ 24,719	$ 26,986	$ 24,719	$ 26,986

(1) Other comprehensive income for the three and six months ended June 30, 2014 includes income tax benefit of $2.9 million and income tax expense of $2.5 million, respectively, compared to an income tax benefit of $2.9 million and $10.0 million for same periods in 2013.

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

Convertible debt

In August 2012, we completed a $201.3 million offering of convertible senior notes, which mature in 2019 and bear interest at 2 ¾ percent. In September 2012, we used a substantial portion of the net proceeds from the issuance of the 2 ¾ percent notes to redeem our 2 5/8 percent convertible subordinated notes. We account for our 2 ¾ percent notes by separating the liability and equity components of the instrument in a manner that reflects our nonconvertible debt borrowing rate. As a result, we assigned a value to the debt component of our 2 ¾ percent notes equal to the estimated fair value of similar debt instruments without the conversion feature, which resulted in us recording the debt instrument at a discount. We are amortizing the debt discount over the life of these 2 ¾ percent notes as additional non-cash interest expense utilizing the effective interest method.

Segment information

We operate in a single segment, Drug Discovery and Development operations, because our chief decision maker reviews operating results on an aggregate basis and manages our operations as a single operating 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 Employee Stock Purchase Plan, or 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 the 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 six months ended June 30, 2014 and 2013, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Six Months Ended June 30,	
	2014	2013
Risk-free interest rate	1.6%	1.0%
Dividend yield	0.0%	0.0%
Volatility	50.6%	51.5%
Expected life	4.6 years	5.1 years

ESPP:

	Six Months Ended June 30,	
	2014	2013
Risk-free interest rate	0.1%	0.1%
Dividend yield	0.0%	0.0%
Volatility	59.0%	61.4%
Expected life	6 months	6 months

Board of Director Stock Options:

	Six Months Ended June 30,	
	2014	2013
Risk-free interest rate	2.3%	2.3%
Dividend yield	0.0%	0.0%
Volatility	53.3%	52.4%
Expected life	7.1 years	7.3 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 and the Board of Directors for the six months ended June 30, 2014 was $46.49 and $49.09, respectively.

The following table summarizes stock-based compensation expense for the three and six months ended June 30, 2014 and 2013 (in thousands), which was allocated as follows:

	Three Months Ended June 30,		Six Months Ended June 30,	
	2014	2013	2014	2013
Research, development and patent expenses	$ 6,401	$ 2,252	$ 12,274	$ 4,798
General and administrative	1,307	384	2,503	707
Total	$ 7,708	$ 2,636	$ 14,777	$ 5,505

Non-cash stock-based compensation was $7.7 million and $14.8 million for the three and six months ended June 30, 2014, respectively, and increased compared to $2.6 million and $5.5 million for the same periods in 2013 primarily due to the increase in our stock price. As of June 30, 2014, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $29.0 million and $13.2 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 1.3 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 is effective for fiscal years, and interim periods within those years, beginning after December 15, 2016. The guidance allows entities 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 will adopt this guidance in our fiscal year beginning January 1, 2017. We are currently evaluating an adoption method and the impact this guidance will have on our consolidated financial position, results of operations, cash flows and disclosures and are currently unable to estimate the impact of this guidance.

3. Investments

As of June 30, 2014, we have invested our excess cash primarily 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 (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 June 30, 2014:

One year or less	53%
After one year but within two years	36%
After two years but within three years	11%
Total	100%

As illustrated above, we primarily invest our excess cash in short-term instruments with 89 percent of our available-for-sale securities having 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 June 30, 2014, we had an ownership interest of less than 20 percent in each of two private companies and four public companies with which we conduct business. The privately-held companies are Santaris Pharma A/S (formerly Pantheco A/S) and Atlantic Pharmaceuticals Limited. The publicly-traded companies are Antisense Therapeutics Limited, Achaogen Inc., iCo Therapeutics Inc., and Regulus. We account for equity investments in the privately-held companies 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):

June 30, 2014	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Available-for-sale securities:					
Corporate debt securities(1)	$ 166,635	$ 115	$ (39)	$ —	$ 166,711
Debt securities issued by U.S. government agencies (1)	61,421	14	(38)	—	61,397
Debt securities issued by the U.S. Treasury	9,245	17	—	—	9,262
Debt securities issued by states of the United States and political subdivisions of the states	43,527	17	(42)	—	43,502
Total securities with a maturity of one year or less	280,828	163	(119)	—	280,872
Corporate debt securities	173,089	186	(139)	—	173,136
Debt securities issued by U.S. government agencies	37,048	4	(76)	—	36,976
Debt securities issued by the U.S. Treasury	1,997	5	—	—	2,002
Debt securities issued by states of the United States and political subdivisions of the states	22,861	68	(40)	—	22,889
Total securities with a maturity of more than one year	234,995	263	(255)	—	235,003
Total available-for-sale securities	$ 515,823	$ 426	$ (374)	$ —	$ 515,875

	Cost	Unrealized		Other-Than-Temporary Impairment	Estimated

June 30, 2014	Basis	Gains	Losses	Loss	Fair Value
Equity securities:					
Regulus Therapeutics Inc.	$ 15,526	$ 41,152	$ —	$ —	$ 56,678
Securities included in other current assets	1,269	1,856	—	(1,269)	1,856
Securities included in deposits and other assets	625	—	—	—	625
Total equity securities	$ 17,420	$ 43,008	$ —	$ (1,269)	$ 59,159
Total available-for-sale and equity securities	$ 533,243	$ 43,434	$ (374)	$ (1,269)	$ 575,034

December 31, 2013	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Available-for-sale securities:					
Corporate debt securities(1)	$ 142,096	$ 75	$ (27)	$ —	$ 142,144
Debt securities issued by U.S. government agencies (1)	23,242	22	(16)	—	23,248
Debt securities issued by the U.S. Treasury	6,239	6	—	—	6,245
Debt securities issued by states of the United States and political subdivisions of the states	8,082	6	(28)	—	8,060
Total securities with a maturity of one year or less	179,659	109	(71)	—	179,697
Corporate debt securities	265,969	177	(393)	—	265,753
Debt securities issued by U.S. government agencies	41,308	3	(127)	—	41,184
Debt securities issued by the U.S. Treasury	9,062	21	—	—	9,083
Debt securities issued by states of the United States and political subdivisions of the states	14,186	37	(28)	—	14,195
Total securities with a maturity of more than one year	330,525	238	(548)	—	330,215
Total available-for-sale securities	$ 510,184	$ 347	$ (619)	$ —	$ 509,912

December 31, 2013	Cost Basis	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Equity securities:					
Regulus Therapeutics Inc.	$ 15,526	$ 36,570	$ —	$ —	$ 52,096
Securities included in other current assets	1,538	618	—	(880)	1,276
Securities included in deposits and other assets	625	—	—	—	625
Total equity securities	$ 17,689	$ 37,188	$ —	$ (880)	$ 53,997
Total available-for-sale and equity securities	$ 527,873	$ 37,535	$ (619)	$ (880)	$ 563,909

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

Investments we considered to be temporarily impaired at June 30, 2014 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	135	$ 130,498	$ (167)	$ 8,342	$ (11)	$ 138,840	$ (178)
Debt securities issued by U.S. government agencies	12	65,917	(114)	-	-	65,917	(114)
Debt securities issued by states of the United States and political subdivisions of the states	12	9,800	(82)	-	-	9,800	(82)
Total temporarily impaired securities	159	$ 206,215	$ (363)	$ 8,342	$ (11)	$ 214,557	$ (374)

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 an entity to develop its own assumptions. Our Level 3 investments include 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. 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 six months ended June 30, 2014 there were no transfers between our Level 1 and Level 2 investments. We use the end of reporting period method for determining transfers between levels.

We measure the following major security types at fair value on a recurring basis. We break down the inputs used to measure fair value for these assets at June 30, 2014 and December 31, 2013 as follows (in thousands):

	At June 30, 2014	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents	$ 70,638	$ 70,638	$ —	$ —
Corporate debt securities (1)	339,847	—	339,847	—
Debt securities issued by U.S. government agencies (1)	98,373	—	98,373	—
Debt securities issued by the U.S. Treasury	11,264	11,264	—	—
Debt securities issued by states of the United States and political subdivisions of the states (1)	66,391	—	66,391	—
Investment in Regulus Therapeutics Inc.	56,678	56,678	—	—
Equity securities (2)	2,481	625	—	1,856
Total	$ 645,672	$ 139,205	$ 504,611	$ 1,856

	At December 31, 2013	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents	$ 133,233	$ 133,233	$ —	$ —
Corporate debt securities (1)	407,897	—	407,897	—
Debt securities issued by U.S. government agencies	64,432	—	64,432	—
Debt securities issued by the U.S. Treasury	15,328	15,328	—	—
Debt securities issued by states of the United States and political subdivisions of the states	22,255	—	22,255	—
Investment in Regulus Therapeutics Inc.	52,096	52,096	—	—
Equity securities (2)	1,276	1,276	—	—
Total	$ 696,517	$ 201,933	$ 494,584	$ —

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

(2) Included in other current assets on our condensed consolidated balance sheet.

We classified as Level 3 the fair value of our investments in the equity securities of publicly-held biotechnology companies that are subject to trading restrictions for which we calculate a lack of marketability discount on the fair value of the investments. We consider the inputs we used to calculate the lack of marketability discount and, as a result, we categorized these investments as Level 3. We determined 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 ended.

As of January 1, 2013, we classified the fair value measurements of our investments in the equity securities of Regulus and Sarepta Therapeutics, Inc. as Level 3. In the six months ended June 30, 2013, we sold all of the common stock of Sarepta that we owned resulting in a realized gain of $1.1 million. As of June 30, 2013, our Level 3 investments consisted of our investment in Regulus, with a gross fair value of $69.2 million and a lack of marketability discount of $7.0 million. In the fourth quarter of 2013, we re-classified our investment in Regulus to a Level 1 investment because the contractual trading restrictions on the Regulus shares we own ended. We recognize transfers between levels of the fair value hierarchy on the date of the event or change in circumstances that caused the transfer. In March 2014, Achaogen completed an initial public offering. As a result, we stopped using the cost method of accounting for our equity investment in Achaogen and instead we began accounting for it at fair value, which includes a lack of marketability discount because there are restrictions on when we can trade the securities. As of June 30, 2014, we classified our investment in the equity securities of Achaogen as Level 3 with a gross fair value of $2.1 million and a lack of marketability discount of $214,000.

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 June 30, 2014 (in thousands):

Beginning balance of Level 3 investments	$ -
Total gain included in accumulated other comprehensive income (loss)	1,856
Ending balance of Level 3 investments	$ 1,856

Other Fair Value Disclosures

Our 2¾ percent convertible notes had a fair value of $448.3 million at June 30, 2014. We determine the fair value of our 2¾ percent convertible notes based on quoted market prices for these notes, which is a Level 2 measurement.

5. Concentration of Business Risk

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2014	2013	2014	2013

Partner A	60%	19%	52%	14%
Partner B	27%	40%	22%	22%
Partner C	0%	20%	0%	40%
Partner D	6%	6%	8%	15%

Contract receivables from three significant partners comprised approximately 97 percent of our contract receivables at June 30, 2014. Contract receivables from three significant partners comprised approximately 91 percent of our contract receivables at December 31, 2013.

6. 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 six months ended June 30, 2014 and 2013, we recorded unrealized gains on our investments in available-for-sale securities in other comprehensive income net of taxes. As a result, for the six months ended June 30, 2014 and 2013, we recorded a $1.4 million and $1.2 million tax benefit, respectively, on our condensed consolidated statements of operations and a $2.5 million and $10.0 million tax expense, respectively, in other comprehensive income.

7. Collaborative Arrangements and Licensing Agreements

Traditional Pharmaceutical Alliances and Licensing

AstraZeneca

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 agreement, we granted AstraZeneca an exclusive license to develop and commercialize ISIS-STAT3$_{Rx}$ and ISIS-AR$_{Rx}$ for the treatment of cancer and an option to license up to three cancer drugs under a separate research program. We are eligible to receive milestone payments and license fees from AstraZeneca as programs advance in development. In addition, we are eligible to receive royalties up to the low to mid-teens on any product sales of drugs resulting from this collaboration. Under the terms of the agreement, we received $31 million in upfront and near-term payments comprised of a $25 million upfront payment we received in December 2012 and a $6 million payment we received in June 2013, of which we recognized $11.5 million upon receipt of the payments. We are recognizing the remaining $19.5 million as follows:

- $11.2 million related to the ISIS-AR$_{Rx}$ program, which we amortized through March 2014;
- $7.6 million related to the option to license three drugs under a separate research program, which we are amortizing through December 2016; and
- $0.7 million related to the ISIS-STAT3$_{Rx}$ program, which we are amortizing through November 2014.

Together with AstraZeneca, we are evaluating ISIS-STAT3$_{Rx}$ in patients with advanced cancer. AstraZeneca is conducting a Phase 1b/2a clinical study of ISIS-STAT3$_{Rx}$ in patients with advanced metastatic hepatocellular carcinoma, or HCC. We are also conducting a clinical study evaluating ISIS-STAT3$_{Rx}$ in patients with advanced lymphomas, including patients with diffuse large b-cell lymphoma. We are responsible for completing our clinical study in patients with advanced lymphomas and AstraZeneca is responsible for all other development activities for ISIS-STAT3$_{Rx}$. In June 2013, we and AstraZeneca added a second development candidate, ISIS-AR$_{Rx}$, to our collaboration. ISIS-AR$_{Rx}$ is an antisense drug we designed to treat patients with prostate cancer by inhibiting the production of the androgen receptor, or AR. Through June 2014, we have earned $25 million in milestone payments related to the development of ISIS-AR$_{Rx}$, including a $15 million milestone payment we earned in June 2014 when we initiated a Phase 1 study of ISIS-AR$_{Rx}$. If AstraZeneca successfully develops ISIS-STAT3$_{Rx}$, ISIS-AR$_{Rx}$, and three drugs under the research program, we could receive substantive milestone payments of more than $955 million, including up to $300.5 million for the achievement of development milestones and up to $655 million for the achievement of regulatory milestones. We could earn the next milestone payment of $15 million if we meet pre-agreed efficacy and safety criteria in our ongoing ISIS-STAT3$_{Rx}$ study in patients with advanced cancer.

In August 2013, we added another collaboration program with AstraZeneca to discover and develop an antisense drug against an undisclosed target. AstraZeneca has the option to license a drug resulting from this research collaboration, and if AstraZeneca exercises its option, it will be responsible for all further development and commercialization of the drug. We received a $750,000 upfront payment, which we are amortizing through December 2015. We are eligible to receive license fees and substantive milestone payments of $163.2 million, including up to $45.3 million for the achievement of research and development milestones and up to $105 million for regulatory milestones. We will earn the next $3.3 million milestone payment if AstraZeneca selects a development candidate under this collaboration. In addition, we are eligible to receive royalties up to the low teens on sales from any product that AstraZeneca successfully commercializes under this collaboration program.

Our agreement with AstraZeneca 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:

- AstraZeneca may terminate the agreement or any program at any time by providing written notice to us;
- AstraZeneca may terminate the agreement or any program by providing written notice if we undergo a change of control with a third party; and
- Either we or AstraZeneca 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.

During the three and six months ended June 30, 2014, we earned revenue of $15.6 million and $19.1 million, respectively, from our relationship with AstraZeneca which represented 27 percent and 22 percent, respectively, of our total revenue for those periods. In comparison, we earned revenue of $15.3 million and $17.8 million for the same periods in 2013. Our balance sheet at June 30, 2014 included deferred revenue of $5.5 million related to our relationship with AstraZeneca.

Biogen Idec

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

ISIS-SMN$_{Rx}$

In January 2012, we entered into a global collaboration agreement with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ for the treatment of SMA. We received an upfront payment of $29 million, which we are amortizing through February 2017. We are eligible to receive a license fee, milestone payments and royalties up to the mid-teens on any product sales of ISIS-SMN$_{Rx}$. Biogen Idec has the option to license ISIS-SMN$_{Rx}$ until completion of the first successful Phase 2/3 study or the completion of two Phase 2/3 studies. If Biogen Idec exercises its option, it will pay us a license fee and will assume global development, regulatory and commercialization responsibilities.

We and Biogen Idec amended our original agreement to reflect changes made to the clinical development plan for ISIS-SMN$_{Rx}$ in January 2014. We and Biogen Idec added a new open-label extension study, which is being offered to those children with SMA who have completed dosing in our previous studies. We also expanded the dosing in the Phase 2 study in infants with SMA. In addition, we increased the number of patients to be included in the Phase 3 studies in infants. As a result of these changes, we and Biogen Idec agreed to increase the payments that we are eligible to receive under this collaboration by nearly $35 million.

In July 2014, we initiated the Phase 3 study evaluating ISIS-SMN$_{Rx}$ in infants with SMA. In addition, we are evaluating ISIS-SMN$_{Rx}$ in a Phase 2 open-label, multiple-dose, dose-escalation study in children with SMA and a Phase 2 open-label, multiple-dose, dose-escalation pilot study in infants with SMA. Through July 2014, we have earned $17.3 million in payments for advancing ISIS-SMN$_{Rx}$, including $9.3 million in payments we earned in the first quarter of 2014 related to the amendments made to the clinical development plan for ISIS-SMN$_{Rx}$. Accounting rules require us to amortize the $9.3 million we received related to the amendment of the clinical development plan for ISIS-SMN$_{Rx}$ over our estimated period of performance, which is as follows:

- $3.8 million related to the Phase 2 studies in children and infants with SMA, which we are amortizing through July 2014; and
- $5.5 million related to an open-label extension study in children with SMA, which we are amortizing through December 2014.

Under the terms of the amended agreement, we are eligible to receive up to $303.8 million in a license fee and payments, including $78.8 million in substantive milestone and other payments associated with the clinical development of ISIS-SMN$_{Rx}$ prior to licensing and $150 million in substantive milestone payments if Biogen Idec achieves pre-specified regulatory milestones. We will earn the next milestone payment of $18 million if we dose the first patient in the Phase 3 study in infants with SMA, which is designed to support marketing registration for ISIS-SMN$_{Rx}$ in the United States and Europe.

ISIS-DMPK$_{Rx}$

In June 2012, we and Biogen Idec entered into a second and separate collaboration and license agreement to develop and commercialize a novel antisense drug targeting DMPK for the treatment of myotonic dystrophy type 1, or DM1, ISIS-DMPK$_{Rx}$. We are responsible for global development of the drug through the completion of the first Phase 2 clinical trial. Biogen Idec has the option to license the drug through the completion of the first Phase 2 trial. 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. As of June 30, 2014, we have earned $24 million in substantive milestone payments associated with the clinical development of ISIS-DMPK$_{Rx}$, including a $14 million milestone payment we earned in June 2014 when we initiated a Phase 1 study for ISIS-DMPK$_{Rx}$. We are eligible to receive up to another $35 million in milestone payments associated with the development of ISIS-DMPK$_{Rx}$ prior to licensing. We are also eligible to receive up to $130 million in milestone payments if Biogen Idec 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. We will earn the next milestone payment of $35 million if we initiate a Phase 2 study for ISIS-DMPK$_{Rx}$.

Neurology

In December 2012, we and Biogen Idec entered into a third and separate collaboration to develop and commercialize novel antisense drugs to three targets to treat neurological or neuromuscular diseases. We are responsible for the development of the drugs through the completion of the initial Phase 2 clinical study. Biogen Idec has the option to license a drug from each of the three programs through the completion of Phase 2 studies. 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 could 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 could also receive up to $130 million in milestone payments if Biogen Idec 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. We will earn the next milestone payment of $10 million if we initiate an IND-enabling toxicology study for a development candidate identified under this collaboration.

Strategic Neurology

In September 2013, we and Biogen Idec entered into a fourth and separate collaboration, 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 Idec 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 six years, and may be extended for any drug development programs being pursued under the collaboration. 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 Idec. If we have a change of control during the first six years of the collaboration, we may be required to refund Biogen Idec 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 Idec 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. We will usually be responsible for drug discovery and early development of antisense drugs and Biogen Idec will have the option to license antisense drugs after Phase 2 proof of concept. Biogen Idec will then be responsible for later phase development and commercialization of the licensed drug. 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, such as small molecules or monoclonal antibodies are chosen, we are eligible to receive up to $90 million in substantive milestone payments, including up to $57 million for the achievement of research and development milestones and up to $55 million for the achievement of regulatory milestones. Biogen Idec will be responsible for all of the drug discovery and development activities for drugs using other modalities. In addition, we are eligible to receive single-digit royalties on any product sales of any drugs using non-antisense modalities developed under this collaboration. In June 2014, we earned a $10 million milestone payment when Biogen Idec chose the first target to advance under this collaboration. We could earn the next milestone payment of up to $10 million if we initiate an IND-enabling toxicology study for a target under this collaboration.

Each of our agreements with Biogen Idec will continue until the earlier of the date all of Biogen Idec's options to obtain the exclusive licenses under the applicable agreement expire unexercised or, if Biogen Idec 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 Idec 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 Idec 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 Idec may terminate the affected program by providing written notice to the other party; and
- Either we or Biogen Idec 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 and six months ended June 30, 2014, we earned revenue of $34.5 million and $44.7 million, respectively, from our relationship with Biogen Idec, which represented 60 percent and 52 percent of our total revenue for those periods. In comparison, we earned revenue of $7.4 million and $11.2 million for the same periods in 2013. Our balance sheet at June 30, 2014 included deferred revenue of $136.3 million related to our relationship with Biogen Idec.

GlaxoSmithKline

In March 2010, we entered into a strategic alliance with GSK, for up to six programs, 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. This alliance allows us to control and facilitate development of drugs while still being eligible to receive milestone payments as we advance these drugs in clinical development. Our strategic alliance currently includes five active programs. Under the terms of the agreement, we received a $35 million upfront payment and in May 2011 we received a $3 million payment when GSK expanded the collaboration. In addition, we are eligible to receive on average up to $20 million in milestone payments through Phase 2 proof-of-concept for each program, except for ISIS-TTR_{Rx} and the fifth target, which we describe below. 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 development and commercialization for such drug.

In October 2012, we and GSK amended the original agreement to reflect an accelerated clinical development plan for ISIS-TTR_{Rx}. Under the amended terms of the agreement, we received a $2.5 million upfront payment in December 2012. Through June 2014, we have received $26 million primarily in milestone payments from GSK related to the development of ISIS-TTR_{Rx}. In July 2014, we earned a $1 million milestone payment for further advancing the Phase 2/3 study of ISIS-TTR_{Rx}. We are eligible to earn an additional $43 million in pre-licensing milestone payments 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 September 2013, we designated ISIS-HBV_{Rx}, formerly ISIS-$GSK3_{Rx}$, as a development candidate under our collaboration with GSK. ISIS-HBV_{Rx} is an antisense drug designed to reduce the production of viral proteins associated with hepatitis B virus, or HBV, infection and replication. In June 2014, we amended our agreement to modify the development plans for ISIS-HBV_{Rx}. As a result, we received a $1 million payment. Through June 2014, we have earned $10 million in substantive milestone payments associated with advancing the ISIS-HBV_{Rx} program.

In November 2013, we designated ISIS-$GSK4_{Rx}$ as a development candidate under our collaboration with GSK and earned a $5 million milestone payment. ISIS-$GSK4_{Rx}$ is an antisense drug we designed to treat an undisclosed ocular disease. In April 2014, we and GSK amended our agreement to modify the development plans for ISIS-$GSK4_{Rx}$ and for the fifth target in our collaboration. Under the amended terms of the agreement, we are eligible to receive up to $142 million in a license fee, milestone and other payments for the advancement of the fifth target.

Under our agreement, if GSK successfully develops all five programs for one or more indications and achieves pre-agreed sales targets, we could receive license fees and substantive milestone payments of more than $1.2 billion, including up to $172 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. We will earn the next $1.5 million milestone payment if we initiate an IND-enabling study of ISIS-$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 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 and six months ended June 30, 2014, we earned revenue of $3.5 million and $6.8 million, respectively, from our relationship with GSK, which represented six percent and eight percent, respectively, of our total revenue for those periods. In comparison, we earned revenue of $2.3 million and $12.2 million for the same periods in 2013. Our balance sheet at June 30, 2014 included deferred revenue of $9.1 million related to our relationship with GSK, $7.9 million of which is related to the upfront payments associated with our collaboration with GSK that we are amortizing through our estimated period of performance of July 2015.

Roche

In April 2013, we formed an alliance with Hoffman-La Roche Inc. and F. Hoffmann-La Roche Ltd., collectively Roche, to develop treatments for Huntington's disease based on our antisense technology. Roche has the option to license the drugs from us through the completion of the first Phase 1 trial. Prior to option exercise, we are responsible for the discovery and development of an antisense drug targeting huntingtin, or HTT, protein. We are also working collaboratively with Roche on the discovery of an antisense drug utilizing Roche's "brain shuttle" program. If Roche exercises its option, it will be responsible for global development, regulatory and commercialization activities for any drug arising out of the collaboration. Under the terms of the agreement, we received an upfront payment of $30 million in April 2013, which we are amortizing through April 2017. We are eligible to receive up to $362 million in a license fee and substantive milestone payments including up to $67 million for the achievement of development milestones, up to $170 million for the achievement of regulatory milestones and up to $80 million for the achievement of commercialization milestones. In addition, we are eligible to receive up to $136.5 million in milestone payments for each additional drug successfully developed and up to $50 million in commercial milestones if a drug using Roche's proprietary brain shuttle technology is successfully commercialized. We are also eligible to receive tiered royalties up to the mid-teens on any product sales of drugs resulting from this alliance. We will earn the next milestone payment of $22 million if we initiate a Phase 1 trial for a drug targeting HTT protein.

Our alliance with Roche will continue until the earlier of the date Roche's option to obtain the exclusive license under the agreement expires unexercised or, if Roche exercises its option, until the expiration of all payment obligations under the agreement. In addition, the agreement may terminate early under the following situations:

- Roche may terminate the agreement at any time by providing written notice to us;
- Either we or Roche may terminate the agreement by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement or if the other party becomes insolvent; and

- Either we or Roche may terminate the brain shuttle program if at least one development candidate is not designated under such program by a mutually agreed deadline.

During the three and six months ended June 30, 2014, we earned revenue of $2.4 million and $4.4 million, respectively, from our relationship with Roche. In comparison, we earned revenue of $1.3 million for the three and six months ended June 30, 2013. Our balance sheet at June 30, 2014 included deferred revenue of $21.0 million related to our relationship with Roche.

Satellite Company Collaborations

Achaogen, Inc.

In 2006, we exclusively outlicensed to Achaogen, Inc. specific know-how, patents and patent applications relating to aminoglycosides. In exchange, Achaogen agreed to certain payment obligations related to aminoglycosides Achaogen developed. Aminoglycosides are a class of small molecule antibiotics that inhibit bacterial protein synthesis and that physicians use to treat serious bacterial infections. Achaogen is developing plazomicin, an aminoglycoside Achaogen discovered based on the technology we licensed to Achaogen. Plazomicin has displayed broad-spectrum activity in animals against multi-drug resistant gram-negative bacteria that cause systemic infections, including E. coli. The compound has also demonstrated activity against methicillin-resistant staphylococcus aureus, or MRSA.

In connection with the license, Achaogen issued to us $1.5 million of Achaogen Series A Preferred Stock. Since early 2009, we have received $3 million in milestone payments from Achaogen, of which $500,000 was in Achaogen securities. Assuming Achaogen successfully develops and commercializes the first two drugs under our agreement, we will receive payments totaling up to $46.3 million for the achievement of key clinical, regulatory and sales events. We will earn the next payment of $4 million if Achaogen initiates a Phase 3 study for plazomicin. We are also eligible to receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of plazomicin.

In March 2014, Achaogen completed an initial public offering. Upon the close of the offering, our investment in Achaogen's preferred stock converted into approximately 148,000 shares of common stock. As of June 30, 2014, the fair value of our investment in Achaogen was $1.9 million, which includes a lack of marketability discount because there are restrictions on when we can trade the securities. At June 30, 2014 and December 31, 2013, we owned less than 10 percent of Achaogen's equity.

Alnylam Pharmaceuticals, Inc.

In March 2004, we entered into a strategic alliance with Alnylam to develop and commercialize RNA interference therapeutics. Under the terms of the agreement, we exclusively licensed to Alnylam our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5 million technology access fee, participation in fees from Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. In August 2012, we expanded the license to include using the double-stranded RNAi technology for agricultural products. For each drug Alnylam develops under this alliance, we may receive up to $3.4 million in substantive milestone payments, including up to $1.1 million for the achievement of development milestones and $2.3 million for regulatory milestones. In 2013, we earned a $750,000 milestone payment when Alnylam initiated a Phase 3 study for a drug targeting transthyretin amyloidosis, or TTR. We will earn the next milestone payment of $375,000 if Alnylam initiates a Phase 1 study for a drug in Alnylam's pipeline. We retained rights to a limited number of double-stranded RNAi therapeutic targets and all rights to single-stranded RNAi, or ssRNAi, therapeutics.

In turn, Alnylam nonexclusively licensed to us its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize ssRNAi therapeutics and to research double-stranded RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on a nonexclusive basis. If we develop or commercialize an RNAi-based drug using Alnylam's technology, we will pay Alnylam milestone payments and royalties. For each drug, the potential milestone payments to Alnylam total $3.4 million, which we will pay if we achieve specified development and regulatory events. To date, we do not have an RNAi-based drug in clinical development. Our Alnylam alliance provides us with an opportunity to realize substantial value from our pioneering work in antisense mechanisms and oligonucleotide chemistry and is an example of our strategy to participate in all areas of RNA-targeting drug discovery.

We have the potential to earn sublicense revenue and a portion of milestone payments and royalty payments that Alnylam receives from licenses of our technology it grants to its partners. Through June 2014, we have earned a total of $48.2 million from Alnylam resulting from licenses of our technology for the development of RNAi technology that we granted to Alnylam and Alnylam has granted to its partners, including $7.7 million we earned in the first quarter of 2014 related to Alnylam's recently announced collaboration with Genzyme. During the six months ended June 30, 2014 and 2013, we earned revenue of $7.7 million and $0.3 million, respectively, from our relationship with Alnylam.

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, Symphony GenIsis, Inc., which is currently inactive.

Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, this Report includes forward-looking statements regarding our business, the therapeutic and commercial potential of our technologies and products in development, and the financial position of Isis Pharmaceuticals, Inc. 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, 2013, which is on file with the U.S. Securities and Exchange Commission, and those identified within this Item in the section entitled "Risk Factors" beginning on page 23 of this Report.

Overview

We are the leading company in antisense drug discovery and development, exploiting a proven novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Our strategy is to do what we do best—to discover and develop unique 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, including severe and rare, cardiovascular, neurologic and metabolic diseases 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 flagship product, KYNAMRO (mipomersen sodium) injection, is on the market in the United States for patients with homozygous familial hypercholesterolemia, or HoFH. Patients with HoFH are at high cardiovascular risk and cannot reduce their low-density lipoprotein cholesterol, or LDL-C, sufficiently with currently available lipid-lowering therapies. In January 2013, the U.S. Food and Drug Administration, or 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 and South Korea, and is pursuing marketing approval in multiple additional markets. Genzyme has substantial expertise in successfully marketing drugs in the United States and internationally for severe and rare diseases and is leveraging this expertise to reach patients with HoFH who are in desperate need of new treatment options. Genzyme is concentrating marketing and sales efforts on lipid specialists, and physicians who refer HoFH patients to these specialists, to reach patients with HoFH in the United States and other countries.

We have created a mature and broad pipeline that goes well beyond KYNAMRO. We have a pipeline of 32 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. One of these drugs, ISIS-APOCIII$_{Rx}$, is a triglyceride-lowering 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. We have completed a broad Phase 2 program demonstrating that ISIS-APOCIII$_{Rx}$ significantly reduced triglyceride and apolipoprotein C-III, or apoC-III, levels in patients when evaluated as a single agent and in combination with fibrates. We plan to initiate a Phase 3 program in 2014 to support a potential 2016 regulatory filing for marketing approval for ISIS-APOCIII$_{Rx}$. In addition to ISIS-APOCIII$_{Rx}$, we are also evaluating ISIS-TTR$_{Rx}$ and ISIS-SMN$_{Rx}$ in later-stage development. We designed these drugs to treat patients with severe and rare diseases, such as transthyretin amyloidosis, or TTR, and spinal muscular atrophy, or SMA, who have very limited therapeutic options. Because of the significant unmet medical need and the severity of these diseases, new therapeutic approaches could warrant an accelerated path to market. ISIS-TTR$_{Rx}$ is already in Phase 3 development, and we initiated a Phase 3 program for ISIS-SMN$_{Rx}$ in July 2014. We believe that 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. We reported Phase 2 data for ISIS-GCGR$_{Rx}$ and ISIS-FXI$_{Rx}$ in May 2014 and we plan to report data for ISIS-GCCR$_{Rx}$ and ISIS-PTP1B$_{Rx}$, in late 2014 or early 2015.

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 an optimal time to maximize the near- and long-term value for each drug. 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. We form traditional partnering alliances that enable us to discover and conduct early development of new drugs, outlicense our drugs to partners, such as Genzyme, and build a base of license fees, milestone payments, profit share and royalty income. We also form preferred partner transactions that provide us with a vested partner, such as AstraZeneca, Biogen Idec, GSK, 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 Idec, we are capitalizing on Biogen Idec's extensive resources and expertise in neurological diseases to create a franchise of novel treatments for neurological disorders. Similar to our other partnerships, with our preferred partner transactions we benefit financially from upfront payments, milestone payments, licensing fees and royalties.

We also work with a consortium of smaller companies that can exploit our drugs and technology. We call these smaller companies our 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. We also maintain our broad ribonucleic acid, or RNA, technology leadership through collaborations with satellite companies. All of these different types of relationships are part of our partnership strategy, which allow us 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 six new partnerships that involve antisense drugs for the treatment of neurological diseases or cancer, including four strategic alliances with Biogen Idec to discover and develop antisense drugs for the treatment of 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. We have received more than $230 million in upfront payments and have the potential to earn nearly $6 billion in future milestone payments and licensing fees from these partnerships. In addition, we have the potential to earn nearly $3 billion in future milestone payments and licensing fees from our other partnered programs. 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. Since 2007, our partnerships have generated an aggregate of more than $1.2 billion in payments from upfront and licensing fees, equity purchase payments, milestone payments and research and development funding.

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. To date, we have generated nearly $420 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

Recent Events

Corporate and Drug Development Highlights

- We reported positive clinical results from five drugs in later-stage development. These data exemplify the broad applicability and potential for antisense drugs to provide therapeutic benefit to many different diseases.
  - We reported positive Phase 2 data on ISIS-APOCIII$_{Rx}$ in patients with high to extremely high triglyceride levels as a single agent and in combination with fibrates. In these studies, patients experienced substantial reductions of triglyceride and apoC-III levels with significant increases in HDL-cholesterol. These Phase 2 data were presented at the Arteriosclerosis, Thrombosis and Vascular Biology and the National Lipid Association meetings.
  - We presented positive results from both of the ongoing multiple-dose open label Phase 2 studies of ISIS-SMN$_{Rx}$ in infants and children with SMA, which were consistent with earlier reported data. In these studies, we reported increases in muscle function scores in infants and children treated with ISIS-SMN$_{Rx}$. These Phase 2 data were presented at the American Academy of Neurology meeting.
  - We reported positive Phase 2 data for ISIS-GCGR$_{Rx}$ in patients with type 2 diabetes. In this study, patients with type 2 diabetes uncontrolled on stable metformin therapy experienced up to a 2.25 percentage point mean reduction in hemoglobin A1c levels after 13 weeks of dosing. These Phase 2 data were presented at the American Diabetes Association Scientific Sessions.
  - We reported positive top-line Phase 2 clinical results for ISIS-FXI$_{Rx}$ in patients undergoing total knee replacement. In this study, ISIS-FXI$_{Rx}$-treated patients experienced a dose-dependent decrease in venous thromboembolism and numerically fewer bleeding events compared to patients treated with enoxaparin.
  - We reported Phase 2 results showing that ISIS-CRP$_{Rx}$ produced statistically significant mean reductions of C-reactive protein, or CRP, protein of 65 % with reductions as great as 84% in patients with atrial fibrillation, or AF. In addition, two patients who had elevated levels of CRP (>5 mg/L) experienced a reduction of CRP that was associated with a decline to zero in overall AF burden while on treatment.
- We continued to advance our pipeline of drugs.
  - We initiated a Phase 3 study, ENDEAR, of ISIS-SMN$_{Rx}$ in infants with SMA and will earn an $18 million milestone payment upon dosing of the first infant. This is the first of several planned studies in a broad and comprehensive late-stage clinical development program for ISIS-SMN$_{Rx}$.
  - We initiated a Phase 2 study of ISIS-APO(a)$_{Rx}$ in patients with high levels of lipoprotein(a), an independent risk factor for cardiovascular disease.
  - We initiated a Phase 1 study of ISIS-PKK$_{Rx}$, an antisense drug to treat patients with hereditary angioedemia, and a Phase 1 study of ISIS-DMPK$_{Rx}$, an antisense drug to treat patients with myotonic dystrophy type 1.
  - AstraZeneca initiated a Phase 1 study of ISIS-AR$_{Rx}$, an antisense drug discovered by us to treat patients with cancer.
  - We added a new drug, ISIS-HTT$_{Rx}$, to our pipeline. ISIS-HTT$_{Rx}$ is part of our alliance with Roche and is in development to treat patients with Huntington's Disease.
- We and our partners were recognized by the drug development community for our innovative and collaborative alliances and our commitment to developing drugs to treat patients with serious, unmet medical needs.
  - We and Genzyme received the 2014 Partners in Progress Corporate Award from the National Organization for Rare Disorders, or NORD, for the development and approval of KYNAMRO, a drug selected for being a very important orphan therapy to reach the market in the

United States. This award honors companies that have brought important and innovative treatments to market for patients with rare disorders.

- Ours and Biogen Idec's innovative collaboration was voted breakthrough alliance of 2014 by Thomson Reuters Recap.
- Frank Bennett, Ph.D., our senior vice president, research, was a recipient of the Commitment to a Cure Award by the ALS Association for his and our research and commitment to develop a treatment for amyotrophic lateral sclerosis, or ALS.

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;
- 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, 2013.

Results of Operations

Revenue

Total revenue for the three and six months ended June 30, 2014 was $57.1 million and $85.2 million, respectively, compared to $38.1 million and $81.5 million for the same periods in 2013. 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. We earned $40.5 million in revenue from milestone payments in the second quarter of 2014 compared to $1.0 million in the first quarter.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the three and six months ended June 30, 2014 was $56.6 million and $76.2 million, respectively, compared to $37.6 million and $79.3 million for the same periods in 2013. Our revenue from the amortization of payments from our partners was $31.4 million in the first half of 2014, compared to $19.2 million for the same period in 2013, and increased primarily due to the amortization of upfront fees related to the strategic neurology partnership we entered into with Biogen Idec in September 2013. We also earned $41.5 million in milestone payments in the first half of 2014. The revenue from milestone payments in 2014 was comprised of:

- $24.5 million from Biogen Idec related to advancing ISIS-SMN$_{Rx}$, initiating a Phase 1 study for ISIS-DMPK$_{Rx}$, and validating an undisclosed target to treat a neurological disorder;
- $15 million from AstraZeneca related to initiating a Phase 1 clinical study of ISIS-AR$_{Rx}$; and
- $2 million from GSK related to advancing ISIS-TTR$_{Rx}$.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the three and six months ended June 30, 2014 was $0.4 million and $9.1 million, respectively, compared to $0.5 million and $2.2 million for the same periods in 2013. The increase in the first half of 2014 was primarily a result of the $7.7 million in sublicensing revenue we earned from Alnylam related to its collaboration with Genzyme.

Operating Expenses

Operating expenses for the three and six months ended June 30, 2014 were $63.7 million and $121.6 million, respectively, compared to $46.0 million and $87.8 million for the same periods in 2013 due to higher development costs associated with our maturing pipeline of drugs.

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 2014 compared to 2013 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 June 30,		Six Months Ended June 30,	
	2014	2013	**2014**	**2013**
Research, development and patent expenses	$ 52,863	$ 40,379	$ 100,438	$ 76,146
Non-cash compensation expense related to equity awards	6,401	2,252	12,274	4,798
Total research, development and patent expenses	$ 59,264	$ 42,631	$ 112,712	$ 80,944

For the three and six months ended June 30, 2014, our total research, development and patent expenses were $52.9 million and $100.4 million, respectively, and were higher compared to $40.4 million and $76.1 million for the same periods in 2013 primarily due to the progression of numerous drugs in our pipeline into later stage clinical trials. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the costs of development increase. For example, we initiated Phase 2 studies for several of the drugs in our pipeline in the second half of 2013, which are ongoing. In addition, we incurred more costs in 2014 compared to 2013 associated with the clinical studies of ISIS-SMN$_{Rx}$ and the Phase 3 study of ISIS-TTR$_{Rx}$ as we continued to advance those drugs. 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 antisense drug discovery partners. Antisense drug discovery is also the function within Isis that is responsible for advancing antisense core technology.

As we continue to advance our antisense technology, we are investing in our 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 June 30,		Six Months Ended June 30,	
	2014	2013	2014	2013
Antisense drug discovery expenses	$ 10,759	$ 10,854	$ 19,855	$ 20,251
Non-cash compensation expense related to equity awards	1,844	682	3,530	1,451
Total antisense drug discovery	$ 12,603	$ 11,536	$ 23,385	$ 21,702

Antisense drug discovery costs for the three and six months ended June 30, 2014 were $10.8 and $19.9 million, respectively, and were essentially flat compared to $10.9 million and $20.3 million for the same periods in 2013. 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 June 30,		Six Months Ended June 30,	
	2014	2013	2014	2013
KYNAMRO	$ 637	$ 1,647	$ 2,464	$ 3,591
ISIS-TTR$_{Rx}$	2,321	1,218	5,032	1,984
Other antisense development products	24,383	13,710	42,504	23,588
Development overhead costs	2,803	1,743	6,543	3,561
Non-cash compensation expense related to equity awards	2,325	721	4,402	1,576
Total antisense drug development	$ 32,469	$ 19,039	$ 60,945	$ 34,300

Antisense drug development expenses were $30.1 million and $56.5 million, respectively, for the three and six months ended June 30, 2014, compared to $18.3 million and $32.7 million for the same periods in 2013. Expenses in the first half of 2014 were higher compared to the same period in 2013 primarily due to an increase in development costs associated with the progression of numerous drugs in our pipeline into later stage clinical trials. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies the costs of development increase. For example, we initiated Phase 2 studies for several of the drugs in our pipeline in the second half of 2013, which are ongoing. In addition, we incurred more costs in 2014 compared to 2013 associated with the clinical studies of ISIS-SMN$_{Rx}$ and the Phase 3 study of ISIS-TTR$_{Rx}$ as we continued to advance those drugs. All amounts exclude non-cash compensation expense related to equity awards.

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 continually adjust the development strategy for each product. Although we may characterize a product as "in Phase 1" or "in Phase 2," it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product's particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous 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 discovery and antisense drug development, including the analytical testing to satisfy good laboratory and good manufacturing practices requirements.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2014	2013	2014	2013
Manufacturing and operations	$ 5,226	$ 4,354	$ 10,992	$ 8,575
Non-cash compensation expense related to equity awards	750	305	1,449	659
Total manufacturing and operations	$ 5,976	$ 4,659	$ 12,441	$ 9,234

Manufacturing and operations expenses were $5.2 million and $11.0 million, respectively, for the three and six months ended June 30, 2014, compared to $4.4 million and $8.6 million for the same periods in 2013. Manufacturing increased primarily because we manufactured more drug product to support our drug development activities, including drug product to support the upcoming Phase 3 trial for ISIS-APOCIII$_{Rx}$. All amounts exclude non-cash compensation expense related to equity awards.

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 June 30,		Six Months Ended June 30,	
	2014	2013	2014	2013
Personnel costs	$ 2,385	$ 2,318	$ 4,948	$ 4,656
Occupancy	1,819	1,688	3,554	3,334
Patent expenses	706	1,096	1,080	3,074
Depreciation and amortization	578	595	1,149	595
Insurance	300	280	594	567
Other	946	876	1,723	876
Non-cash compensation expense related to equity awards	1,482	544	2,893	1,112
Total antisense drug development	$ 8,216	$ 7,397	$ 15,941	$ 14,214

R&D support costs for the three and six months ended June 30, 2014 were $6.7 million and $13.0 million, respectively, and were essentially flat compared to $6.9 million and $13.1 million for the same periods in 2013. 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, utilities, information technology and procurement costs that we need to support the corporate functions listed above.

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

	Three Months Ended June 30,		Six Months Ended June 30,	
	2014	2013	2014	2013
General and administrative expenses	$ 3,155	$ 3,005	$ 6,339	$ 6,104
Non-cash compensation expense related to equity awards	1,307	384	2,503	707
Total general and administrative expenses	$ 4,462	$ 3,389	$ 8,842	$ 6,811

General and administrative expenses were $3.2 million and $6.3 million, respectively, for the three and six months ended June 30, 2014, and were essentially flat compared to $3.0 million and $6.1 million for the same periods in 2013. All amounts exclude non-cash compensation expense related to equity awards.

Investment Income

Investment income for the three and six months ended June 30, 2014 was $671,000 and $1.3 million, respectively, compared to $589,000 and $967,000 for the same periods in 2013. The increase in investment income was primarily due to a higher average cash balance and market conditions during the first half of 2014.

Interest Expense

Interest expense for the three and six months ended June 30, 2014 was $5.0 million and $9.9 million, respectively, and was essentially flat compared to $4.8 million and $9.6 million for the same periods in 2013.

Gain (loss) on Investments, net

We recorded a loss on investments of $260,000 and a gain on investments of $137,000 for the three and six months ended June 30, 2014, respectively, compared to a gain on investments of $840,000 and $1.9 million for the same periods in 2013. The net gain on investments in the first half of 2013 was primarily due to $1.1 million we received in the first quarter of 2013 when we sold the stock we held in Sarepta Therapeutics, Inc. and the $844,000 payment we received from Pfizer, Inc. in the second quarter of 2013 related to its acquisition of Excaliard Pharmaceuticals, Inc.

Income Tax Benefit

We recorded a tax expense of $0.9 million and a tax benefit of $1.4 million for the three and six months ended June 30, 2014, respectively, compared to a $1.2 million tax benefit for both the three and six month periods ended June 30, 2013. 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 half of 2014 and 2013 is primarily related to the unrealized gains associated with our investments in Regulus and Achaogen.

Net Loss and Net Loss per Share

Net loss for the three and six months ended June 30, 2014 was $12.1 million and $43.4 million, respectively, compared to $10.1 million and $11.8 million for the same periods in 2013. Basic and diluted net loss per share for the three and six months ended June 30, 2014 was $0.10 and $0.37 per share, respectively, compared to $0.09 and $0.11 per share for the same periods in 2013. Our net loss increased in the first half of 2014 primarily due to the planned increase in operating expenses associated with our maturing pipeline of drugs.

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 June 30, 2014, we have earned approximately $1.3 billion in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through June 30, 2014, we have raised net proceeds of approximately $1.1 billion from the sale of our equity securities and we have borrowed approximately $786.9 million under long-term debt arrangements to finance a portion of our operations.

At June 30, 2014, we had cash, cash equivalents and short-term investments of $590.8 million and stockholders' equity of $366.9 million. In comparison, we had cash, cash equivalents and short-term investments of $656.8 million and stockholders' equity of $378.4 million at December 31, 2013. At June 30, 2014, we had consolidated working capital of $605.0 million, compared to $637.7 million at December 31, 2013. The decrease in our cash and working capital relates to cash used to fund our operations. Our cash balance at June 30, 2014 does not include approximately $41 million in payments that we recognized into revenue in the second quarter and received in the third quarter.

As of June 30, 2014, our debt and other obligations totaled $281.5 million compared to $283.5 million at December 31, 2013. The decrease was primarily due to rent and principal payments we made in the first half of 2014 on our lease obligations and notes payable.

The following table summarizes our contractual obligations as of June 30, 2014. 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:

Contractual Obligations (selected balances described below)	Payments Due by Period (in millions) Total	Less than 1 year	1-3 years	3-5 years	After 5 years
2¾ percent Convertible Senior Notes (principal and interest payable)	$ 231.7	$ 5.5	$ 11.1	$ 11.1	$ 204.0
Facility Rent Payments	$ 134.8	$ 6.2	$ 12.9	$ 13.7	$ 102.0
Equipment Financing Arrangements (principal and interest payable)	$ 5.4	$ 4.2	$ 1.2	$ -	$ -
Other Obligations (principal and interest payable)	$ 1.3	$ 0.1	$ 0.1	$ 0.1	$ 1.0
Capital Lease	$ 0.3	$ 0.2	$ 0.1	$ -	$ -
Operating Leases	$ 25.9	$ 1.5	$ 3.1	$ 2.9	$ 18.4
Total	$ 399.4	$ 17.7	$ 28.5	$ 27.8	$ 325.4

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

In August 2012, we completed a $201.3 million convertible debt offering, which raised proceeds of approximately $194.7 million, net of $6.6 million in issuance costs. The $201.3 million of convertible senior notes mature in 2019 and bear interest at 23¤4 percent, which is payable semi-annually. We used a substantial portion of the net proceeds from the issuance of these notes to redeem the entire $162.5 million in principal of our 25¤8 percent convertible subordinated notes. The 23¤4 percent notes are convertible under certain conditions, at the option of the note holders, into approximately 12.1 million shares of our common stock at a conversion price of $16.63 per share. We will settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both. We can redeem the 23¤4 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 23¤4 percent notes on each such day. The redemption price for the 23¤4 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 23¤4 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 23¤4 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.

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 June 30, 2014, our outstanding borrowings under this loan agreement were at a weighted average interest rate of 4.28 percent. The carrying balance under this loan agreement at June 30, 2014 and December 31, 2013 was $5.2 million and $7.5 million, respectively. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

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 June 30, 2014 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, 2013.

Risks Associated with our Drug Discovery and Development Business

If the market does not accept KYNAMRO or 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 use 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 our drug discovery and development business fails 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 all areas of 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, 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 products for use in health care. 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 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 will 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 pradigastat and CAT-2003 could compete with ISIS-APOCIII$_{Rx}$, and the 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. Even if approved, we or our partners may not obtain the labeling claims necessary or desirable for successfully commercializing our drug products, including KYNAMRO, 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 a drug 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 June 30, 2014, we had an accumulated deficit of approximately $1.0 billion and stockholders' equity of approximately $366.9 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 Idec, 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 Idec, 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 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, and 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. These 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 unresolved.

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 June 30, 2014, we had cash, cash equivalents and short-term investments equal to $590.8 million. If we do not meet our goals to successfully commercialize KYNAMRO or our other drugs, including ISIS-APOCIII$_{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 June 30, 2014, the market price of our common stock ranged from $22.25 to $62.66 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, 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.

We depend on Regulus for development of our microRNA technology.

Regulus is a company that we and Alnylam established to focus on discovering, developing, and commercializing microRNA therapeutics. We exclusively licensed to Regulus our intellectual property rights covering microRNA technology. Regulus operates as an independent company and Regulus and its employees are responsible for researching and developing our microRNA technology. If Regulus is not successful, the value of our microRNA technology would be harmed and we would lose part or all of our investment in Regulus.

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

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 June 30, 2014. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to June 30, 2014.

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 alleges that Santaris' activities providing antisense drugs and antisense drug discovery services to several pharmaceutical companies infringes 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 the lawsuit we are seeking monetary damages and an injunction enjoining Santaris from conducting or participating in the infringing activities. In December 2011, Santaris filed an answer to our complaint, denying our allegations, and seeking a declaration from the court that Santaris has not, and does not, infringe the patents we asserted against Santaris in the suit. In January 2012, Santaris filed a motion for summary judgment asking the court to decide as a matter of law that Santaris' activities do not infringe the patents we assert in the suit. In September 2012, the court denied Santaris' motion for summary judgment and opened limited discovery related to whether Santaris' alleged infringing activities are permitted by the safe harbor under 35 U.S.C. Section 271(e)(1). 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 infringes 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 December 2013, Santaris filed a new motion for summary judgment asking the court to decide as a matter of law that Santaris' alleged infringing activities are permitted by the safe harbor under 35 U.S.C. Section 271(e)(1). On February 27, 2014, the court denied this motion.

In March 2014, Santaris filed a motion asking the court to decide that Santaris' alleged infringing sales of Isis' patented methods are not actionable as a matter of law. In June 2014, the court granted Santaris' motion and dismissed our allegations to the extent the allegations are based on Santaris' sale or offer for sale of such method claims; and that we did not plead sufficient facts to establish that Santaris entering into its agreement with Enzon constituted the sale or offer for sale of the compounds claimed in U.S. Patent No. 6,066,500 and U.S. Patent No. 6,440,739. The rest of the case is proceeding.

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. Isis and Merck Sharp & Dohme Corp. filed their 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 Isis' 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
3.1	Certificate of Amendment to Restated Certificate of Incorporation filed June 17, 2014.
3.2	Restated Certificate of Incorporation filed June 19, 1991.
3.3	Certificate of Designation of Series C Junior Participating Preferred Stock filed December 13, 2000.
10.1	Amendment No. 3 to the Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated July 10, 2013. Portions of this exhibit have been omitted and separately filed with the SEC.
10.2	Amendment #4 to the Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated April 10, 2014. Portions of this exhibit have been omitted and separately filed with the SEC.
10.3	Amendment #5 to the Research, Development and License Agreement among the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated June 27, 2014. 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 Offic5er 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 June 30, 2014, 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).

Isis Pharmaceuticals, Inc.

(Registrant)

SIGNATURES

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

Signatures	Title	Date
/s/ Stanley T. Crooke Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	August 4, 2014
/s/ Elizabeth L. Hougen Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	August 4, 2014

Exhibit 3.1

CERTIFICATE OF AMENDMENT TO THE RESTATED CERTIFICATE OF INCORPORATION

Isis Pharmaceuticals, Inc., a corporation organized and existing under and by virtue of the General Corporation Law of the State of Delaware, does hereby certify:

FIRST: The name of the Corporation is Isis Pharmaceuticals, Inc. (the "Corporation").

SECOND: The date on which the Corporation's original Certificate of Incorporation was filed with the Secretary of State of the State of Delaware is March 25, 1991.

THIRD: The Board of Directors of the Corporation, acting in accordance with the provisions of Sections 141 and 242 of the General Corporation Law of the State of Delaware, adopted resolutions at a meeting held on February 11, 2014 to amend Article V of the Restated Certificate of Incorporation of the Corporation to read in its entirety as follows:

> The Corporation is authorized to issue two classes of shares designated respectively "Common Stock" and "Preferred Stock." The total number of shares of all classes of stock which the Corporation has authority to issue is 315,000,000 shares, consisting of 300,000,000 shares of Common Stock, each having a par value of $.001, and 15,000,000 shares of Preferred Stock, each having a par value of $.001. The Preferred Stock may be issued in one or more series. The Board of Directors is authorized to fix the number of shares of any such series of Preferred Stock and to determine the designation of any such series (a "Preferred Stock Designation"), subject to (a) such stockholder approvals as may be provided for herein and (b) the number of shares of Preferred Stock authorized at that time by this Article V. Subject to such stockholder approvals as may be provided for herein, the Board of Directors is further authorized to determine or alter the rights, preferences, privileges and restrictions granted to or imposed upon any wholly unissued series of Preferred Stock, and to increase or decrease (but not below the number of shares of such series then outstanding) the number of shares of any series of Preferred Stock. In case the number of shares of any series shall be so decreased, the shares constituting such decrease shall resume the status that they had prior to the adoption of the resolution or amendment originally fixing the number of shares of such series.

FOURTH: The foregoing amendment was submitted to the stockholders of the Corporation for their approval and was duly adopted in accordance with the provisions of Section 242 of the General Corporation Law of the State of Delaware.

IN WITNESS WHEREOF, Isis Pharmaceuticals, Inc. has caused this Certificate of Amendment to be signed by its duly authorized officers this 13th day of June, 2014.

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

Exhibit 3.2

RESTATED CERTIFICATE OF INCORPORATION
OF
ISIS PHARMACEUTICALS, INC.

Isis Pharmaceuticals, Inc., a corporation organized and existing under the General Corporation Law of the State of Delaware, does hereby certify as follows:

FIRST: The name of the corporation is Isis Pharmaceuticals, Inc.

SECOND: The Certificate of Incorporation of the corporation was filed by the Secretary of State on March 25, 1991.

THIRD: The Restated Certificate of Incorporation of the corporation, in the form attached hereto as Exhibit A, has been duly adopted in accordance with the provisions of Section 245 of the General Corporation Law of the State of Delaware by the Board of Directors of the corporation.

FOURTH: Pursuant to Section 245 of the Delaware General Corporation Law, approval of the stockholders of the corporation is not required.

FIFTH: The Restated Certificate of Incorporation so adopted reads in full as set forth in Exhibit A attached hereto and hereby incorporated by reference.

IN WITNESS WHEREOF, Isis Pharmaceuticals, Inc. has caused this Restated Certificate of Incorporation to be signed by its President and attested to by its Assistant Secretary this 31st day of May 1991.

ISIS PHARMACEUTICALS, INC.

By */s/ Stanley T. Crooke*
Stanley T. Crooke
President

ATTEST:

/s/ Aron P. Stern
Aron P. Stern
Assistant Secretary

EXHIBIT A

RESTATED CERTIFICATE OF INCORPORATION
OF
ISIS PHARMACEUTICALS, INC.

I.

The name of the Corporation is Isis Pharmaceuticals, Inc.

II.

The address of the registered office of the Corporation in the State of Delaware is 32 Lookerman Square, Suite L-100, City of Dover, County of Kent, and the name of the registered agent of the Corporation in the State of Delaware at such address is The Prentice-Hall Corporation System, Inc.

III.

The purpose of the Corporation is to engage in any lawful act or activity for which a Corporation may be organized under the General Corporation Law of Delaware.

IV.

(a) The liability of the directors of the Corporation for monetary damages shall be eliminated to the fullest extent permissible under Delaware law.

(b) The Corporation is authorized to provide indemnification of agents (as defined in Section 145 of the Delaware General Corporation Law) for breach of duty to the Corporation and its stockholders through bylaw provisions, through agreements with the agents, and/or through stockholder resolutions, or otherwise, in excess of the indemnification otherwise permitted by Section 145 of the Delaware General Corporation Law, subject to the limitations on such excess indemnification set forth in Section 102 of the Delaware General Corporation Law.

(c) Any repeal or modification of this Article IV shall be prospective and shall not affect the rights under this Article IV in effect at the time of the alleged occurrence of any act or omission to act giving rise to liability or indemnification.

V.

The Corporation is authorized to issue two classes of shares designated respectively "Common Stock" and "Preferred Stock." The total number of shares of all classes of stock which the Corporation has authority to issue is 65,000,000 shares, consisting of 50,000,000 shares of Common Stock, each having a par value of $.001, and 15,000,000 shares of Preferred Stock, each having a par value of $.001. The Preferred Stock may be issued in one or more series. The Board of Directors is authorized to fix the number of shares of any such series of Preferred Stock and to determine the designation of any such series (a "Preferred Stock Designation"), subject to (a) such stockholder approvals as may be provided for herein and (b) the number of shares of Preferred Stock authorized at that time by this Article V. Subject to such stockholder approvals as may be provided for herein, the Board of Directors is further authorized to determine or alter the rights, preferences, privileges and restrictions granted to or imposed upon any wholly unissued series of Preferred Stock, and to increase or decrease (but not below the number of shares of such series then outstanding) the number of shares of any series of Preferred Stock. In case the number of shares of any series shall be so decreased, the shares constituting such decrease shall resume the status that they had prior to the adoption of the resolution or amendment originally fixing the number of shares of such series.

VI.

For the management of the business and for the conduct of the affairs of the Corporation, and in further definition, limitation and regulation of the powers of the Corporation, of its directors and of its stockholders or any class thereof, as the case may be, it is further provided that:

Section 1. Board of Directors.

(a) Management of Corporation. The management of the business and the conduct of the affairs of the Corporation shall be vested in its Board of Directors. The number of directors which shall constitute the whole Board of Directors shall be fixed exclusively by one or more resolutions adopted from time to time by the Board of Directors.

(b) Classified Board. Following the closing of the initial public offering pursuant to an effective registration statement under the Securities Act of 1933, as amended (the "1933 Act"), covering the offer and sale of Common Stock to the public (the "Initial Public Offering"):

(i) Designation of Classes. The directors shall be divided with respect to the time for which they generally hold office into three classes designated as Class I, Class II and Class III. Class I shall consist of two directors, with Class II and Class III consisting of three directors each. At the first annual meeting of stockholders held after the closing of the Initial Public Offering, the term of office of the Class I directors shall expire and Class I directors shall be elected for a full term of three years. At the second annual meeting of stockholders held after the closing of the Initial Public Offering, the term of office of the Class II directors shall expire and Class II directors shall be elected for a full term of three years. At the third annual meeting of stockholders held after the closing of the Initial Public Offering, the term of office of the Class III directors shall expire and Class III directors shall be elected for a full term of three years. At each succeeding annual meeting of stockholders, directors shall be elected for a full term of three years to succeed the directors of the class whose terms expire at such annual meeting.

(ii) Change in Directorships. In case of any increase in the number of directorships, the additional directorships so created shall be classified so that, as nearly as possible, each class shall consist of one third of the number of directors then constituting the whole board. Newly created directorships resulting from any increase in the number of directors shall, unless the Board of Directors determines by resolution that any such newly created directorship shall be filled by the stockholders, be filled only by the affirmative vote of the directors then in office, even though less than a quorum of the Board of Directors. Any director elected in accordance with the preceding sentence shall serve until the next election of the class to which such additional directorship shall have been assigned. Notwithstanding the requirement that the three classes shall be as nearly equal in the number of directorships as possible, no change in the number of directorships shall operate to prevent a director then in office from continuing to serve as such until the expiration of his term or his earlier death, resignation or removal.

(iii) Modification of Section 1(b). Notwithstanding any other provisions of this Certificate of Incorporation (other than the provision for the change in the number of directorships set forth in Section 1(b)(ii)) or any provision of law which might otherwise permit a lesser vote or no vote, but in addition to any affirmative vote of the holders of any particular class or series of the Voting Stock (as defined in Section 1(a) of Article VII) required by law or this Certificate of Incorporation or any Preferred Stock Designation, the affirmative vote of the holders of at least 66-2/3% of the voting power of all of the then outstanding shares of the Voting Stock, voting together as a single class, shall be required to alter, amend or repeal this Section 1(b).

(c) Removal. Subject to any limitations imposed by law, the Board of Directors or any individual director may be removed from office at any time (i) with cause by the affirmative vote of the holders of at least a majority of the outstanding Voting Stock; or (ii) without cause by the affirmative vote of the holders of at least 66-2/3% of the outstanding Voting Stock.

Section 2 General.

(a) The Board of Directors may from time to time make, amend, supplement or repeal the Bylaws; provided, however, that the stockholders may change or repeal any Bylaw adopted by the Board of Directors by the affirmative vote of the holders of at least 66-2/3% of the voting power of all of the then outstanding shares of the capital stock of the Corporation (considered for this purpose as one class); and, provided further, that no amendment or supplement to the Bylaws adopted by the Board of Directors shall vary or conflict with any amendment or supplement thus adopted by the stockholders.

(b) The directors of the Corporation need not be elected by written ballot unless the Bylaws so provide.

(c) Following the closing of the Initial Public Offering, no action shall be taken by the stockholders of the Corporation except at an annual or special meeting of stockholders called in accordance with the Bylaws and no action shall be taken by the stockholders by written consent.

(d) Advance notice of stockholder nominations for the election of directors and of business to be brought by stockholders before any meeting of the stockholders of the Corporation shall be given in the manner provided in the Bylaws of the Corporation.

VII.

Following the closing of the Initial Public Offering:

Section 1. Stockholder Vote Required for Business Combinations.

(a) Stockholder Votes. In addition to any affirmative vote required by law or by this Certificate of Incorporation or by any Preferred Stock Designation, and except as otherwise expressly provided in Section 2 of this Article VII:

(i) any merger or consolidation of the Corporation or any Subsidiary (as hereinafter defined) with (A) any Interested Stockholder (as hereinafter defined) or (B) any other corporation (whether or not itself an Interested Stockholder) which is, or after such merger or consolidation would be, an Affiliate (as hereinafter defined) of an Interested Stockholder; or

(ii) any sale, lease, exchange, mortgage, pledge, transfer or other disposition (in one transaction or a series of transactions) to or with any Interested Stockholder or any Affiliate of any Interested Stockholder of any assets of the Corporation or any Subsidiary having an aggregate Fair Market Value (as hereinafter defined) equal to or greater than 10% of the Corporation's assets as set forth on the Corporation's most recent audited consolidated financial statements; or

(iii) the issuance or transfer by the Corporation or any Subsidiary (in one transaction or a series of transactions) of any securities of the Corporation or any Subsidiary to any Interested Stockholder or any Affiliate of any Interested Stockholder in exchange for cash, securities or other property (or a combination thereof) having an aggregate Fair Market Value equal to or greater than 10% of the Corporation's assets as set forth on the Corporation's most recent audited consolidated financial statements; or

(iv) the adoption of any plan or proposal for the liquidation or dissolution of the Corporation proposed by or on behalf of any Interested Stockholder or any Affiliate of any Interested Stockholder; or

(v) any reclassification of securities (including any reverse stock split), or recapitalization of the Corporation, or any merger or consolidation of the Corporation with any of its Subsidiaries or any other transaction (whether or not with or into or otherwise involving any Interested Stockholder) which has the effect, directly or indirectly, of increasing the proportionate share of the outstanding shares of any class of equity or convertible securities of the Corporation or any Subsidiary which is Beneficially Owned (as hereinafter defined) by any Interested Stockholder or any Affiliate of any Interested Stockholder;

shall require the affirmative vote of the holders of at least 66-2/3% of the voting power of all of the then outstanding shares of capital stock of the Corporation entitled to vote generally in the election of directors (the "Voting Stock"), voting together as a single class. Such affirmative vote shall be required notwithstanding any other provisions of this Certificate of Incorporation or any provision of law or of any agreement with any national securities exchange or otherwise which might otherwise permit a lesser vote or no vote.

(b) Definition of Business Combination. The term "Business Combination" as used in this Article VII shall mean any transaction which is referred to in any one or more of subparagraphs (i) through (v) of paragraph (a) of this Section 1.

Section 2. Exceptions to Stockholder Vote Requirement.

The provisions of Section 1 of this Article VII shall not be applicable to any particular Business Combination, and such Business Combination shall require only such affirmative vote as is required by law and any other provision of this Certificate of Incorporation and any Preferred Stock Designation, if, in the case of a Business Combination that does not involve any cash or other consideration being received by the stockholders of the Corporation, solely in their respective capacities as stockholders of the Corporation, the condition specified in the following paragraph (a) is met, or, in the case of any other Business Combination, the conditions specified in either of the following paragraph (a) or paragraph (b) are met:

(a) The Business Combination shall have been approved by a majority of the Continuing Directors (as hereinafter defined); provided however, that this condition shall not be capable of satisfaction unless there are at least two Continuing Directors.

(b) All of the following conditions shall have been met:

(i) The consideration to be received by holders of shares of a particular class (or series) of outstanding capital stock of the Corporation (including Common Stock and other than Excluded Preferred Stock (as hereinafter defined)) shall be in cash or in the same form as the Interested Stockholder or any of its Affiliates has previously paid for shares of such class (or series) of capital stock. If the Interested Stockholder or any of its Affiliates have paid for shares of any class (or series) of capital stock with varying forms of consideration, the form of consideration to be received per share by holders of shares of such class (or series) of capital stock shall be either cash or the form used to acquire the largest number of shares of such class (or series) of capital stock previously acquired by the Interested Stockholder.

(ii) The aggregate amount of (x) the cash and (y) the Fair Market Value, as of the date (the "Consummation Date") of the consummation of the Business Combination, of the consideration other than cash to be received per share by holders of Common Stock in such Business Combination shall be at least equal to the higher of the following (in each case appropriately adjusted in the event of any stock dividend, stock split, combination of shares or similar event):

(A) (if applicable) the highest per share price (including any brokerage commissions, transfer taxes and soliciting dealers' fees) paid by the Interested Stockholder or any of its Affiliates for any shares of Common Stock acquired by them within the two-year period immediately prior to the date of the first public announcement of the proposal of the Business Combination (the "Announcement Date") or in any transaction in which the Interested Stockholder became an Interested Stockholder, whichever is higher, plus interest compounded annually from the first date on which the Interested Stockholder became an Interested Stockholder (the "Determination Date") through the Consummation Date at the publicly announced reference rate of interest of Bank of America, N.T.& S.A. (or such other major bank headquartered in the State of California as may be selected by the Continuing Directors) from time to time in effect in the City of San Francisco less the aggregate amount of any cash dividends paid, and the Fair Market Value of any dividends paid in other than cash, on each share of Common Stock from the Determination Date through the Consummation Date in an amount up to but not exceeding the amount of interest so payable per share of Common Stock; and

(B) the Fair Market Value per share of Common Stock on the Announcement Date or the Determination Date, whichever is higher.

(iii) The aggregate amount of (x) the cash and (y) the Fair Market Value, as of the Consummation Date, of the consideration other than cash to be received per share by holders of shares of any class (or series), other than Common Stock or Excluded Preferred Stock, of outstanding Voting Stock shall be at least equal to the highest of the following (in each case appropriately adjusted in the event of any stock dividend, stock split, combination of shares or similar event), it being intended that the requirements of this paragraph (b)(iii) shall be required to be met with respect to every such class (or series) of outstanding Voting Stock whether or not the Interested Stockholder or any of its Affiliates has previously acquired any shares of a particular class (or series) of Voting Stock):

(A) (if applicable) the highest per share price (including any brokerage commissions, transfer taxes and soliciting dealers' fees) paid by the Interested Stockholder or any of its Affiliates for any shares of such class (or series) of Voting Stock acquired by them within the two-year period immediately prior to the Announcement Date or in any transaction in which it became an Interested Stockholder, whichever is higher, plus interest compounded annually from the Determination Date through the Consummation Date at the publicly announced reference rate of interest of Bank of America, N.T. & S.A. (or such other major bank headquartered in the State of California as may be selected by the Continuing Directors) from time to time in effect in the City of San Francisco less the aggregate amount of any cash dividends paid, and the Fair Market Value of any dividends paid in other than cash, on each share of such class (or series) of Voting Stock from the Determination Date through the Consummation Date in an amount up to but not exceeding the amount of interest so payable per share of such class (or series) of Voting Stock;

(B) the Fair Market Value per share of such class (or series) of Voting Stock on the Announcement Date or on the Determination Date, whichever is higher; and

(C) the highest preferential amount per share, if any, to which the holders of shares of such class (or series) of Voting Stock would be entitled in the event of any voluntary or involuntary liquidation, dissolution or winding up of the corporation.

(iv) After such Interested Stockholder has become an Interested Stockholder and prior to the consummation of such Business Combination: (x) except as approved by a majority of the Continuing Directors, there shall have been no failure to declare and pay at the regular date therefor any full quarterly dividends (whether or not cumulative) on any outstanding Preferred Stock; (y) there shall have been (A) no reduction in the annual rate of dividends paid on the Common Stock (except as necessary to reflect any subdivision of the Common Stock), except as approved by a majority of the Continuing Directors, and (B) an increase in such annual rate of dividends as necessary to reflect any reclassification (including any reverse stock split), recapitalization, reorganization or any similar transaction which has the effect of reducing the number of outstanding shares of the Common Stock, unless the failure so to increase such annual rate is approved by a majority of the Continuing Directors; and (z) neither such Interested Stockholder nor any of its Affiliates shall have become the beneficial owner of any additional shares of Voting Stock except as part of the transaction which results in such Interested Stockholder becoming an Interested Stockholder; provided, however, that no approval by Continuing Directors shall satisfy the requirements of this subparagraph (iv) unless at the time of such approval there are at least two Continuing Directors.

(v) After such Interested Stockholder has become an Interested Stockholder, such Interested Stockholder and any of its Affiliates shall not have received the benefit, directly or indirectly (except proportionately, solely in such Interested Stockholder's or Affiliate's capacity as a stockholder of the Corporation), of any loans, advances, guarantees, pledges or other financial assistance or any tax credits or other tax advantages provided by the Corporation, whether in anticipation of or in connection with such Business Combination or otherwise.

(vi) A proxy or information statement describing the proposed Business Combination and complying with the requirements of the Securities Exchange Act of 1934, as amended (the "1934 Act") and the rules and regulations thereunder (or any subsequent provisions replacing such Act, rules or regulations) shall be mailed to all stockholders of the Corporation at least 30 days prior to the consummation of such Business Combination (whether or not such proxy or information statement is required to be mailed pursuant to such Act or subsequent provisions).

(vii) Such Interested Stockholder shall have supplied the Corporation with such information as shall have been requested pursuant to Section 5 of this Article VII within the time period set forth therein.

Section 3. Definitions.

For the purposes of this Article VII:

(a) A "person" means any individual, limited partnership, general partnership, corporation or other firm or entity.

(b) "Interested Stockholder" means any person (other than the Corporation or any Subsidiary) who or which:

(i) is the Beneficial Owner (as hereinafter defined), directly or indirectly, of 15% or more of the voting power of the then outstanding Voting Stock; or

(ii) is an Affiliate of the Corporation and at any time within the two-year period immediately prior to the date in question was the Beneficial Owner, directly or indirectly, of 15% or more of the voting power of the then outstanding Voting Stock; or

(iii) is an assignee of or has otherwise succeeded to any shares of Voting Stock which were at any time within the two-year period immediately prior to the date in question Beneficially Owned by an Interested Stockholder, if such assignment or succession shall have occurred in the course of a transaction or series of transactions not involving a public offering within the meaning of the 1933 Act.

(c) A person shall be a "Beneficial Owner" of or shall "Beneficially Own" any Voting Stock:

(i) which such person or any of its Affiliates or Associates (as hereinafter defined) beneficially owns, directly or indirectly, within the meaning of Rule 13d-3 under the 1934 Act as in effect on March 14, 1988; or

(ii) which such person or any of its Affiliates or Associates has (A) the right to acquire (whether such right is exercisable immediately or only after the passage of time), pursuant to any agreement, arrangement or understanding or upon the exercise of conversion rights, exchange rights, warrants or options, or otherwise, or (B) the right to vote pursuant to any agreement, arrangement or understanding (but shall not be deemed to be the beneficial owner of any shares of Voting Stock solely by reason of a revocable proxy granted for a particular meeting of stockholders, pursuant to a public solicitation of proxies for such meeting, and with respect to which shares neither such person nor any such Affiliate or Associate is otherwise deemed the beneficial owner); or

(iii) which is beneficially owned, directly or indirectly, within the meaning of Rule 13d-3 under the 1934 Act as in effect on the adoption date of this Certificate of Incorporation, by any other person with which such person or any of its Affiliates or Associates has any agreement, arrangement or understanding for the purpose of acquiring, holding, voting (other than solely by reason of a revocable proxy as described in subparagraph (ii) of this paragraph (c)) or disposing of any shares of Voting Stock;

provided, however, that in case of any employee stock ownership or similar plan of the Corporation or of any Subsidiary in which the beneficiaries thereof possess the right to vote any shares of Voting Stock held by such plan, no such plan nor any trustee with respect thereto (nor any Affiliate of such trustee), solely by reason of such capacity of such trustee, shall be deemed, for any purposes hereof, to Beneficially Own any shares of Voting Stock held under any such plan.

(d) For the purposes of determining whether a person is an Interested Stockholder pursuant to paragraph (b) of this Section 3, the number of shares of Voting Stock deemed to be outstanding shall include shares deemed Beneficially Owned through application of paragraph (c) of this Section 3 but shall not include any other unissued shares of Voting Stock which may be issuable pursuant to any agreement, arrangement or understanding, or upon exercise of conversion rights, warrants or options, or otherwise.

(e) "Affiliate" or "Associate" shall have the respective meanings ascribed to such terms in Rule 12b-2 under the 1934 Act as in effect on the adoption date of this Certificate of Incorporation.

(f) "Subsidiary" means any corporation of which a majority of the outstanding shares of any class of equity security is owned, directly or indirectly, by the Corporation; provided, however, that for the purposes of the definition of Interested Stockholder set forth in paragraph (b) of this Section 3, the term "Subsidiary" shall mean only a corporation of which a majority of the outstanding shares of each class of equity security is owned, directly or indirectly, by the Corporation.

(g) "Continuing Director" means a member of the Board of Directors of the Corporation who is originally elected upon the incorporation of the Corporation or who is not an Interested Stockholder or affiliated with an Interested Stockholder or in connection with his or her initial assumption of office is recommended and approved for an appointment or election by a majority of Continuing Directors then on the Board.

(h) "Fair Market Value" means: (i) in the case of stock, the highest closing sale price during the 30-day period immediately preceding the date in question of a share of such stock on the Composite Tape for New York Stock Exchange-Listed Stocks, or, if such stock is not quoted on the Composite Tape, on the New York Stock Exchange, or, if such stock is not listed on such Exchange, on the principal United States securities exchange registered under the 1934 Act on which such stock is listed, or, if such stock is not listed on any such exchange, the highest closing sale price quotation with respect to a share of such stock during the 30-day period preceding the date in question on the National Association of Securities Dealers, Inc. Automated Quotations System or any system then in use, or if no such quotations are available, the fair market value on the date in question of a share of such stock as determined by the Board in accordance with Section 4 of this Article VII; and (ii) in the case of property other than cash or stock, the fair market value of such property on the date in question as determined by the Board in accordance with Section 4 of this Article VII.

(i) In the event of any Business Combination in which the Corporation survives, the phrase "consideration other than cash to be received" as used in paragraphs (b)(ii) and (b)(iii) of Section 2 of this Article VII shall include the shares of Common Stock and/or the shares of any other class (or series) of outstanding Voting Stock retained by the holders of such shares.

(j) "Whole Board" means the total number of directors which this corporation would have if there were no vacancies.

(k) "Excluded Preferred Stock" means any series of Preferred Stock with respect to which the Preferred Stock Designation creating such series expressly provides that the provisions of this Article VII shall not apply.

Section 4. Board Enforcement.

(a) Compliance. A majority of the Whole Board but only if a majority of the Whole Board shall then consist of Continuing Directors or, if a majority of the Whole Board shall not then consist of Continuing Directors, a majority of the then Continuing Directors, shall have the power and duty to determine, on the basis of information known to them after reasonable inquiry, all facts necessary to determine compliance with this Article VII, including, without limitation, (i) whether a person is an Interested Stockholder, (ii) the number of shares of Voting Stock beneficially owned by any person, (iii) whether a person is an Affiliate or Associate of another, (iv) whether the applicable conditions set forth in paragraph (b) of Section 2 have been met with respect to any Business Combination, (v) the Fair Market Value of stock or other property in accordance with paragraph (h) of Section 3, and (vi) whether the assets which are the subject of any Business Combination referred to in paragraph (a)(ii) of Section 1 have or the consideration to be received for the issuance or transfer of securities by the Corporation or any Subsidiary in any Business Combination referred to in paragraph (a)(iii) of Section 1 has, an aggregate Fair Market Value equal to or greater than 10% of the Corporation's assets as set forth on the Corporation's most recent audited consolidated financial statements.

(b) Demand as to Interested Stockholder. A majority of the Whole Board shall have the right to demand, but only if a majority of the Whole Board shall then consist of Continuing Directors, or, if a majority of the Whole Board shall not then consist of Continuing Directors, a majority of the then Continuing Directors shall have the right to demand, that any person who it is reasonably believed is an Interested Stockholder (or holds of record shares of Voting Stock Beneficially Owned by any Interested Stockholder) supply this Corporation with complete information as to (i) the record owner(s) of all shares Beneficially Owned by such person who it is reasonably believed is an Interested Stockholder, (ii) the number of, and class or series of, shares Beneficially Owned by such person who it is reasonably believed is an Interested Stockholder and held of record by each such record owner and the number(s) of the stock certificate(s) evidencing such shares, and (iii) any other factual matter relating to the applicability or effect of this Article VII, as may be reasonably requested of such person, and such person shall furnish such information within 10 days after receipt of such demand.

(c) Fiduciary Obligation of Interested Stockholder. Nothing contained in this Article VII shall be construed to relieve any Interested Stockholder from any fiduciary obligation imposed by law.

(d) Modification of Article VII. Notwithstanding any other provisions of this Certificate of Incorporation or any provision of law which might otherwise permit a lesser vote or no vote, but in addition to any affirmative vote of the holders of any particular class or series of the Voting Stock required by law or this Certificate of Incorporation or any Preferred Stock Designation, the affirmative vote of the holders of at least 66-2/3% of the voting power of all of the then outstanding shares of the Voting Stock, voting together as a single class, shall be required to alter, amend or repeal this Article VII.

VIII.

No holder of shares of stock of the Corporation shall have any preemptive or other right, except as such rights are expressly provided by contract, to purchase or subscribe for or receive any shares of any class, or series thereof, of stock of the Corporation, whether now or hereafter authorized, or any warrants, options, bonds, debentures or other securities convertible into, exchangeable for or carrying any right to purchase any share of any class, or series thereof, of stock; but such additional shares of stock and such warrants, options, bonds, debentures or other securities convertible into, exchangeable for or carrying any right to purchase any shares of any class, or series thereof, of stock may be issued or disposed of by the Board of Directors to such persons, and on such terms and for such lawful consideration, as in its discretion it shall deem advisable or as the Corporation shall have by contract agreed.

CERTIFICATE OF DESIGNATION

OF

SERIES C JUNIOR PARTICIPATING PREFERRED STOCK

(Pursuant to Section 151 of the
Delaware General Corporation Law)

ISIS PHARMACEUTICALS, INC., a corporation organized and existing under the General Corporation Law of the State of Delaware (hereinafter called the "Company"), hereby certifies that the following resolution was adopted by the Board of Directors of the Corporation as required by Section 151 of the General Corporation Law at a meeting duly called and held on December 8, 2000:

> **RESOLVED,** that pursuant to the authority granted to and vested in the Board of Directors of the Company in accordance with the provisions of its Restated Certificate of Incorporation, the Board of Directors hereby creates a series of Preferred Stock, par value $.001 per share, of the Company and hereby states the designation and number of shares, and fixes the relative designations and the powers, preferences and rights, and the qualifications, limitations and restrictions thereof (in addition to the provisions set forth in the Restated Certificate of Incorporation of the Company, which are applicable to the Preferred Stock of all classes and series), as follows:

Series C Junior Participating Preferred Stock:

Section 1. Designation and Amount. One million (1,000,000) shares of Preferred Stock, $.001 par value, are designated "Series C Junior Participating Preferred Stock" with the designations and the powers, preferences and rights, and the qualifications, limitations and restrictions specified herein (the "Junior Preferred Stock"). Such number of shares may be increased or decreased by resolution of the Board of Directors; *provided*, that no decrease shall reduce the number of shares of Junior Preferred Stock to a number less than the number of shares then outstanding plus the number of shares reserved for issuance upon the exercise of outstanding options, rights or warrants or upon the conversion of any outstanding securities issued by the Company convertible into Junior Preferred Stock.

Section 2. Dividends and Distributions.

(A) Subject to the rights of the holders of any shares of any series of Preferred Stock (or any similar stock) ranking prior and superior to the Junior Preferred Stock with respect to dividends, the holders of shares of Junior Preferred Stock, in preference to the holders of Common Stock, par value $.001 per share (the "Common Stock"), of the Company, and of any other junior stock, shall be entitled to receive, when, as and if declared by the Board of Directors out of funds legally available for the purpose, quarterly dividends payable in cash on the first day of April, July, October and January in each year (each such date being referred to herein as a "Quarterly Dividend Payment Date"), commencing on the first Quarterly Dividend Payment Date after the first issuance of a share or fraction of a share of Junior Preferred Stock, in an amount per share (rounded to the nearest cent) equal to the greater of (a) $l.00 or (b) subject to the provision for adjustment hereinafter set forth, 100 times the aggregate per share amount of all cash dividends, and 100 times the aggregate per share amount (payable in kind) of all non-cash dividends or other distributions, other than a dividend payable in shares of Common Stock or a subdivision of the outstanding shares of Common Stock (by reclassification or otherwise), declared on the Common Stock since the immediately preceding Quarterly Dividend Payment Date or, with respect to the first Quarterly Dividend Payment Date, since the first issuance of any share or fraction of a share of Junior Preferred Stock. In the event the Company shall at any time declare or pay any dividend on the Common Stock payable in shares of Common Stock, or effect a subdivision or combination or consolidation of the outstanding shares of Common Stock (by reclassification or otherwise than by payment of a dividend in shares of Common Stock) into a greater or lesser number of shares of Common Stock, then in each such case the amount to which holders of shares of Junior Preferred Stock were entitled immediately prior to such event under clause (b) of the preceding sentence shall be adjusted by multiplying such amount by a fraction, the numerator of which is the number of shares of Common Stock outstanding immediately after such event and the denominator of which is the number of shares of Common Stock that were outstanding immediately prior to such event.

(B) The Company shall declare a dividend or distribution on the Junior Preferred Stock as provided in paragraph (A) of this Section immediately after it declares a dividend or distribution on the Common Stock (other than a dividend payable in shares of Common Stock); *provided*, that in the event no dividend or distribution shall have been declared on the Common Stock during the period between any Quarterly Dividend Payment Date and the next subsequent Quarterly Dividend Payment Date, a dividend of $1.00 per share on the Junior Preferred Stock shall nevertheless be payable on such subsequent Quarterly Dividend Payment Date.

(C) Dividends shall begin to accrue and be cumulative on outstanding shares of Junior Preferred Stock from the Quarterly Dividend Payment Date next preceding the date of issue of such shares, unless the date of issue of such shares is prior to the record date for the first Quarterly Dividend Payment Date, in which case dividends on such shares shall begin to accrue from the date of issue of such shares, or unless the date of issue is a Quarterly Dividend Payment Date or is a date after the record date for the determination of holders of shares of Junior Preferred Stock entitled to receive a quarterly dividend and before such Quarterly Dividend Payment Date, in either of which events such dividends shall begin to accrue and be cumulative from such Quarterly Dividend Payment Date. Accrued but unpaid dividends shall not bear interest. Dividends paid on the shares of Junior Preferred Stock in an amount less than the total amount of such dividends at the time accrued and payable on such shares shall be allocated pro rata on a share-by-share basis among all such shares at the time outstanding. The Board of Directors may fix a record date for the determination of holders of shares of Junior Preferred Stock entitled to receive payment of a dividend or distribution declared thereon, which record date shall be not more than 60 days prior to the date fixed for the payment thereof.

Section 3. Voting Rights. The holders of shares of Junior Preferred Stock shall have the following voting rights:

(A) Subject to the provision for adjustment hereinafter set forth, each share of Junior Preferred Stock shall entitle the holder thereof to 100 votes on all matters submitted to a vote of the stockholders of the Company. In the event the Company shall at any time declare or pay any dividend on the Common Stock payable in shares of Common Stock, or effect a subdivision or combination or consolidation of the outstanding shares of Common Stock (by reclassification or otherwise than by payment of a dividend in shares of Common Stock) into a greater or lesser number of shares of Common Stock, then in each such case the number of votes per share to which holders of shares of Junior Preferred Stock were entitled immediately prior to such event shall be adjusted by multiplying such number by a fraction, the numerator of which is the number of shares of Common Stock outstanding immediately after such event and the denominator of which is the number of shares of Common Stock that were outstanding immediately prior to such event.

(B) Except as otherwise provided herein, in any other Certificate of Designation creating a series of Preferred Stock or any similar stock, or by law, the holders of shares of Junior Preferred Stock and the holders of shares of Common Stock and any other capital stock of the Company having general voting rights shall vote together as one class on all matters submitted to a vote of stockholders of the Company.

(C) Except as set forth herein, or as otherwise provided by law, holders of Junior Preferred Stock shall have no special voting rights and their consent shall not be required (except to the extent they are entitled to vote with holders of Common Stock as set forth herein) for taking any corporate action.

Section 4. Certain Restrictions.

(A) Whenever quarterly dividends or other dividends or distributions payable on the Junior Preferred Stock as provided in Section 2 are in arrears, thereafter and until all accrued and unpaid dividends and distributions, whether or not declared, on shares of Junior Preferred Stock outstanding shall have been paid in full, the Company shall not:

(i) declare or pay dividends, or make any other distributions, on any shares of stock ranking junior (either as to dividends or upon liquidation, dissolution or winding up) to the Junior Preferred Stock;

(ii) declare or pay dividends, or make any other distributions, on any shares of stock ranking on a parity (either as to dividends or upon liquidation, dissolution or winding up) with the Junior Preferred Stock, except dividends paid ratably on the Junior Preferred Stock and all such parity stock on which dividends are payable or in arrears in proportion to the total amounts to which the holders of all such shares are then entitled;

(iii) redeem or purchase or otherwise acquire for consideration shares of any stock ranking junior (either as to dividends or upon liquidation, dissolution or winding up) to the Junior Preferred Stock, provided that the Company may at any time redeem, purchase or otherwise acquire shares of any such junior stock in exchange for shares of any stock of the Company ranking junior (either as to dividends or upon dissolution, liquidation or winding up) to the Junior Preferred Stock; or

(iv) redeem or purchase or otherwise acquire for consideration any shares of Junior Preferred Stock, or any shares of stock ranking on a parity (either as to dividends or upon liquidation, dissolution or winding up) with the Junior Preferred Stock, except in accordance with a purchase offer made in writing or by publication (as determined by the Board of Directors) to all holders of such shares upon such terms as the Board of Directors, after consideration of the respective annual dividend rates and other relative rights and preferences of the respective series and classes, shall determine in good faith will result in fair and equitable treatment among the respective series or classes.

(B) The Company shall not permit any subsidiary of the Company to purchase or otherwise acquire for consideration any shares of stock of the Company unless the Company could, under paragraph (A) of this Section 4, purchase or otherwise acquire such shares at such time and in such manner.

Section 5. Reacquired Shares. Any shares of Junior Preferred Stock purchased or otherwise acquired by the Company in any manner whatsoever shall be retired and cancelled promptly after the acquisition thereof. All such shares shall upon their cancellation become authorized but unissued shares of Preferred Stock and may be reissued as part of a new series of Preferred Stock subject to the conditions and restrictions on issuance set forth herein, in the Restated Certificate of Incorporation, or in any other Certificate of Designation creating a series of Preferred Stock or any similar stock or as otherwise required by law.

Section 6. Liquidation, Dissolution or Winding Up. Upon any liquidation, dissolution or winding up of the Company, no distribution shall be made (1) to the holders of shares of stock ranking junior (either as to dividends or upon liquidation, dissolution or winding up) to the Junior Preferred Stock unless, prior thereto, the holders of shares of Junior Preferred Stock shall have received $100 per share, plus an amount equal to accrued and unpaid dividends and distributions thereon, whether or not declared, to the date of such payment, or if greater, the holders of shares of Junior Preferred Stock shall be entitled to receive an aggregate amount per share, subject to the provision for adjustment hereinafter set forth, equal to 100 times the aggregate amount to be distributed per share to holders of shares of Common Stock; or (2) to the holders of shares of stock ranking on a parity (either as to dividends or upon liquidation, dissolution or winding up) with the Junior Preferred Stock, except distributions made ratably on the Junior Preferred Stock and all such parity stock in proportion to the total amounts to which the holders of all such shares are entitled upon such liquidation, dissolution or winding up. In the event the Company shall at any time declare or pay any dividend on the Common Stock payable in shares of Common Stock, or effect a subdivision or combination or consolidation of the outstanding shares of Common Stock (by reclassification or otherwise than by payment of a dividend in shares of Common Stock) into a greater or lesser number of shares of Common Stock, then in each such case the aggregate amount to which holders of shares of Junior Preferred Stock were entitled immediately prior to such event under the proviso in clause (1) of the preceding sentence shall be adjusted by multiplying such amount by a fraction the numerator of which is the number of shares of Common Stock outstanding immediately after such event and the denominator of which is the number of shares of Common Stock that were outstanding immediately prior to such event.

Section 7. Consolidation, Merger, Etc. In case the Company shall enter into any consolidation, merger, combination or other transaction in which the shares of Common Stock are exchanged for or changed into other stock or securities, cash and/or any other property, then in any such case each share of Junior Preferred Stock shall at the same time be similarly exchanged or changed into an amount per share, subject to the provision for adjustment hereinafter set forth, equal to 100 times the aggregate amount of stock, securities, cash and/or any other property (payable in kind), as the case may be, into which or for which each share of Common Stock is changed or exchanged. In the event the Company shall at any time declare or pay any dividend on the Common Stock payable in shares of Common Stock, or effect a subdivision or combination or consolidation of the outstanding shares of Common Stock (by reclassification or otherwise than by payment of a dividend in shares of Common Stock) into a greater or lesser number of shares of Common Stock, then in each such case the amount set forth in the preceding sentence with respect to the exchange or change of shares of Junior Preferred Stock shall be adjusted by multiplying such amount by a fraction, the numerator of which is the number of shares of Common Stock outstanding immediately after such event and the denominator of which is the number of shares of Common Stock that were outstanding immediately prior to such event.

Section 8. No Redemption. The shares of Junior Preferred Stock shall not be redeemable.

Section 9. Rank. The Junior Preferred Stock shall rank, with respect to the payment of dividends and the distribution of assets, junior to all series of any other class of the Company's Preferred Stock.

Section 10. Amendment. The Restated Certificate of Incorporation of the Company shall not be amended in any manner which would materially alter or change the powers, preferences or special rights of the Junior Preferred Stock so as to affect them adversely without the affirmative vote of the holders of at least two-thirds of the outstanding shares of Junior Preferred Stock, voting together as a single class.

In Witness Whereof, the undersigned have executed this certificate as of December 12, 2000.

By: */s/ B. Lynne Parshall*
Print Name: **B. Lynne Parshall**
Executive Vice President,
Chief Financial Officer and Secretary

Exhibit 10.1

AMENDMENT NO. 3 TO THE RESEARCH, DEVELOPMENT AND LICENSE AGREEMENT

This **AMENDMENT NO. 3 TO THE RESEARCH, DEVELOPMENT AND LICENSE AGREEMENT** (the "***Amendment No. 3***") is effective as of the 10th day of July 2013 (the "***Amendment No. 3 Effective Date***") by and between Glaxo Group Limited ("***GSK***") and Isis Pharmaceuticals, Inc. ("***Isis***"), and amends that certain Research, Development and License Agreement dated March 30, 2010, as amended by that certain Amendment No. 1 on May 11, 2011 (the "***Amendment No. 1***"), and by that certain Amendment No. 2 on October 30, 2012 (the "***TTR Amendment***") (the Research, Development and License Agreement, as amended, the "***Collaboration Agreement***"). Each of GSK and Isis may be referred to herein as a "Party" or collectively as the "Parties". Capitalized terms used but not defined herein shall have the meaning ascribed to such terms in the Collaboration Agreement.

WHEREAS, pursuant to Section 1.3.6 of the Collaboration Agreement the Parties established a separate IDJSC with a remit over the ID/Additional Programs under the Collaboration Agreement and pursuant to Section 6 of the TTR Amendment, the Parties established a TTR Steering Committee to oversee the TTR Program; and

WHEREAS, the Parties have now agreed to dissolve the IDJSC and the TTR Steering Committee in order to combine such separate committees into a single JSC with a remit over all of the Collaboration Programs under the Collaboration Agreement, on the terms and conditions set forth more fully herein.

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 do hereby agree as follows:

AGREEMENT

1. ***Dissolution of the TTR Steering Committee***. Section 6 (TTR Steering Committee) of the TTR Amendment shall be deleted in its entirety and shall be of no further force or effect. The TTR Steering Committee hereafter shall be deemed to be dissolved. For the avoidance of doubt, the dissolving of the TTR Steering Committee shall not affect any decisions which were made by the TTR Steering Committee prior to the Amendment No. 3 Effective Date and which were documented in the final, approved minutes of the relevant TTR Steering Committee meeting. Such prior decisions of the TTR Steering Committee, unless and until any such decisions are modified by the JSC, shall continue to be valid. From the Amendment No. 3 Effective Date and going forward, the JSC as established by the Collaboration Agreement shall also have governance oversight for the TTR Program in accordance with the terms set forth in Section 1.3 of the Collaboration Agreement (as such Section is modified by this Amendment No. 3).

2. ***Dissolution of the IDJSC.*** Sections 1.3.6 through 1.3.10 of the Collaboration Agreement shall be deleted in their entirety and shall be of no further force or effect. The IDJSC hereafter shall be deemed to be dissolved. For the avoidance of doubt, the dissolving of the IDJSC shall not affect any decisions which were made by the IDJSC prior to the Amendment No. 3 Effective Date and which were documented in the final, approved minutes of the relevant IDJSC meeting. Such prior decisions of the IDJSC, unless and until any such decisions are modified by the JSC, shall continue to be valid. From the Amendment No. 3 Effective Date and going forward, the JSC as established by the Collaboration Agreement shall also have governance oversight for the ID/Additional Programs in accordance with the terms set forth in Section 1.3 of the Collaboration Agreement (as such Section is modified by this Amendment No. 3).

3. ***Amendment of Section 1.3.1 of the Collaboration Agreement.*** The first paragraph of Section 1.3.1 of the Collaboration Agreement shall be deleted in its entirety and replaced with the following:

"**JSC.** The Parties will establish a joint steering committee (the "*JSC*") to provide advice and make recommendations on how to conduct the Collaboration for all Collaboration Programs. The JSC will be made up of representatives from each Party, and each of Isis and GSK may appoint up to [***] ([***]) representatives to the JSC, with such appointed individuals each representing expertise in at least one of the areas of collaboration between the Parties under the Agreement (such areas of expertise to initially include rare diseases, ophthalmology, and infectious diseases) and no more than one (1) of such representatives acting generally as a scientific R&D advisor to the JSC. Each Party will designate one (1) of the aforementioned representatives who possesses a thorough understanding of the scientific and business issues relevant to this Agreement to act as the co-chair of the JSC for the ID/Additional Programs and one (1) of its representatives who possesses a thorough understanding of the scientific and business issues relevant to this Agreement to act as the co-chair of the JSC for the non-ID/Additional Programs. The co-chairs will be responsible for ensuring that activities occur as set forth in this Agreement, including ensuring that the JSC meetings occur, material recommendations of the JSC are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Sections 1.3.3 and 12.1. Either Party may change their designated JSC members at any time upon written notice to the other Party. The designated JSC members of each Party as of the Amendment No.3 Effective Date are set forth on the attached Exhibit 1."

4. ***Amendment of Section 1.3.2 of the Collaboration Agreement.*** Section 1.3.2 of the Collaboration Agreement shall be deleted in its entirety and replaced with the following:

"1.3.2 **Role of the JSC.** Without limiting any of the foregoing, subject to Section 1.3.3, the JSC will perform the following functions, some or all of which may be addressed directly at any given meeting of the JSC:

(a) review progress on improvements to Antisense technology and advances in mechanistic understandings of Antisense technology;

(b) review and provide advice on the Collaboration Program Research Plan (defined below) for each Collaboration Program, and the Early Development Plan (defined below) for each Development Candidate;

(c) review the overall progress of Isis' efforts to discover, identify, optimize and otherwise Develop Compounds under each Collaboration Program;

(d) in each case subject to [***], review and provide advice on (i) the design and content of the Phase I Success Criteria and the Phase I Trial Design/Endpoints for each ID/Additional Program, including design of, and human patient allocation in, all Clinical Studies, (ii) the design and content of the PoC Success Criteria for each Collaboration Program, and (iii) the PoC Trial Design/Endpoints for each Collaboration Program;

(e) discuss and approve the design and expenditure for animal efficacy studies for the ID/Additional Programs;

(f) review and determine whether In Vivo Efficacy has been demonstrated under the ID/Additional Programs;

(g) coordinate and manage activities to develop the regulatory strategy and CMC strategy for the TTR Program through Option exercise to ensure a smooth transition of such activities; and

(h) such other review and advisory responsibilities as may be assigned to the JSC pursuant to this Agreement or as may be mutually agreed upon in writing by the Parties from time to time."

5. JSC Subcommittee(s). The following new Section 1.3.6 shall be added to the Collaboration Agreement:

"**1.3.6 Subcommittee(s).** The JSC may establish a subcommittee to function as a project team to oversee each specific Collaboration Program, projects or activities, as it deems necessary or advisable (each, a "***Subcommittee***"). Each Subcommittee shall consist of an equal number of representatives of each Party as the JSC determines is appropriate from time to time. Such members shall be individuals with expertise and responsibilities that are relevant to the stage of development of the project or activity, for example discovery research, preclinical development, Patents or process sciences. Each Subcommittee shall meet with such frequency as the JSC shall determine. Each Subcommittee shall operate by unanimous vote in all decisions, with each Party having one (1) vote and with at least one (1) representative from each Party participating in such vote. If, with respect to a matter that is subject to a Subcommittee's decision-making authority, the Subcommittee cannot reach unanimity, the matter shall be immediately referred to the JSC, which shall resolve such matter in accordance with Section 1.3.3."

6. TTR Project Team. The following new Section 1.3.7 shall be added to the Collaboration Agreement:

"**1.3.7** Subject to Section 1.3.3 and solely in connection with the TTR Program, the TTR Project Team will be established and will include representatives designated by each of GSK and Isis. The TTR Project Team will perform the following functions with respect to the TTR Program:

(i) Review the TTR Registration-Directed Program Documents from time to time and prepare Material Amendments, if any, to the TTR Registration-Directed Program Documents to be approved by the JSC;

(ii) Develop CMC strategy and manage development activities, including process development, formulation development, quality control, stability tests, scale up, etc.;

(iii) Manage the manufacture and supply of API and/or finished product for Clinical Studies;

(iv) Review and oversee the clinical monitoring program and the statistical analysis plan (including establishing a mutually agreed process for GSK to participate in in-stream safety data review with Isis);

(v) Develop regulatory strategy and coordinate, review and oversee regulatory activities conducted under the TTR Registration-Directed Program Documents;

(vi) Facilitate sharing of data and information between the Parties' regulatory teams to ensure each Party's access to all data;

(vii) Coordinate meetings and other interactions (including written correspondence with Regulatory Authorities); and

(viii) Develop a transition plan prior to GSK's exercise of the Option, including coordinating the transfer of manufacturing technology and delivery of regulatory materials, and execute such plan.

7. As of the Amendment No. 3 Effective Date, each reference to the TTR Steering Committee and to the IDJSC as set forth in the Collaboration Agreement shall be construed and interpreted to mean and to refer solely to the JSC.

8. Miscellaneous. Except as expressly set forth herein, this Amendment No. 3 shall not be construed to modify any of the Parties' respective rights and obligations under the Collaboration Agreement. This Amendment No. 3 shall be construed and interpreted according to the laws of the State of Delaware, without regard to conflicts of laws principles. This Amendment No. 3 may be executed in more than one counterpart, each of which shall be deemed to be an original but all of which taken together shall be deemed a single instrument. A facsimile transmission of the signed Amendment No. 3 will be legal and binding on both Parties. This Amendment No. 3 shall be incorporated into and shall, as of the Amendment No. 3 Effective Date, form part of the Collaboration Agreement between the Parties.

[Remainder of Page Intentionally Left Blank – Signatures on Following Page]

Exhibit 10.1

IN WITNESS WHEREOF, the Parties have caused this Amendment No. 3 to be executed by their duly authorized representatives as of the Amendment No. 3 Effective Date.

ISIS PHARMACEUTICALS, INC.

By: */s/ B. Lynne Parshall*

Name: B. Lynne Parshall

Title: Chief Operating Officer

Date: July 10, 2013

GLAXO GROUP LIMITED

By: */s/ Balbir Kelly-Bisla*

Name: Balbir Kelly-Bisla

Title: Authorised Signatory for and on behalf of

Edinburgh Pharmaceutical Industries Limited

Corporate Director

Date:

Exhibit 10.1

EXHIBIT 1

INITIAL DESIGNATED JSC MEMBERS FOR GSK:

[***]

INITIAL DESIGNATED JSC MEMBERS FOR ISIS:

[***]

EXHIBIT 10.2

AMENDMENT #4 TO RESEARCH, DEVELOPMENT AND LICENSE AGREEMENT

This **AMENDMENT #4 TO THE RESEARCH, DEVELOPMENT AND LICENSE AGREEMENT** (this "***Amendment No. 4***") is entered into and made effective as of the 10th day of April, 2014 (the "***Amendment No. 4 Effective 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 **Glaxo Group Limited**, a company existing under the laws of England and Wales, having its registered office at 980 Great West Road, Brentford London TW8 9GS, United Kingdom ("***GSK***"). Isis and GSK are each referred to herein by name or as a "***Party***" or, collectively, as "***Parties***."

RECITALS

WHEREAS, Isis and GSK are parties to the Research, Development and License Agreement dated March 30, 2010, as amended (the "***Agreement***"); and

WHEREAS, Isis and GSK desire to amend certain terms of the Agreement solely with respect to the Collaboration Program focused on the [***] (the "***GSK-5 Program***"), including to extend the Collaboration Term for the GSK-5 Program to March 30, 2015, on the terms and conditions set forth herein.

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, and solely with respect to the GSK-5 Program, the Parties, intending to be legally bound, do hereby agree as follows:

Capitalized terms used but not defined herein shall have the meaning ascribed to such terms in the Agreement.

1. GSK-5 Program – Natural History Study.

a. The Parties will conduct the Natural History Study as part of the GSK-5 Development Plan. GSK and Isis [***] a clinical research organization ("***CRO***") to conduct the Natural History Study, and Isis will thereafter negotiate and enter into an agreement with such CRO for the conduct of such study with terms reasonably acceptable to GSK (the "***CRO Contract***"), it being understood that GSK will provide Isis comments to the terms of the CRO Contract, if any, within [***] ([***]) Business Days of receiving a draft of such CRO Contract from Isis. Notwithstanding the preceding sentence, and subject to Section 1.b and Section 1.c, if GSK and Isis cannot agree on a term in the CRO Contract, [***] will have final decision-making authority with respect to such term (provided that, such decision is in accordance with the GSK-5 Development Plan and would not result in an increase in External Costs above [***]). For avoidance of doubt, nothing in this Amendment No. 4 requires Isis to amend any agreement between Isis and any Third Party CRO that is in effect as of the Amendment No. 4 Effective Date. The Parties intend that the CRO Contract will be executed by Isis as soon as reasonably practicable after the Amendment No. 4 Effective Date. Such CRO Contract will specify that [***] and that, as between GSK and Isis, [***]. Isis will ensure that the CRO Contract includes provisions that [***] and [***].

b. Promptly after the Amendment No. 4 Effective Date, the Parties will agree upon a protocol for the conduct of the Natural History Study (the "***Initial Natural History Study Protocol***"). Isis shall be responsible for all of the costs for the conduct of the mutually-agreed Natural History Study (excluding any costs incurred by GSK), provided that Isis shall only be responsible for external costs for the Natural History Study (the "***External Costs***") up to [***] ($[***]) (the "***Isis Natural History Study Cost Cap***"). GSK will use reasonable efforts to [***] in accordance with the timeline included in the Natural History Study protocol. GSK will be responsible for the payment of all External Costs that exceed the Isis Natural History Study Cost Cap except to the extent such excessive costs result from [***].

c. Isis will not make any changes to the Initial Natural History Study Protocol or authorize or direct the CRO to do any work that is outside the scope of the Initial Natural History Study Protocol that would result in External Costs above the Isis Natural History Study Cost Cap, without GSK's prior written consent. GSK will not make any changes to the Initial Natural History Study Protocol or authorize or direct the CRO to do any work that is outside the scope of the Initial Natural History Study Protocol that would increase Isis's internal FTE costs for the conduct of such Natural History Study as compared to Isis's internal FTE costs for the conduct of the Initial Natural History Study Protocol without Isis's prior written consent.

2. GSK-5 Program – PoC Trial.

a. ***Proof of Concept (PoC) Trial***. The initial agreed-upon GSK-5 Development Plan is attached to this Amendment No. 4 as Attachment 1. The Parties [***] as set forth in the attached GSK-5 Development Plan. The Parties will meet approximately [***] ([***]) [***] after the [***] to evaluate the progress of the Natural History Study, determine [***], discuss [***] the Natural History Study and discuss [***] on the [***]. As soon as reasonably practicable and in no event later than the [***] ([***]) day following the date when [***] ([***]) of the subjects participating in the Natural History Study complete [***] ([***]) [***], the Parties will discuss in good faith and, subject to [***], will [***] the final study design and endpoints for the multiple-dose portion of the PoC Trial, which the Parties anticipate will be substantially in the form set forth for the PoC Trial study design and endpoints in the initial GSK-5 Development Plan.

b. As soon as reasonably practicable, Isis will provide GSK a summary of the data under the single-dose portion of the PoC Trial up to and including the [***] ([***]) day after the day on which the [***] in the single-dose portion of the PoC Trial (the "[***]"). Provided Isis has delivered the [***] to GSK, Isis may deliver to GSK a written notice stating Isis' desire to begin the multiple-dose portion of the PoC Trial (a "***Request to Continue***"). Within [***] ([***]) days after receipt of a Request to Continue, GSK will (subject to Section 2.c of this Amendment No. 4 below) deliver to Isis a written notice ("***Notice to Continue***") authorizing Isis to begin the multiple-dose portion of the PoC Trial pursuant to either (i) [***], or (ii) [***]. GSK will specify in its Notice to Continue whether the study design and endpoints for the multiple-dose portion of the PoC Trial for which GSK has authorized Isis to proceed are as set forth in (i) or (ii) above. For clarity, if GSK has not received a Request to Continue, GSK may deliver a Notice to Continue to Isis at any time.

c. If, by [***] ([***]) days after receipt of the Request to Continue, GSK has not provided Isis a Notice to Continue, then GSK's Option with respect to the GSK-5 Program will automatically expire and, subject to Section 5.10 of the Agreement (as amended by this Amendment No. 4), Isis will be free to develop and commercialize any Compounds that were included in the GSK-5 Program on its own or with a Third Party and, except as specified in Section 5.10 of the Agreement (as amended by this Amendment No. 4), GSK will have no further rights to the GSK-5 Program (including all Compounds included therein) and [***] will no longer be a Collaboration Target. Following any expiration of an Option under this Section 2.c, GSK will promptly transfer to Isis all data, results and information related to the testing and studies in the GSK-5 Program in the possession of GSK and its contractors to the extent such data, results and information were generated by or on behalf of GSK under the Agreement (as amended by this Amendment No. 4).

d. Except as provided under Section 2.c of this Amendment No. 4, the multiple-dose portion of the PoC Trial shall not be initiated until the final GSK-5 Development Plan, including the final study design and endpoints for the multiple-dose portion of the PoC Trial (which shall be subject to [***]), have been agreed upon. Following GSK's Option exercise, decision-making for the GSK-5 Program will be governed in accordance with Section 3.c.ii of this Amendment No. 4.

3. GSK-5 Program –Costs.

a. ***Development Costs Paid by Isis***. Isis will be responsible for, and will use Commercially Reasonable Efforts to perform, Isis' activities under the GSK-5 Development Plan and will be responsible for all costs and expenses associated therewith, except to the extent such costs and expenses have otherwise been allocated to GSK under Section 1, Section 3.c or Section 5 of this Amendment No. 4.

b. ***Manufacturing Costs Paid by Isis***. Subject to Section 5 of this Amendment No. 4 and until GSK exercises its Option for the GSK-5 Program in accordance with the Agreement (as amended by this Amendment No. 4), Isis will be solely responsible for the costs and expense for the Costs of Goods for the GSK-5 Development Plan. As included herein, "***Cost of Goods***" means [***].

c. Development Costs Paid by GSK.

i. ***Before Option Exercise.*** Until GSK exercises its Option for the GSK-5 Program in accordance with the Agreement (as amended by this Amendment No. 4), GSK will be responsible for and will use Commercially Reasonable Efforts to perform the activities allocated to GSK under the GSK-5 Development Plan, and shall be responsible for payment of all costs and expenses related to GSK's conduct of such activities. In addition, GSK will be responsible for External Costs above the Isis Natural History Study Cost Cap as set forth in Section 1.b of this Amendment No. 4, and for any Additional Costs resulting from Approved Changes. If Additional Costs result from Approved Changes (excluding changes to the Natural History Study), then Isis will deliver to GSK [***] an invoice for such portion of the Additional Costs that is allocated for the activities [***] [***], and GSK will pay each such invoice within [***] ([***]) days after GSK's receipt.

ii. ***After Option Exercise***. Without limiting the terms set forth in the Agreement, after GSK exercises its Option for the GSK-5 Program, GSK will be solely responsible for and will have sole decision making authority over all Development and Commercialization activities for the GSK-5 Program; *provided, however*, that Isis will continue to be responsible for the completion of the PoC Trial in accordance with the GSK-5 Development Plan in place at the time of such Option exercise, including payment of the costs and expenses associated therewith except to the extent such costs and expenses have otherwise been allocated to GSK under Section 1, Section 3.c or Section 5 of this Amendment No. 4, and Isis will continue to be responsible for all activities allocated to Isis under the GSK-5 Development Plan, including completion of reports and other activities allocated to Isis under such GSK-5 Development Plan. In addition, after such Option exercise by GSK, GSK will be solely responsible for all costs and expenses associated with Development, Manufacture and Commercialization of Licensed Compounds and related Licensed Products from the GSK-5 Program, excluding those costs and expenses for those activities for which Isis is responsible under the GSK-5 Development Plan, or for which Isis is otherwise responsible to provide at no cost to GSK under Section 4.2 of the Agreement.

4. Option.

a. Following GSK's receipt of (i) a notice from Isis that the PoC Trial is Completed, and (ii) the PoC Data Package (as defined in this Amendment No. 4) for the GSK-5 Program (such notice and package, the "***GSK-5 PoC Trial Completion Package***"), GSK will provide written notice to Isis of its decision whether to exercise its Option to the GSK-5 Program on or before 5:00 p.m. (Eastern time) on the [***] day following GSK's receipt of the GSK-5 PoC Trial Completion Package (the "***GSK-5 Option Deadline***"). If GSK does not provide written notice to Isis of GSK's exercise of the GSK Option for the GSK-5 Program before the GSK-5 Option Deadline, then GSK's Option to the GSK-5 Program will expire and, subject to Section 5.10 of the Agreement (as amended by this Amendment No. 4), Isis will be free to Develop and Commercialize any Compounds that were included in the GSK-5 Program on its own or with a Third Party and, except as specified in Section 5.10 of the Agreement (as Amended by this Amendment No. 4), GSK will have no further rights to the GSK-5 Program (including all Compounds included therein) and [***] will no longer be a Collaboration Target. Following any expiration of an Option under this Section 4, GSK will promptly transfer to Isis all data, results and information related to the testing and studies in the GSK-5 Program in the possession of GSK and its contractors to the extent such data, results and information were generated by or on behalf of GSK under the Agreement (as amended by this Amendment No. 4).

b. **Early Exercise of an Option.** For the avoidance of doubt, notwithstanding anything to the contrary in this Amendment No. 4 or in the Agreement, GSK will have the right to exercise its Option for the GSK-5 Program prior to GSK's receipt of a GSK-5 PoC Trial Completion Package in accordance with the terms of the Agreement (as amended by this Amendment No. 4).

5. Material Amendments to the GSK-5 Development Plan for the PoC Trial.

a. ***Overview***. As of the Amendment No. 4 Effective Date, the Parties have agreed to the GSK-5 Development Plan (which is attached hereto as Attachment 1).

b. ***Material Amendments***. Subject to Section 5.d of this Amendment No.4, no Material Amendments may be made without both Parties' prior written consent. If any Regulatory Authority requires or, based on feedback from a Regulatory Authority, either Party requests a change to the PoC Trial or the GSK-5 Development Plan that would require the Parties to make Material Amendment to the GSK-5 Development Plan to effect such a change, the Parties will use good faith and commercially reasonable efforts to mutually agree on such Material Amendment (including any associated Additional Costs and payment schedule thereof) within [***] ([***]) days of receiving such proposed change from such Regulatory Authority or a Party.

c. ***Material Amendments Process.***

i. If the Parties mutually agree to make such a Material Amendment (excluding Material Amendments to the Natural History Study) (including any associated Additional Costs and the payment schedule thereof), such proposed Material Amendment shall be deemed an Approved Change, and the GSK-5 Development Plan will be amended to expressly incorporate such Approved Change. Thereafter, Isis and GSK (as applicable) will continue to conduct the GSK-5 Development Plan in accordance with such amended GSK-5 Development Plan.

ii. If, despite the Parties' good faith and Commercially Reasonable Efforts, the Parties cannot agree (i) on whether to make the proposed Material Amendment to the GSK-5 Development Plan (including agreement on the scope of such proposed Material Amendment or any associated Additional Costs, and the payment schedule thereof) or (ii) whether such proposed amendment qualifies as a Material Amendment, in each case, within [***] ([***]) days of receiving such proposed change from such Regulatory Authority or a Party, the dispute will be promptly (but no later than [***] days after the end of such [***] ([***]) day period) referred to the [***]. If the [***] cannot resolve the matter within [***] ([***]) Business Days after receiving such dispute then, subject to Section 2.c of this Amendment No. 4, the Parties will continue the activities under the GSK-5 Program (including the PoC Trial) under the then-current GSK-5 Development Plan, until such matter is resolved by the Parties (if ever) or the GSK-5 Program is terminated in accordance with the Agreement or this Amendment No. 4. Notwithstanding anything to the contrary in the Agreement or this Amendment No. 4, [***] with respect to changes to the study design and endpoints for the multiple-dose portion of the PoC Trial, *provided that* (i) changes made as a result of [***] shall be deemed Approved Changes for which [***] and (ii) with respect to the multiple-dose portion of the PoC Trial, [***] to (x) [***], (y) [***], or (z) [***].

d. ***Non-Material Amendments***. Isis will consider in good faith any changes to the GSK-5 Development Plan that are requested by GSK that do not require the Parties to make a Material Amendment to the GSK-5 Development Plan to affect such a change. Isis shall have the ability to make any changes to the GSK-5 Development Plan that do not require the Parties to make a Material Amendment to the GSK-5 Development Plan to affect such a change without the prior consent of GSK, *provided, that* such changes [***].

e. The process for Approved Changes as set forth in this Section 5 shall not apply to Approved Changes for the Natural History Study, which are addressed exclusively by Section 1 of this Amendment No. 4.

6. **Financial Provisions**. The following revised financial provisions will apply solely to the GSK-5 Program:

a. ***Milestone Payments for First Achievement of Development Milestone Event***. Solely with respect to a Compound under the GSK-5 Program that first achieves a Development Milestone Event by or on behalf of GSK or its Affiliates or Sublicensees, Column 1 of Table 2 set forth in Section 5.5.1 (Milestone Payments for First Achievement of Development Milestone Event) of the Agreement is hereby deleted in its entirety and replaced with TABLE 2A below.

TABLE 2A	
Development Milestone Events for the GSK-5 Program	**Milestone Payment**
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]*	[***]
[***]*	[***]
Total Development Milestone Payments for the GSK-5 Program	[***]

***[***].**

For avoidance of doubt, except as expressly amended by this Amendment No. 4, the terms and conditions of Section 5.5.2 of the Agreement continue to apply to the GSK-5 Program. Isis understands and acknowledges that, as of the Amendment No. 4 Effective Date, [***].

b. ***GSK-5 Program Option Exercise Fee***. Upon the exercise by GSK of the Option for the GSK-5 Program, if exercised by GSK in accordance with the Agreement (as amended by this Amendment No. 4), in lieu of the [***] ([***]) Option exercise fee set forth in Column 1 of Table 1 in Section 5.4 (Option Exercise Fees) of the Agreement, GSK will pay Isis an Option exercise fee of [***] ([***]) for the GSK-5 Program. Such Option Exercise Fee will be paid within [***] ([***]) days after receipt by GSK of an invoice sent from Isis on or after such Option exercise under the Agreement (as amended by this Amendment No. 4).

c. ***Milestone Payments for First Achievement of Sales Milestone Event***. Solely with respect to a Licensed Product under the GSK-5 Program that first achieves the listed events (as set forth in Table 4A below) by or on behalf of GSK, its Affiliates or Sublicensees, TABLE 4 set forth in Section 5.7.1 (Milestone Payments for First Achievement of Sales Milestone Event) of the Agreement is deleted in its entirety and replaced with TABLE 4A below:

TABLE 4A	
GSK-5 Sales Milestones for each Licensed Product in the GSK-5 Program	**Milestone Payment**
[***] in worldwide Annual Net Sales	[***]
[***] in worldwide Annual Net Sales	[***]
[***] in worldwide Annual Net Sales	[***]
[***] in worldwide Annual Net Sales	[***]
Total GSK-5 Sales Milestone Payments for the GSK-5 Program	**[***]**

7. **GSK-5 Program Royalties**. Solely with respect to the Licensed Products under the GSK-5 Program sold by GSK, its Affiliates or Sublicensees, TABLE 5 set forth in Section 5.9.1 (GSK Patent Royalty) of the Agreement is deleted in its entirety and replaced with TABLE 5A below:

TABLE 5A	
Worldwide Annual Net Sales of each Licensed Product in the GSK-5 Program	**Royalty Rate**
For the portion up to and including $[***]	[***]%
For the portion above $[***] and up to and including $[***]	[***]%
For the portion above $[***]	[***]%

8. **GSK-5 Program Reverse Royalties**. Solely with respect to any GSK-5 Program Discontinued Products, TABLE 6 set forth in Section 5.10.1 (Reverse Royalty for Discontinued Products) of the Agreement is deleted in its entirety and replaced with TABLE 6A below:

TABLE 6A	
Development/Regulatory Status of Discontinued Product at time of reversion under this Agreement	**Applicable Royalty Rate on worldwide Annual Net Sales of Discontinued Product**
Discontinued Products for which GSK has paid Isis the [***] milestone payment	[***]%
After [***] but prior to [***]	[***]%
After [***] but prior to [***]	[***]%
After [***]	[***]%

9. **No Impact on Other Collaboration Programs**. Except as otherwise expressly amended by this Amendment No. 4, the Agreement remains in full force and effect in accordance with its terms. For the avoidance of doubt, this Amendment No. 4 is solely intended to modify certain terms of the Agreement regarding the GSK-5 Program, and does not amend the Agreement in any way with respect to the other Collaboration Programs.

10. **GSK's Right to Terminate for Convenience**. This Section 10 of this Amendment No. 4 supersedes and replaces Section 9.2.1 of the Agreement with respect to the GSK-5 Program, including GSK's right to terminate the GSK-5 Program under Section 9.2.1 of the Agreement. In lieu of GSK's right to terminate under Section 9.2.1 of the Agreement, at any time following the Amendment No. 4 Effective Date, GSK will be entitled to terminate the Agreement (as amended by this Amendment No. 4) with respect to the GSK-5 Program by providing Isis ninety (90) days prior written notice; *provided however*, if GSK terminates the Agreement (as amended by this Amendment No. 4) with respect to the GSK-5 Program and at the effective date of such termination, Isis had spent in Development of the GSK-5 Program (including actual external costs and Isis' good faith estimate of its internal FTE costs) at least an amount equal to (a) [***] ([***]) *plus* (b) [***], then if such notice of termination by GSK is:

(i) before [***] for the GSK-5 Program and [***], GSK will pay Isis [***] percent ([***]%) of the milestone payment for [***] for the GSK-5 Program and [***] percent ([***]%) of the milestone payment for [***],

(ii) before [***] for the GSK-5 Program but after [***], GSK will pay Isis [***] percent ([***]%) of the milestone payment for [***] for the GSK-5 Program,

(iii) after [***] for the GSK-5 Program but before [***], GSK will pay Isis [***] percent ([***]%) of the milestone payment for [***],

(iv) after [***] for the GSK-5 Program and after [***] but before [***], GSK will pay Isis [***] percent ([***]%) of the milestone payment for [***],

(v) after [***], GSK will pay Isis [***] percent ([***]%) of the milestone payment for [***]; *provided, that*:

(A) if the [***] does not occur within [***] ([***]) months of such notice of termination by GSK, then [***]: (a) such [***], *minus the sum of:* (b) [***], and (c) [***]; or

(B) if the [***] occurs within [***] ([***]) months of such notice of termination by GSK, *and* [***], then [***]; or

(C) if the [***] occurs within [***] ([***]) months of such notice of termination by GSK, and [***], Isis will [***].

Notwithstanding the foregoing, if under the scenarios set forth in either Section 10.v.A or Section 10.v.B above [***] prior to the end of the [***] ([***]) month period, then [***].

Following Isis's receipt of a notice of termination from GSK under this Section 10 of Amendment No. 4, Isis will invoice GSK for the appropriate payment due under clauses (i)-(v) of this Section 10 of Amendment No. 4, as applicable, and GSK will make the applicable payments under clauses (i)-(v) of this Section 10 within [***] days of receipt of such invoice.

Subject to Section 9.3.4 and Section 9.3.5 of the Agreement, as amended by this Amendment No. 4, immediately following such termination notice date, GSK's obligations under Section 5.5 through Section 5.9 of the Agreement (as amended by this Amendment No. 4) will cease. Notwithstanding the foregoing, in the event GSK believes in good faith that there are safety concerns with respect to the GSK-5 Program or a Licensed Product under the GSK-5 Program, which concerns merit the immediate termination of the GSK-5 Program or such Licensed Product, GSK will have the right to terminate this Amendment No. 4 and the Agreement with respect to the GSK-5 Program or such Licensed Product, as applicable, immediately upon written notice to Isis and without a [***] ([***]) day notice period for termination and [***]. This Section 10 shall survive the termination of this Amendment No. 4 or the Agreement for purposes of determining the applicable payment, if any, due by GSK as a result of such termination.

11. **Special Consequences for Voluntary Termination by GSK under Section 10 of this Amendment No. 4.** In the event of a termination with respect to the GSK-5 Program under Section 10 of this Amendment No. 4, then:

a. the licenses granted by Isis to GSK under the Agreement with respect to the GSK-5 Program will terminate and GSK, its Affiliates and Sublicensees will cease selling all Licensed Products from the GSK-5 Program; provided that GSK, its Affiliates and Sublicensees will have the right to sell any remaining inventory of such Licensed Products over a period of no greater than [***] ([***]) months after the effective date of such termination and GSK will pay Isis royalties in accordance with Section 7 of this Amendment No. 4 on the Net Sales of such inventory of Licensed Products;

b. GSK will perform the obligations under Section 4.2.1 of the Agreement for the GSK-5 Program, as though such obligations under Section 4.2 of the Agreement were obligations owed by GSK to Isis, to the extent applicable and in GSK's Control *mutatis mutandis*; and

c. except as explicitly set forth in this Section 11, or Sections 9.3.3, 9.3.4 or 9.3.5 of the Agreement, GSK will have no further rights and Isis will have no further obligations with respect to the GSK-5 Program.

For clarity, (i) this Section 11 of the Amendment No. 4 supersedes and replaces Section 9.3.2 of the Agreement solely with respect to a voluntary termination by GSK with respect to the GSK-5 Program, (ii) Section 9.3.2 of the Agreement will not apply to GSK's voluntary termination with respect to the GSK-5 Program under Section 10 of this Amendment No. 4, and (iii) Section 9.3.2 of the Agreement will continue to apply in the case of a termination by Isis under Section 9.2.2 or 9.2.3 of the Agreement.

12. **Collaboration Term**. Solely with respect to the GSK-5 Program, notwithstanding anything to the contrary in the Agreement, the Collaboration Term for the GSK-5 Program is extended such that it ends on March 30, 2015.

13. **Definitions**. Capitalized terms not otherwise defined herein will have the meanings given in the Agreement. For purposes of this Amendment No. 4, the following capitalized terms will have the following meanings:

a. "***Additional Costs***" means, [***].

b. "***Approved Changes***" means any changes (including duration of dosing, additional studies, additional endpoints, additional analysis, additional drug supply, etc.) to the GSK-5 Development Plan (i) that are requested by a Party or required by a Regulatory Authority, (ii) that are required to be agreed upon by the Parties under this Amendment No. 4, and (iii) that are in fact agreed upon by GSK and Isis in accordance with this Amendment No. 4 or are decided through [***] final decision making authority under Section 5.c. of this Amendment No. 4. For the avoidance of doubt, changes made to the Natural History Study in accordance with the terms of Section 1 of this Amendment No. 4 and changes made to the GSK-5 Development Plan that do not result in a Material Amendment shall not be considered "Approved Changes" as that term is used in this Amendment No. 4.

c. "***Complete***", "***Completed***", or "***Completion***" means the point in time at which the primary database lock for the study data for the PoC Trial has occurred and the data generated based on that primary database lock under the statistical analysis plan for the PoC Trial are available.

d. "***Cost of Goods***" has the meaning set forth in Section 3.b of this Amendment No. 4.

e. "***CRO***" has the meaning set forth in Section 1.a of this Amendment No. 4.

f. "***CRO Contract***" has the meaning set forth in Section 1.a of this Amendment No. 4.

g. "***External Costs***" has the meaning set forth in Section 1.b. of this Amendment No. 4.

h. "***GSK-5 Development Plan***" means the Development plan attached to this Amendment No. 4 as Attachment 1, which may be amended from time to time pursuant to Section 5 of this Amendment No. 4.

i. "***GSK-5 Option Deadline***" has the meaning set forth in Section 4 of this Amendment No. 4.

j. "***GSK-5 PoC Trial Completion Package***" has the meaning set forth in Section 4 of this Amendment No. 4.

k. "***GSK-5 Program***" has the meaning set forth in the recitals.

l. [***]

m. [***]

n. [***]

o. "***Material Amendment***" means an amendment to one (1) or more of the bullet-point items set forth in the GSK-5 Development Plan included in Appendix A, attached to this Amendment No. 4 and incorporated herein by reference.

p. "***Natural History Study***" means a study intended to follow the natural progression of [***] in patients with the [***], as more fully described in Attachment 1.

q. "***Natural History Study Cost Cap***" has the meaning set forth in Section 1.b. of this Amendment No. 4.

r. "***PoC Data Package***" means, with respect to the GSK-5 Program Development Candidate, (i) [***], (ii) [***], (iii) [***], (iv) [***], (v) copies of all filings submitted to Regulatory Authorities, (vi) [***], and (vii) [***]. In the event that GSK elects to exercise its early Option to the GSK-5 Program in accordance with the Agreement (as amended by this Amendment No. 4), the PoC Data Package will be interpreted to mean the items set forth in this Section 13.r (i) through (vii) to the extent such items are available at the time that GSK notifies Isis of GSK's election to exercise such early Option.

s. "***PoC Trial***" means a clinical study for the GSK-5 Program, consisting of a two-part, multicenter, open-label study of the GSK-5 Development Candidate, including single dose (part 1) and multiple dose (part 2) cohorts, as described in the GSK-5 Development Plan.

*** - * - * - ***

[SIGNATURE PAGE FOLLOWS]

IN WITNESS WHEREOF, THE PARTIES HAVE CAUSED THIS AMENDMENT NO. 4 TO BE EXECUTED BY THEIR DULY AUTHORIZED REPRESENTATIVES AS OF THE AMENDMENT NO. 4 EFFECTIVE DATE.

ISIS PHARMACEUTICALS, INC.

BY: */s/ B. Lynne Parshall*

NAME: B. Lynne Parshall

TITLE: Chief Operating Officer

DATE: _____

GLAXO GROUP LIMITED

BY: */s/ Paul Williamson*

NAME: Paul Williamson

TITLE: Authorised Signatory for and on behalf

Of Edinburgh Pharmaceutical Industries Limited

Corporate Director

DATE: _____

EXECUTION COPY EXHIBIT 10.2

EXECUTION COPY EXHIBIT 10.2

ATTACHMENT 1

GSK – 5 DEVELOPMENT PLAN

[***]

EXHIBIT 10.3

AMENDMENT #5 TO THE RESEARCH, DEVELOPMENT AND LICENSE AGREEMENT

This **AMENDMENT #5 TO THE RESEARCH, DEVELOPMENT AND LICENSE AGREEMENT** (this "***Amendment No. 5***") is entered into and made effective as of the 27th day of June, 2014 (the "***Amendment No. 5 Effective 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 **Glaxo Group Limited**, a company existing under the laws of England and Wales, having its registered office at 980 Great West Road, Brentford London TW8 9GS, United Kingdom ("***GGL***"), and **GlaxoSmithKline Intellectual Property Development Limited**, a company existing under the laws of England and Wales, having its registered office at 980 Great West Road, Brentford London TW8 9GS, United Kingdom ("*GSK IPDL*"). GGL and GSK IPDL are referred to together as "***GSK***". Isis and GSK are each referred to herein by name or as a "***Party***" or, collectively, as "***Parties***."

RECITALS

WHEREAS, Isis and GGL are parties to the Research, Development and License Agreement dated March 30, 2010, as amended (the "***Agreement***") and (to the extent applicable) GGL has sub-licensed its rights under the Agreement to GSK IPDL;

WHEREAS, Isis and GSK are Developing the molecule known as [***] under the Collaboration Program focused on [***] (the "[***] ***Program***"); and

WHEREAS, Isis and GSK desire to amend certain terms of the Agreement solely with respect to the [***] Program, and to amend the activities being conducted under the [***] Program to include work on [***] ASOs discovered by Isis that bind to [***] and [***] (the "[***] ***Compounds***");

WHEREAS, Isis and GSK wish to conduct research and development activities to identify and advance, [***], an [***] on the terms and conditions set forth herein.

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, and solely with respect to the [***] Program, the Parties, intending to be legally bound, do hereby agree as follows:

Capitalized terms used but not defined herein will have the meaning ascribed to such terms in the Agreement.

1. **Amendment of Activities under [***] Program.** The [***] Program is hereby amended to include work on the compounds listed on Appendix 4 attached hereto (each, a ***"Research Lead"***) which (unless excluded under Section 11(a) of this Amendment No. 5) are acknowledged to be Compounds under the [***] Program.

2. **[***] DC Development Plan**. The initial Development plan for the potential [***] DC is attached hereto as Appendix 1. After the selection of the [***] DC in accordance with Section 3 of this Amendment No.5, GSK will promptly provide Isis with an updated Development plan for the [***] DC, and thereafter will update such Development plan on at least [***] basis until such time as the [***] Option is exercised (or otherwise expires). After Option exercise, GSK will provide updates as required under Section 4.3.2 and Section 4.3.3 of the Agreement.

3. **Research Activities; Selection of [***] DC**. Isis will use Commercially Reasonable Efforts to conduct the [***] DC Confirmation Activities set out in Column 3 of Appendix 2 attached hereto, with the goal of achieving the [***] DC Criteria, as follows:

a. Isis will use Commercially Reasonable Efforts to complete a study testing [***] (as further described and in accordance with Column 3 of Appendix 2 of this Amendment No.5) to provide [***] (the ***"Research Lead Study"***).

b. Once the Research Lead Study has been completed, Isis will provide GSK written notice thereof, including a summary of the results of the Research Lead Study (such notice and summary the ***"Research Lead Data Package"***). Within [***] ([***]) days of its receipt of the Research Lead Data Package, GSK will designate [***] (the ***"Prioritized Lead"***) to advance as described in Section 3.c. of this Amendment No. 5.

c. For the Prioritized Lead, Isis will use Commercially Reasonable Efforts to complete (i) [***], and (ii) [***], (all as further described and in accordance with Column 3 of Appendix 2 of this Amendment No.5) such [***] to be agreed and finalized in advance by the JSC (the ***"Prioritized Lead Studies"***). Once the Prioritized Lead Studies have been completed, Isis will provide the JSC written notice thereof, including the data and results of the Prioritized Lead Studies (the ***"Prioritized Lead Data Package"***). Within [***] days of its receipt of the Prioritized Lead Data Package, [***] will determine whether the Prioritized Lead meets the applicable criteria for designating a development candidate under Column 3 of Appendix 2 (the ***"[***] DC Selection Criteria"***). Unless within such [***] day period [***] determines (or by written notice GSK informs Isis that) the Prioritized Lead has not met the [***] DC Selection Criteria, then the Prioritized Lead will be the [***] DC. If within such [***] day period [***] determines (or by written notice GSK informs Isis that) the Prioritized Lead has not met the [***] DC Selection Criteria, then within [***] days of such determination, GSK may designate an additional Research Lead as a Prioritized Lead, and Isis and GSK will repeat the process set forth in this Section 3.c. of this Amendment No. 5 until the earlier of the date (y) an [***] DC is designated, or (z) each Research Lead has been tested in the studies set forth in this Section 3.c of this Amendment No. 5, but no such Research Lead has been designated an [***] DC. If the Parties do not designate an [***] DC under this Section 3.c. of this Amendment No. 5 then, unless otherwise mutually agreed to by the Parties in writing, no Compound will be an [***] DC and Isis will have no further obligations under this Amendment No. 5.

d. Isis will be responsible for all costs and expenses associated with the studies under this Section 3 of this Amendment No. 5.

4. [***] DC Development Activities Conducted by Isis and Paid for by GSK.

a. Isis' Manufacturing Responsibilities; CMC Characterization.

i. Isis will manufacture [***] of API for the Research Lead known as [***], to generate [***] of API. Isis will begin such activities within [***] ([***]) Business Days of Isis' receipt of the $[***] payment under clause (i) of Section 4.c. of this Amendment No. 5. Such API will be manufactured in accordance with cGMP and [***]. In addition, Isis will formulate an amount of such API into drug product that is sufficient (but no more than is necessary) to conduct the [***] and the [***] for the [***] DC, and which meets the requirements of cGLP. As soon as reasonably practicable (and using Commercially Reasonable Efforts to meet such timeframe as necessary to meet the scheduled start of the [***] as agreed between the Parties), Isis will deliver such drug product to the CRO, and deliver the remaining quantity of API to GSK, in each case [***]. GSK will pay Isis for its [***] to manufacture such API and drug product (subject to the principles set out in Section 4(a)(ii) below with respect to failed batches) as set out in Rows A and B of Appendix 3 attached hereto, which include the actual cost charged by its appointed Third Party contract manufacturing organization to perform the conjugation work for such API and Isis' [***].

ii. If Isis encounters any difficulties or hazards during the manufacture of such API that prevents Isis from successfully manufacturing API that meets the requirements of Section 4(a)(i) above with respect to quality and quantity, Isis will notify GSK within [***] days of such failure and will use Commercially Reasonable Efforts to manufacture a replacement batch of API, such that the CRO receives the formulated API in accordance with the requirements of Section 4(a)(i) above as close to the originally-scheduled delivery date as possible. For any such failed batch, the cost of the manufacture incurred by Isis will be [***] as follows: [***]; and, to the extent [***], [***]; *except*, that [***]. Any such [***] under Section 4.a.i of this Amendment No. 5.

iii. Isis will also use Commercially Reasonable Efforts to [***] (and perform the related [***] for the [***] for the [***] for the [***] DC. GSK will pay Isis for its internal FTE costs reasonably estimated to conduct such activities which have been calculated in accordance with [***] set out in Section 4(d) of this Amendment No. 5 and included in the costs outlined in Row A of Appendix 3 hereto.

iv. Isis and GSK will agree to a technology transfer plan and schedule pursuant to which Isis will provide to GSK (or to a Third Party manufacturer selected by GSK and reasonably agreed to by Isis) a technology transfer under Section 4.2.1 of the Agreement solely to the extent necessary to enable GSK to fulfill its obligations to Develop the [***] DC under Section 5 of this Amendment No. 5 prior to the [***] Option Deadline (including use of the API and formulated product supplied by Isis according to this Amendment No.5), and solely for the sole purpose of Developing the [***] DC. Isis will provide such transfer in a timely manner to facilitate GSK's activities in accordance with the [***] DC Development plan. If GSK believes in good faith that additional API for the [***] DC is necessary for GSK to fulfill its obligations to Develop the [***] DC under Section 5 of this Amendment No. 5, then GSK will provide Isis written notice thereof, and the technology transfer plan will be expanded accordingly by mutual agreement. Isis will provide the first [***] ([***]) hours of such technology transfer [***], and thereafter GSK will pay Isis for [***] and any out-of-pocket costs to perform such activities ([***] in accordance with the principles set out in Section 4(d) of this Amendment No. 5). Isis will provide GSK an [***] GSK pursuant to this Section 4(a)(iv) in advance of initiating such activities. Until GSK approves the estimated cost to perform such an activity, Isis will not incur such cost and Isis will not be obligated to perform such activity.

v. At GSK's request, Isis will use its Commercially Reasonable Efforts to refer the conduct of [***] for the [***] and [***] for the [***] DC manufactured by Isis to an established contract research organization Isis uses to perform such work; *provided* GSK will be solely responsible for managing such studies and the cost of such studies.

vi. If a Compound that is not [***] is designated as the [***] DC, then at the same time as such designation, GSK will (i) pay Isis the Remaining Payment Due under Section 4.c (iii) of this Amendment No. 5 related to [***], and (ii) notify Isis if GSK intends to manufacture the API and drug product for such [***] DC itself or if GSK intends Isis to manufacture such API and drug product for such [***] DC. If GSK notifies Isis that GSK intends Isis to manufacture such API for such [***] DC, then at GSK's expense, as soon as reasonably practicable Isis will manufacture [***] of the API and related drug product for such [***] DC under the same terms and conditions as set forth in Section 4.a. of this Amendment No. 5 by adding such [***] DC to Isis' then existing queue for manufacturing compounds at Isis' facility [***] and the Parties will adjust the planned start of the [***] and [***] accordingly.

b. **[***].** Following [***], Isis will contract for the conduct of [***] and the [***] under the initial [***] DC Development Plan with an established contract research organization (the ***"CRO"***) consistent with the requirements of Section 4.1.7 and other applicable terms of the Agreement (with respect to sub-contracting), and will monitor the performance of such [***] by such CRO, including compliance with all Applicable Law. GSK will pay Isis for all of [***] and [***], as set out in Row D of Appendix 3.

Isis will also use Commercially Reasonable Efforts to [***] for the [***] DC. GSK will pay Isis [***].

Isis will provide GSK an estimate of all such costs to be charged to GSK pursuant to this Section 4(b) in advance of initiating such activities. Until GSK approves the estimated cost to perform such an activity, Isis will not incur such cost and Isis will not be obligated to perform such activity. Isis currently estimates that it will use [***] to conduct the work under this Section 4.b. of this Amendment No. 5. For clarity, Isis will only be required to conduct the activities under this Section 4.b for [***].

c. **Payment by GSK.** GSK will pay Isis for the activities under this Section 4 in accordance with the amounts set forth in Appendix 3 attached hereto, as follows, (i) with respect to the payments due under Section 4(a) of this Amendment No. 5, upon [***], Isis will issue an invoice to GSK for $[***] (being the total amount due under the Initial Payment Column for Rows A, B and C of Appendix 3), and GSK will pay such invoice within [***] ([***]) Business Days following receipt of such invoice by GSK, (ii) with respect to the payments due under Section 4(b) of this Amendment No. 5, upon [***], Isis will invoice GSK for [***]% of the [***] and [***]% of the [***] to conduct the work under Section 4.b of this Amendment No. 5 (as described in the Initial Payment Column of Row D of Appendix 3), and GSK will pay such invoice within [***] ([***]) days of receipt of such invoice by GSK, and (iii) upon the occurrence of the applicable "Event Triggering Remaining Payment" listed on Appendix 3 for the relevant activity, Isis will issue an invoice to GSK for the balance of any remaining payment due in respect of such activity as shown in the Remaining Payment Due column of Appendix 3, and GSK will pay such invoice within [***] ([***]) days of receipt of such invoice by GSK; *provided always* that in the case of remaining payments under this sub-section (iii) of this Section 4(c), such payments will only be due from GSK to Isis to the extent that [***].

d. **FTEs**. With respect to activities under this Amendment No. 5 that require GSK to reimburse Isis FTE costs, Isis will [***], and the then applicable [***] will apply. Isis' applicable [***] for the 2014 Calendar Year is $[***].

5. **GSK's Manufacturing and Development Responsibilities**.

a. Except as expressly set forth in Section 3 and Section 4 of this Amendment No. 5, without prejudice to GSK's obligations under Section 4.3 of the Agreement, as from the Amendment No.5 Effective Date until such time as GSK exercises its Option to the [***] Program (or until such Option expires), and provided Isis has fulfilled its obligations under Section 4.a and Section 4.b of this Amendment No. 5 (to the extent necessary for GSK to perform its obligations), GSK will use Commercially Reasonable Efforts to conduct all activities related to [***] the [***] DC, including but not limited to (i) [***] and [***] for the [***], (ii) [***], including the [***], (iii) [***], (iv) [***]. GSK will be responsible for all costs and expenses associated with the activities under this Section 5. Following GSK's exercise of its Option to the [***] Program, GSK's Development and Commercialization obligations shall be as set forth in Section 4.3 of the Agreement.

b. **Commitment to Develop [***] DC.** Without limiting GSK's obligations under Section 2.2 of the Agreement and except as otherwise required for GSK to fulfil its obligations under the Agreement or as otherwise requested by Isis, prior to GSK's exercise of its Option to the [***] Program, GSK will [***] without Isis' prior written consent.

c. **Development of Alternative [***] DC.** If based on the results of the [***] or the [***] for the first [***] DC, GSK in good faith (acting in accordance with its Commercially Reasonable Efforts) determines Development of such [***] DC should be terminated, GSK may terminate the Development of such [***] DC by providing Isis a written notice thereof within [***] ([***]) days following the completion of the [***] of such [***], or completion of the [***] (as applicable). In such case, the Parties will, as soon as reasonably practicable, hold a meeting of the JSC to discuss the merits of Developing a different Research Lead. Within [***] ([***]) days following such meeting of the JSC (or, in any event if the JSC has not met within [***] ([***]) days of the termination notice from GSK), GSK may provide Isis a written notice designating a Research Lead as a replacement [***] DC, in which case (i) such Research Lead will be the [***] DC, (ii) Isis will have no obligation to research, Develop or Manufacture such [***] DC, and (iii) GSK will use Commercially Reasonable Efforts to Develop such [***] DC up through the [***] Option Deadline [***].

6. **Safety Reporting; Data Integrity**.

a. ***Safety Reporting.*** GSK will report to Isis any serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) under any Clinical Study for the [***] DC being conducted by or on behalf of GSK prior to the date of [***] Option exercise, strictly in accordance with the timelines set out in the Safety Data Exchange Agreement (such timelines to ensure that each Party is able to meet all applicable legal and regulatory obligations in line with its own respective internal processes). In addition, GSK will provide Isis with [***] and [***] regarding adverse events and material lab findings under any Clinical Study for the [***] DC being conducted by or on behalf of GSK prior to the date of [***] Option exercise.

b. ***Safety Data Exchange Agreement (or equivalent)***. As soon as reasonably practicable following the Amendment No. 5 Effective Date, and in any event no later than [***] days prior to the expected start of the first Clinical Study of the [***] DC (or such other date as may be agreed between the Parties), the pharmacovigilance representatives of each of Isis and GSK will meet and determine the appropriate approach to be taken for the collection, review, assessment, tracking, exchange and filing of information related to adverse events and safety data associated with a [***] DC during the period prior to GSK's exercise of its Option to the [***] Program, based on the activities being conducted by each Party under the Agreement and this Amendment No.5. Such approach will be documented between the Parties in writing in a separate safety data exchange agreement (to the extent such agreement is necessary) or other appropriate documentation, which will control with respect to the subject matter covered therein. Such documentation will be in accordance with, and will enable the Parties to fulfill, local and international regulatory reporting obligations to Regulatory Authorities and other Applicable Law as well as to meet their own respective internal policy requirements. After GSK's exercise of its Option to the [***] Program, the Parties will wind-down and discontinue the activities provided for under any such arrangements, but GSK will continue to provide Isis the cooperation and information described in Section 4.4.1 of the Agreement as it relates to the [***] Program.

c. ***Isis Database***. Notwithstanding the fact that GSK has not exercised its Option for the [***] Program, GSK will provide Isis the cooperation and information described in Section 4.4.1 of the Agreement as it relates to activities undertaken by GSK in relation to the [***] DC prior to the date of [***] Option exercise.

d. ***Data Integrity***. GSK agrees that it will carry out its activities under the [***] Program and collect and record any data generated therefrom in a manner consistent with Good Data Management Practices. Prior to GSK's exercise of its Option for the [***] Program, GSK will, upon reasonable request by Isis permit review of relevant notebooks and records in GSK's possession or control by Isis during normal business hours.

7. Option.

a. Once Isis has obtained the data generated under the statistical analyses plan for the Phase 2 PoC Trial for [***], Isis will provide GSK with (i) a notice from Isis that the PoC Trial is completed, and (ii) the Phase 2 PoC Data Package for [***] (such notice and package, the "[***] ***PoC Trial Completion Package***") in accordance with Section 3.1 of the Agreement. Once the data are generated under the statistical analysis plan for the Phase 2 PoC Trial for the [***] DC, GSK will notify Isis and provide a copy of the data package through the JSC. GSK will provide written notice to Isis of its decision whether to exercise its Option to the [***] Program on or before 5:00 p.m. (US Eastern time) on the [***] day following the earlier of (y) GSK's receipt of the [***] PoC Trial Completion Package, and (z) the data are generated under the statistical analyses plan for the Phase 2 PoC Trial for the [***] DC (the "[***] ***Option Deadline***"). If GSK does not provide written notice to Isis of GSK's exercise of the Option for the [***] Program before the [***] Option Deadline, then GSK's Option to the [***] Program will expire and, subject to Section 5.10 of the Agreement, Isis will be free to Develop and Commercialize any Compounds that had been included in the [***] Program on its own or with a Third Party and, except as specified in Section 5.10 of the Agreement, GSK will have no further rights to the [***] Program (including all Compounds included therein) and [***] will no longer be a Collaboration Target. For the avoidance of doubt, if GSK exercises its Option for the [***] Program, then the license granted to GSK pursuant to Section 4.1 of the Agreement will include all Compounds within the [***] Program, including the Research Leads, *but will not include* any Compounds that are excluded under Section 11 of this Amendment No. 5.

b. **Early Exercise of an Option.** For the avoidance of doubt, notwithstanding anything to the contrary in this Amendment No. 5 or in the Agreement, GSK will have the right to exercise its Option for the [***] Program at any time prior to the [***] Option Deadline.

8. **Financial Provisions**. The following revised financial provisions will apply solely to the [***] Program:

a. ***Upfront Payment***. Upon execution of this Amendment No. 5, in consideration for the amended scope of activities under the [***] Program described in this Amendment No.5, Isis will issue to GSK an invoice for, and GSK will pay to Isis within [***] ([***]) Business Days following the receipt of such invoice for, a payment equal to $[***] ([***] US Dollars).

b. ***Milestone Payments for First Achievement of Development Milestone Event***. Solely with respect to Compounds under the [***] Program that first achieve a Development Milestone Event as a result of activities by or on behalf of GSK or its Affiliates or Sublicensees, Table 3 set forth in Section 5.6.1 (Milestone Payments for First Achievement of Development Milestone Event) of the Agreement is hereby deleted in its entirety and replaced with TABLE 3A below.

TABLE 3A

Development Milestone Events for the [***] Program	**Milestone Payment 1st Indication**	**Milestone Payment 2nd Indication**
[***]	**$[***] ([***])**	**$[***]**
[***]	**$[***] ([***])**	**$[***]**
[***]	**$[***]**	**$[***]**
[***]	**$[***] ([***])**	**$[***]**
[***]	**$[***]**	**$[***]**
[***]†	**$[***]**	**$[***]**
[***]†	**$[***]**	**$[***]**
[***]	**$[***]**	**$[***]**
[***]††	**$[***]**	**$[***]**
[***]††	**$[***]**	**$[***]**
[***]†††	**$[***]**	**$[***]**
[***]	**$[***]**	**$[***]**
Total Development Milestone Payments for the [***] Program	**$[***]**	**$[***]**

† In the unlikely event that the [***] with a [***] DC is achieved prior to the [***] by [***], GSK will pay a total of $[***] at the time that the [***] with a [***] DC is achieved, consisting of the $[***] milestone payment and the $[***] with the [***] DC milestone payment.

†† For clarity with respect to this Milestone Event, "[***]" by the applicable Regulatory Authority in [***] (or any other [***] such as [***] or the [***]) of the equivalent of [***] in [***] (or any other [***] such as [***] or the [***]) will satisfy the requirements for achievement of this Development Milestone Event.

††† For clarity with respect to this Milestone Event, "[***]" by the applicable Regulatory Authority in [***] (or any other [***] such as [***] or the [***]) of the equivalent of [***] in [***] (or any other [***] such as [***] or the [***]) will satisfy the requirements for achievement of this Development Milestone Event.

Except as expressly set forth in Section 5.6.2 of the Agreement (as Section 5.6.2 of the Agreement relates to Compounds that are not [***] or the [***]), each milestone set forth in Table 3A above will be paid only once for the [***] Program upon the first achievement of the Milestone Event, regardless of the number of Licensed Compounds, Follow-On Compounds or Licensed Products resulting under the [***] Program.

For avoidance of doubt, except as expressly amended by this Amendment No. 5, the terms and conditions of Section 5.6.2 of the Agreement continue to apply to the [***] Program with respect to Compounds that are not [***] or the [***] DC.

c. ***Milestone Payments for First Achievement of Sales Milestone Event for [***] DC***. GSK will pay to Isis the applicable one-time milestone payments as set forth in Table 4B below after a Licensed [***] Product first achieves the listed events (as set forth in Table 4B) as a result of sales by or on behalf of GSK, its Affiliates or Sublicensees:

TABLE 4B	
Sales Milestones for each Licensed [***] Product	**Milestone Payment**
$[***] in worldwide Annual Net Sales	$[***]
$[***] in worldwide Annual Net Sales	$[***]
$[***] in worldwide Annual Net Sales	$[***]
Total Sales Milestone Payments for the [***] DC Program	**$[***]**

9. **[***] DC Program Royalties**. Solely with respect to the Licensed [***] Products sold by GSK, its Affiliates or Sublicensees, TABLE 5 set forth in Section 5.9.1 (GSK Patent Royalty) of the Agreement is deleted in its entirety and replaced with TABLE 5B below:

TABLE 5B	
Worldwide Annual Net Sales of each Licensed [***] Product	**Royalty Rate**
For the portion up to and including $[***]	[***]%
For the portion above $[***] and up to and including $[***]	[***]%
For the portion above $[***]	[***]%

10. **No Impact on Other Collaboration Programs**. Except as otherwise expressly amended by this Amendment No. 5, the Agreement (including Section 5.7.1 and Section 5.9.1 as it applies to Licensed Products under the [***] Program that are not Licensed [***] Products) remains in full force and effect in accordance with its terms. For the avoidance of doubt, this Amendment No. 5 is solely intended to modify certain terms of the Agreement regarding the [***] Program, and does not amend the Agreement in any way with respect to the other Collaboration Programs.

11. **Termination by Isis of Rights to [***] DC.** (a) If GSK, in Isis' reasonable determination, fails to use Commercially Reasonable Efforts under Section 5(a) of this Amendment No.5, Isis will notify GSK and within [***] ([***]) days thereafter, Isis and GSK will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to GSK's use of Commercially Reasonable Efforts in Section 5(a). Following such a meeting, if GSK fails to use Commercially Reasonable Efforts as contemplated by Section 5(a), then subject to Section 11(b) below, Isis will have the right, at its sole discretion, to terminate GSK's rights under this Amendment No. 5 and the Agreement with respect to the [***] DC and the other Research Leads. In the case of such a termination, the [***] DC and other Research Leads will be excluded from the [***] Program, including GSK's Option and licenses to the [***] Program under Sections 3.1 and Section 4.1 under the Agreement.

(b) This Section 11 and Section 12 below of this Amendment No. 5 set forth Isis' sole and exclusive remedy for GSK's breach of its obligation to use Commercially Reasonable Efforts under Section 5(a) of this Amendment No.5.

12. **Special Consequences for Termination by Isis or Voluntary Termination by GSK.** In addition to the consequences set forth in Section 9.3.2 of the Agreement (as applicable), in the event of (i) a termination of the Agreement either in its entirety or with respect to the [***] Program by Isis pursuant to Section 9.2.2 or by GSK pursuant to Section 9.2.1, or (ii) a termination by Isis pursuant to Section 11 above of this Amendment No.5, in each case ((i) and (ii)) prior to GSK's exercise of its Option for the [***] Program by GSK or upon the unexercised expiration of GSK's Option for the [***] Program and solely with respect to the [***] DC:

a. GSK will perform the obligations under Section 4.2.1 of the Agreement , as though such obligations under Section 4.2.1 were obligations owed by GSK to Isis, *mutatis mutandis*, with respect to the [***] DC, except for such information as is already in Isis' possession at the date of termination;

b. GSK will, at GSK's election and at its sole cost and expense, either (i) complete any ongoing Clinical Study for the [***] DC or (ii) subject to applicable law and regulatory consents, transfer sponsorship of any ongoing Clinical Study for the [***] DC to Isis together with the transfer of all of the rights and responsibilities thereunder, except as described in Section 12(c) below;

c. If as part of terminating the [***] Program GSK terminates a Clinical Study for a [***] DC due to safety reasons as confirmed by GSK's Global Product Safety Board, then GSK cannot elect to complete such Clinical Study under Section 12(b)(i) above but will: (i) take such action consistent with its internal policies and applicable regulatory requirements to close out such Clinical Study (including, without limitation, notification to the FDA and withdrawal of the IND), and (ii) provide to Isis all data and information contained within or referenced in the IND and such other data and information within GSK's possession or control generated under the [***] Program (except for such information as is already in Isis' possession at the date of termination or as a result of the technology transfer under Section 12.a. above), at GSK's sole cost and expense. For clarity, in the circumstances described in this Section 12(c), GSK will not be required to transfer the sponsorship of such terminated Clinical Study pursuant to Section 12(b)(ii) above.

d. If GSK elects to transfer sponsorship to Isis under Section 12(b)(ii) above, the Parties agree to, as soon as practicable following the date of such termination or expiration according to this Section 12, negotiate in good faith a separate agreement to effect such transfer consistent with industry standards under similar circumstances and in accordance with each Party's respective internal policies.

13. **Governing Law; Counterparts**. This Amendment No. 5 and any dispute arising from the performance or breach hereof will be governed by and construed and enforced in accordance with the laws of the State of Delaware, U.S.A., without reference to conflicts of laws principles. This Amendment No. 5 may be signed in counterparts, each and every one of which will be deemed an original, notwithstanding variations in format or file designation which may result from the electronic transmission, storage and printing of copies of this Amendment No. 5 from separate computers or printers. Facsimile signatures and signatures transmitted via PDF will be treated as original signatures.

14. **Definitions**. Capitalized terms used in this Amendment No. 5 will have the meaning set forth in Appendix A attached hereto.

*** - * - * - ***

[SIGNATURE PAGE FOLLOWS]

IN WITNESS WHEREOF, THE PARTIES HAVE CAUSED THIS AMENDMENT NO. 5 TO BE EXECUTED BY THEIR DULY AUTHORIZED REPRESENTATIVES AS OF THE AMENDMENT NO. 5 EFFECTIVE DATE.

ISIS PHARMACEUTICALS, INC.

BY: */s/ B. Lynne Parshall*

NAME: B. Lynne Parshall

TITLE: Chief Operating Officer

DATE: _____

GLAXO GROUP LIMITED

BY: */s/ Paul Williamson*

NAME: Paul Williamson

TITLE: Authorised Signatory For and on behalf

Of Edinburgh Pharmaceutical Industries Limited

Corporate Director

DATE: _____

GLAXOSMITHKLINE INTELLECTUAL PROPERTY

DEVELOPMENT LIMITED

BY: */s/ Paul Williamson*

NAME: Paul Williamson

TITLE: Authorised Signatory For and on behalf

Of Edinburgh Pharmaceutical Industries Limited

Corporate Director

DATE: _____

APPENDIX A

DEFINED TERMS

Capitalized terms used in this Amendment No. 5 but not otherwise defined herein will have the meanings given in the Agreement. For purposes of this Amendment No. 5, the following capitalized terms will have the following meanings:

a. "***CRO***" has the meaning set forth in Section 4.b of this Amendment No. 5.

b. "[***] ***DC Development Plan***" means the Development plan attached to this Amendment No. 5 as Appendix 1, which may be amended from time to time by the JSC.

c. *"*[***] ***DC"*** means the Compound designated as the [***] DC under Section 3.c. of this Amendment No. 5.

d. ***"[***] DC Selection Criteria"*** has the meaning set forth in Section 3.c of this Amendment No. 5.

e. [***]

f. "[***] ***Option Deadline***" has the meaning set forth in Section 7 of this Amendment No. 5.

g. "[***] ***PoC Trial Completion Package***" has the meaning set forth in Section 7 of this Amendment No. 5.

h. "[***] ***Program***" has the meaning set forth in the recitals of this Amendment No. 5.

i. ***"[***]"*** means the compound known as [***] (which is ISIS [***]).

j. ***"Licensed [***] Product"*** means a Licensed Product having the [***] DC as an active ingredient.

k. ***"Prioritized Lead"*** has the meaning set forth in Section 3.b of this Amendment No. 5.

l. ***"Prioritized Lead Studies"*** has the meaning set forth in Section 3.c of this Amendment No. 5.

m. ***"Prioritized Lead Data Package"*** has the meaning set forth in Section 3.c of this Amendment No. 5.

n. ***"Research Leads***" has the meaning set forth in Section 1 of this Amendment No. 5.

o. "***Research Lead Study***" has the meaning set forth in Section 3.a. of this Amendment No. 5.

p. "***Research Lead Data Package***" has the meaning set forth in Section 3.b. of this Amendment No. 5.

APPENDIX 1

[***] DC DEVELOPMENT PLAN

[***]

APPENDIX 2

ISIS' DEVELOPMENT CANDIDATE CRITERIA AND ACTIVITIES FOR [***] DC

[***]

APPENDIX 3

PAYMENT SCHEDULE FOR [***] DC DEVELOPMENT ACTIVITIES MANAGED OR CONDUCTED BY ISIS

[***]

APPENDIX 4

RESEARCH LEADS

[***]

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: August 4, 2014

/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: August 4, 2014

/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 June 30, 2014, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: August 4, 2014

/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.