UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended March 31, 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 May 2, 2014 was 117,577,403.

ISIS PHARMACEUTICALS, INC.
FORM 10-Q
INDEX

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)

	March 31, 2014 (Unaudited)	December 31, 2013
ASSETS		
Current assets:		
Cash and cash equivalents	$ 161,778	$ 159,973
Short-term investments	469,515	496,788
Contracts receivable	9,823	11,102
Inventories	7,537	8,033
Investment in Regulus Therapeutics Inc.	63,586	52,096
Other current assets	9,814	7,518
Total current assets	722,053	735,510
Property, plant and equipment, net	86,641	86,198
Licenses, net	4,101	4,572
Patents, net	16,383	15,517
Deposits and other assets	5,438	5,359
Total assets	$ 834,616	$ 847,156
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 9,869	$ 11,009
Accrued compensation	4,328	12,168
Accrued liabilities	27,903	22,092
Current portion of long-term obligations	4,308	4,408
Current portion of deferred contract revenue	54,428	48,135
Total current liabilities	100,836	97,812
Long-term deferred contract revenue	130,755	142,790
2¾ percent convertible senior notes	152,005	150,334
Long-term obligations, less current portion	5,523	6,542
Long-term financing liability for leased facility	71,395	71,288
Total liabilities	460,514	468,766
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 117,541,860 and 116,471,371 shares issued and outstanding at March 31, 2014 and December 31, 2013, respectively	118	116
Additional paid-in capital	1,343,874	1,324,804
Accumulated other comprehensive income	29,000	21,080
Accumulated deficit	(998,890)	(967,610)
Total stockholders' equity	374,102	378,390
Total liabilities and stockholders' equity	$ 834,616	$ 847,156

See accompanying notes.

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

	Three Months Ended March 31,	
	2014	**2013**
Revenue:		
Research and development revenue under collaborative agreements	$ 19,550	$ 41,671
Licensing and royalty revenue	8,611	1,689
Total revenue	28,161	43,360
Expenses:		
Research, development and patent expenses	53,448	38,312
General and administrative	4,380	3,423
Total operating expenses	57,828	41,735
Income (loss) from operations	(29,667)	1,625
Other income (expense):		
Investment income	657	376
Interest expense	(4,943)	(4,795)
Gain on investments, net	397	1,058
Loss before income tax benefit	(33,556)	(1,736)
Income tax benefit	2,276	64
Net loss	$ (31,280)	$ (1,672)
Basic and diluted net loss per share	$ (0.27)	$ (0.02)
Shares used in computing basic and diluted net loss per share	117,128	101,875

See accompanying notes.

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

	Three Months Ended March 31,	
	2014	**2013**
Net loss	$ (31,280)	$ (1,672)
Unrealized gains on securities, net of tax	8,261	6,467
Reclassification adjustment for realized gains included in net loss	(341)	(1,163)
Comprehensive income (loss)	$ (23,360)	$ 3,632

See accompanying notes.

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

	Three Months Ended March 31,	
	2014	**2013**
Operating activities:		
Net loss	$ (31,280)	$ (1,672)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	1,561	1,707
Amortization of patents	263	285
Amortization of licenses	471	569
Amortization of premium on investments, net	1,376	1,108
Amortization of debt issuance costs	135	100
Amortization of 2¾ percent convertible senior notes discount	1,671	1,543
Amortization of long-term financing liability for leased facility	1,652	1,637
Stock-based compensation expense	7,069	2,869
Gain on investments, net	(397)	(1,058)
Non-cash losses related to patents, licensing and property, plant and equipment	108	94
Tax benefit from other unrealized gains on securities	(2,276)	(64)
Changes in operating assets and liabilities:		
Contracts receivable	1,279	(650)
Inventories	496	312
Other current and long-term assets	(896)	(1,601)
Accounts payable	(2,646)	(5,569)
Accrued compensation	(7,840)	(4,060)
Deferred rent	25	40
Accrued liabilities	2,643	2,355
Deferred contract revenue	(5,742)	(8,521)
Net cash used in operating activities	(32,328)	(10,576)
Investing activities:		
Purchases of short-term investments	(69,185)	(64,552)
Proceeds from the sale of short-term investments	95,288	49,076
Purchases of property, plant and equipment	(1,403)	(222)
Acquisition of licenses and other assets, net	(333)	(702)
Proceeds from the sale of strategic investments	454	1,094
Net cash provided by (used in) investing activities	24,821	(15,306)
Financing activities:		
Proceeds from equity awards	12,003	11,823
Principal payments on debt and capital lease obligations	(2,691)	(2,773)
Net cash provided by financing activities	9,312	9,050
Net increase (decrease) in cash and cash equivalents	1,805	(16,832)
Cash and cash equivalents at beginning of period	159,973	124,482
Cash and cash equivalents at end of period	$ 161,778	$ 107,650
Supplemental disclosures of cash flow information:		
Interest paid	$ 83	$ 113
Income taxes paid	$ —	$ 2
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 1,506	$ 715

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
March 31, 2014
(Unaudited)

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three month periods ended March 31, 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 are responsible for completing IND-enabling studies for ISIS-AR$_{Rx}$, which we recently completed. 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 are performing 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. Because of the early stage of research for ISIS-AR$_{Rx}$, we believe that our knowledge and expertise with antisense technology is essential for AstraZeneca or another third party to successfully develop ISIS-AR$_{Rx}$. As a result, we concluded 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, in 2013 we adjusted the period of performance on our GlaxoSmithKline, or GSK, collaboration and our ISIS-SMN_{Rx} collaboration with Biogen Idec. As a result of adding two new development candidates, ISIS-$GSK3_{Rx}$ 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 $2.6 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 March 31, 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 three months ended March 31, 2014 and 2013. Total inventory, which consisted of raw materials, was $7.5 million and $8.0 million as of March 31, 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 months ended March 31, 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 March 31, 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 March 31, 2014, the total carrying value of our investments in variable interest entities was $66.5 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 investments, net of taxes, and adjustments we made to reclassify realized gains and losses on investments from other accumulated comprehensive income to our condensed consolidated statement of operations. The following table summarizes changes in accumulated other comprehensive income for the three months ended March 31, 2014 and 2013 (in thousands):

	Three Months Ended March 31,	
	2014	2013
Beginning balance accumulated other comprehensive income	$ 21,080	$ 12,480
Other comprehensive income before reclassifications, net of tax (1)	8,261	6,467
Amounts reclassified from accumulated other comprehensive income (2)	(341)	(1,163)
Net current period other comprehensive income	7,920	5,304
Ending balance accumulated other comprehensive income	$ 29,000	$ 17,784

(1) Other comprehensive income includes income tax expense of $5.4 million and $3.6 million for the three months ended March 31, 2014 and 2013, respectively.

(2) Included in gain 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 2¾ percent. In September 2012, we used a substantial portion of the net proceeds from the issuance of the 2¾ percent notes to redeem our 25¤8 percent convertible subordinated notes. We account for our 2¾ 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 2¾ 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 2¾ 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 three months ended March 31, 2014 and 2013, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Three Months Ended March 31,	
	2014	2013
Risk-free interest rate	1.6%	1.0%
Dividend yield	0.0%	0.0%
Volatility	50.5%	51.5%
Expected life	4.6 years	5.1 years

ESPP:

	Three Months Ended March 31,	
	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:

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

For the three months ended March 31, 2013, we did not grant stock options to the Board of Directors.

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 three months ended March 31, 2014 was $47.66 and $49.09, respectively. The weighted-average grant date fair value of RSUs granted to employees for the three months ended March 31, 2013 was $14.21. We did not grant any RSUs to the Board of Directors for the three months ended March 31, 2013.

The following table summarizes stock-based compensation expense for the three months ended March 31, 2014 and 2013 (in thousands), which was allocated as follows:

	Three Months Ended March 31,	
	2014	2013
Research, development and patent expenses	$ 5,873	$ 2,546
General and administrative	1,196	323
Total	$ 7,069	$ 2,869

Non-cash stock-based compensation was $7.1 million in 2014 and increased compared to $2.9 million in 2013 primarily due to the increase in our stock price. As of March 31, 2014, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $33.5 million and $14.6 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 1.4 years and 2.0 years, respectively.

3. Investments

As of March 31, 2014, we have primarily invested our excess cash in debt instruments of the U.S. Treasury, financial institutions, corporations, and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's (S&P) or Fitch, respectively. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

The following table summarizes the contract maturity of the available-for-sale securities we held as of March 31, 2014:

One year or less	48%
After one year but within two years	35%
After two years but within three years	17%
Total	100%

As illustrated above, we primarily invest our excess cash in short-term instruments with 83 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 March 31, 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. During the first quarter of 2014, we recognized a $397,000 net gain on investments primarily consisting of the $341,000 gain we realized when we sold a portion of the stock we hold in iCo Therapeutics Inc. In the first quarter of 2013, we sold all of the common stock of Sarepta Therapeutics, Inc. that we owned resulting in a realized gain of $1.1 million.

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

March 31, 2014	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Available-for-sale securities:					
Corporate debt securities(1)	$ 176,874	$ 104	$ (32)	$ —	$ 176,946
Debt securities issued by U.S. government agencies (1)	18,427	17	—	—	18,444
Debt securities issued by the U.S. Treasury	9,272	14	—	—	9,286
Debt securities issued by states of the United States and political subdivisions of the states	23,211	9	(29)	—	23,191
Total securities with a maturity of one year or less	227,784	144	(61)	—	227,867
Corporate debt securities	173,937	101	(177)	—	173,861
Debt securities issued by U.S. government agencies	49,303	4	(153)	—	49,154
Debt securities issued by the U.S. Treasury	5,998	14	—	—	6,012
Debt securities issued by states of the United States and political subdivisions of the states	21,559	48	(55)	—	21,552
Total securities with a maturity of more than one year	250,797	167	(385)	—	250,579
Total available-for-sale securities	$ 478,581	$ 311	$ (446)	$ —	$ 478,446

March 31, 2014	Cost Basis	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Equity securities:					
Regulus Therapeutics Inc.	$ 15,526	$ 48,060	$ —	$ —	$ 63,586
Securities included in other current assets	1,426	2,357	—	(880)	2,903
Securities included in deposits and other assets	625	—	—	—	625
Total equity securities	$ 17,577	$ 50,417	$ —	$ (880)	$ 67,114
Total available-for-sale and equity securities	$ 496,158	$ 50,728	$ (446)	$ (880)	$ 545,560

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

Investments we considered to be temporarily impaired at March 31, 2014 were as follows (in thousands):

	Number of Investments	Less than 12 months of temporary impairment		More than 12 months of temporary impairment		Total temporary impairment	
		Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
Corporate debt securities	124	$ 144,662	$ (207)	$ 6,057	$ (2)	$ 150,719	$ (209)
Debt securities issued by U.S. government agencies	7	47,622	(153)	—	—	47,622	(153)
Debt securities issued by states of the United States and political subdivisions of the states	19	14,860	(84)	—	—	14,860	(84)
Total temporarily impaired securities	150	$ 207,144	$ (444)	$ 6,057	$ (2)	$ 213,201	$ (446)

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 three months ended March 31, 2014 and 2013 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 March 31, 2014 and December 31, 2013 as follows (in thousands):

	At March 31, 2014	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 149,945	$ 141,013	$ 8,932	$ —
Corporate debt securities (2)	344,930	—	344,930	—
Debt securities issued by U.S. government agencies (2)	67,598	—	67,598	—
Debt securities issued by the U.S. Treasury (2)	15,298	15,298	—	—
Debt securities issued by states of the United States and political subdivisions of the states (2)	41,689	—	41,689	—
Investment in Regulus Therapeutics Inc.	63,586	63,586	—	—
Equity securities (3)	2,903	985	—	1,918
Total	$ 685,949	$ 220,882	$ 463,149	$ 1,918

	At December 31, 2013	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 146,357	$ 133,233	$ 13,124	$ —
Corporate debt securities (2)	394,773	—	394,773	—
Debt securities issued by U.S. government agencies (2)	64,432	—	64,432	—
Debt securities issued by the U.S. Treasury (2)	15,328	15,328	—	—
Debt securities issued by states of the United States and political subdivisions of the states (2)	22,255	—	22,255	—
Investment in Regulus Therapeutics Inc.	52,096	52,096	—	—
Equity securities (3)	1,276	1,276	—	—
Total	$ 696,517	$ 201,933	$ 494,584	$ —

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

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

(3) 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 Level 3 inputs 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 first quarter of 2013, we sold all of the common stock of Sarepta that we owned resulting in a realized gain of $1.1 million. As of March 31, 2013, our Level 3 investments consisted of our investment in Regulus, with a gross fair value of $54.6 million and a lack of marketability discount of $9.7 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 the first quarter of 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 March 31, 2014, we classified our investment in the equity securities of Achaogen as Level 3 with a gross fair value of $2.3 million and a lack of marketability discount of $365,000.

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 March 31, 2014 and 2013 (in thousands):

	Three Months Ended March 31,	
	2014	2013
Beginning balance of Level 3 investments	$ —	$ 34,350
Total gains and losses:		
Included in gain on investments	—	(1,163)
Included in accumulated other comprehensive income (loss)	1,918	11,716
Cost basis of shares sold	—	(40)
Ending balance of Level 3 investments	$ 1,918	$ 44,863

Other Fair Value Disclosures

Our 2¾ percent convertible notes had a fair value of $505.2 million at March 31, 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 March 31,	
	2014	2013
Partner A	36%	9%
Partner B	27%	1%
Partner C	12%	23%
Partner D	12%	6%
Partner E	0%	58%

Contract receivables from two significant partners comprised approximately 89 percent of our contract receivables at March 31, 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 three months ended March 31, 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 three months ended March 31, 2014 and 2013, we recorded a $2.3 million and $64,000 tax benefit, respectively, on our condensed consolidated statements of operations and a $5.4 million and $3.6 million tax expense, respectively, in other comprehensive income.

7. Collaborative Arrangements and Licensing Agreements

Traditional Pharmaceutical Alliances and Licensing

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 $29 million, which we are amortizing through August 2016. We are eligible to receive a license fee, milestone payments and double-digit royalties on any product sales of ISIS-SMN$_{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 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. In January 2014, we and Biogen Idec amended the original agreement to reflect changes made to the clinical development plan for ISIS-SMN$_{Rx}$. 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 infant Phase 3 study. 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. 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.

As of March 31, 2014, we have received $16.3 million in payments for advancing the ISIS-SMN_{Rx} Phase 2 program, including $9.3 million in payments we received 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:

- $1.8 million related to a Phase 2 study in children with SMA through June 2014;
- $2.0 million related to a Phase 2 study in infants with SMA through July 2014; and
- $5.5 million related to an open-label extension study in children with SMA through December 2014.

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. In October 2013, we earned a $10 million milestone payment when we initiated an IND-enabling toxicology study on ISIS-$DMPK_{Rx}$, and we are eligible to receive up to another $49 million in milestone payments associated with the development of ISIS-$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 double-digit royalties on any product sales of the drug. We will earn the next milestone payment of $14 million if we initiate a Phase 1 study for ISIS-$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 double-digit royalties 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 double-digit royalties 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 $35 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. We could earn the next milestone payment of up to $10 million if we choose a target to advance under this collaboration.

During the three months ended March 31, 2014 and 2013, we earned revenue of $10.2 million and $3.9 million, respectively, from our relationship with Biogen Idec, which represented 36 percent and nine percent, respectively, of our total revenue for those periods. Our balance sheet at March 31, 2014 included deferred revenue of $145.9 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 addition, we are eligible to receive double-digit royalties on sales from any product that GSK successfully commercializes under this alliance.

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. To date, we have received $25.0 million primarily in milestone payments from GSK related to the development of ISIS-TTR$_{Rx}$, including a $1 million milestone payment we earned in March 2014 when we initiated an open-label extension study of ISIS-TTR$_{Rx}$. We are eligible to earn an additional $45 million in pre-licensing milestone payments associated with the ISIS-TTR$_{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. To date, we have earned $10 million in milestone payments associated with advancing the ISIS-HBV$_{Rx}$ program including a $3 million milestone payment we earned in November 2013 when we initiated a Phase 1 study for ISIS-HBV$_{Rx}$. In November 2013, we designated ISIS-GSK4$_{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 $173 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 $1 million milestone payment if we further advance the ongoing Phase 2/3 study of ISIS-TTR$_{Rx}$.

During the three months ended March 31, 2014 and 2013, we earned revenue of $3.3 million and $9.9 million, respectively, from our relationship with GSK, which represented 12 percent and 23 percent, respectively, of our total revenue for those periods. Our balance sheet at March 31, 2014 included deferred revenue of $10.1 million related to our relationship with GSK, $9.7 million of which is related to the upfront payments associated with our collaboration with GSK that we were amortizing through July 2016. As a result of the recent amendments to our agreement, in the second quarter of 2014 we will begin amortizing the $9.7 million through our amended period of performance of September 2016.

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 March 31, 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 March 31, 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. To date, 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 three months ended March 31, 2014 and 2013, we earned revenue of $7.7 million and $250,000, respectively, from our relationship with Alnylam, which represented 27 percent and less than one percent, respectively, of our total revenue for those periods.

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 31 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 believe five drugs in our pipeline could be in registration for marketing approval or on the market by 2018. 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 have several drugs in late-stage development that we believe represent significant near-term commercial opportunities, such as ISIS-TTR$_{Rx}$ and ISIS-SMN$_{Rx}$. 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 plan to initiate a Phase 3 program for ISIS-SMN$_{Rx}$ midyear in 2014. We believe that both 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 Phase 2 clinical development. Each of these drugs, including ISIS-GCCR$_{Rx}$, ISIS-GCGR$_{Rx}$, ISIS-FXI$_{Rx}$ and ISIS-PTP1B$_{Rx}$, could represent significant near and mid-term licensing opportunities with the potential for Phase 2 data through 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 more than $410 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 Phase 2 data on ISIS-APOCIII$_{Rx}$ in patients with high to extremely high triglyceride levels and as a single agent as well as in combination with fibrates.
  - We presented final Phase 2 data on ISIS-APOCIII$_{Rx}$ in combination with fibrates in patients with high triglycerides. In this study, patients achieved statistically significant reductions in triglycerides, apoC-III protein and statistically significant increases in HDL-C on top of improvements achieved with each patient's existing therapeutic regimen of triglyceride lowering drugs. These data were presented at the American College of Cardiology meeting.
  - We presented final Phase 2 data on ISIS-APOCIII$_{Rx}$ in patients with type 2 diabetes and high triglycerides. In this study, patients with diabetes experienced statistically significant improvements in glucose control with trends toward enhanced insulin sensitivity. These data were presented at the Arteriosclerosis, Thrombosis and Vascular Biology meeting.
  - We presented final Phase 2 data on ISIS-APOCIII$_{Rx}$ in patients with familial chylomicronemia. In this study, patients with extremely high triglycerides experienced substantial reductions of triglycerides that correlated with substantial reductions in triglyceride-rich chylomicrons. These data were presented at the National Lipid Association meeting.

  - We received European Orphan Drug Designation for ISIS-APOCIII$_{Rx}$ for the treatment of patients with familial chylomicronemia syndrome.
- We reported positive clinical results for ISIS-SMN$_{Rx}$ in children and infants with SMA. These data were presented at the American Academy of Neurology meeting.
  - We presented results from both of the ongoing multiple-dose Phase 2 studies of ISIS-SMN$_{Rx}$ in infants and children with SMA, which were consistent with earlier reported data. In the ongoing studies, we reported increases in muscle function scores in infants and children treated with multiple-doses of ISIS-SMN$_{Rx}$.
  - We reported results from an assay that measures SMN protein levels in the cerebral spinal fluid. We observed dose-dependent increases in SMN protein levels which were more than two fold greater than baseline levels at the highest dose in children treated with ISIS-SMN$_{Rx}$ from both the single- and multiple-dose studies.
- Our collaborators presented preclinical data on an antisense drug targeting hepatitis B virus, or HBV, demonstrating that antisense targeting of HBV produced dose-dependent reductions in HBV. We initiated a Phase 1 clinical trial on ISIS-HBV$_{Rx}$, an antisense drug to treat patients with HBV.
- We initiated a Phase 1 study of ISIS-ANGPTL3$_{Rx}$, an antisense drug to treat patients with hyperlipidemia.
- 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 received a positive opinion on European Orphan Drug Designation in the EU for ISIS-TTR$_{Rx}$ to treat patients with TTR amyloidosis.
- In 2014 to date, we have received more than $31 million in payments from our partners, including $11.9 million from Biogen Idec related to the development of ISIS-SMN$_{Rx}$, $7.7 million from Alnylam related to Alnylam's alliance with Genzyme and $9 million from GSK related to the development of ISIS-TTR$_{Rx}$ and ISIS-HBV$_{Rx}$.
- We added Joseph Loscalzo, M.D., Ph.D. to our Board of Directors.

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 months ended March 31, 2014 was $28.2 million compared to $43.4 million for the same period in 2013. Our revenue fluctuates based on the nature and timing of payments under agreements with our partners, including license fees, milestone-related payments and other payments. For example, in the first quarter of 2014 we earned $7.7 million in sublicensing revenue from Alnylam related to our collaboration with Genzyme. In contrast, in the first quarter of 2013, we earned $32.5 million from milestone payments we received from Genzyme and GSK.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the three months ended March 31, 2014 was $19.6 million compared to $41.7 million for the same period in 2013. The difference is primarily due to the $25 million milestone payment from Genzyme for FDA approval of the KYNAMRO NDA and the $7.5 million milestone payment from GSK related to the Phase 2/3 study of ISIS-TTR_{Rx} that we earned in the first quarter of 2013.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the three months ended March 31, 2014 was $8.6 million compared to $1.7 million for the same period in 2013. The increase in the first quarter 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 months ended March 31, 2014 were $57.8 million compared to $41.7 million for the same period in 2013 due to higher development costs associated with the progression of numerous drugs in our pipeline into later stage clinical trials.

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 March 31,	
	2014	**2013**
Research, development and patent expenses	$ 47,575	$ 35,766
Non-cash compensation expense related to equity awards	5,873	2,546
Total research, development and patent expenses	$ 53,448	$ 38,312

For the three months ended March 31, 2014, our total research, development and patent expenses were $47.6 million, and were higher compared to $35.8 million for the same period 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 associated with our Phase 3 study of ISIS-TTR_{Rx} in 2014 compared to 2013 as we continued to advance that study. 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 March 31,	
	2014	2013
Antisense drug discovery expenses	$ 9,097	$ 9,397
Non-cash compensation expense related to equity awards	1,685	769
Total antisense drug discovery	$ 10,782	$ 10,166

Antisense drug discovery costs for the three months ended March 31, 2014 were $9.1 million and were essentially flat compared to $9.4 million for the same period 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 March 31,	
	2014	2013
KYNAMRO	$ 1,827	$ 1,943
ISIS-TTR$_{Rx}$	2,710	767
Other antisense development products	18,121	9,878
Development overhead costs	3,740	1,816
Non-cash compensation expense related to equity awards	2,078	856
Total antisense drug development	$ 28,476	$ 15,260

Antisense drug development expenses were $26.4 million for the three months ended March 31, 2014, compared to $14.4 million for the same period in 2013. Expenses in the first quarter of 2014 were higher compared to the same period in 2013 primarily due to an increase in development costs associated with the progression of numerous drugs in our pipeline into later stage clinical trials. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies the costs of development increase. For example, we initiated Phase 2 studies for several of the drugs in our pipeline in the second half of 2013, which are ongoing. In addition, we incurred more costs associated with our Phase 3 study of ISIS-TTR$_{Rx}$ in 2014 compared to 2013 as we continued to advance that study. 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 March 31,	
	2014	2013
Manufacturing and operations	$ 5,766	$ 4,220
Non-cash compensation expense related to equity awards	699	354
Total manufacturing and operations	$ 6,465	$ 4,574

Manufacturing and operations expenses were $5.8 million for the three months ended March 31, 2014, compared to $4.2 million for the same period in 2013. Manufacturing increased primarily because we manufactured more drug product to support our drug development activities, a significant portion of which was related to ISIS-APOCIII$_{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 March 31,	
	2014	2013
Personnel costs	$ 2,562	$ 2,340
Occupancy	1,735	1,646
Patent expenses	374	1,978
Depreciation and amortization	571	702
Insurance	294	287
Other	778	792
Non-cash compensation expense related to equity awards	1,411	567
Total R&D support costs	$ 7,725	$ 8,312

R&D support costs for the three months ended March 31, 2014 were $6.3 million, compared to $7.8 million for the same period in 2013. Expenses decreased in the first quarter of 2014 compared to the same period in 2013 primarily due to a decrease in litigation costs for our patent infringement lawsuit against Santaris Pharma A/S. 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 March 31,	
	2014	2013
General and administrative expenses	$ 3,184	$ 3,100
Non-cash compensation expense related to equity awards	1,196	323
Total general and administrative expenses	$ 4,380	$ 3,423

General and administrative expenses were $3.2 million for the three months ended March 31, 2014, and were essentially flat compared to $3.1 million for the same period in 2013. All amounts exclude non-cash compensation expense related to equity awards.

Investment Income

Investment income for the three months ended March 31, 2014 was $657,000, compared to $376,000 for the same period in 2013. The increase in investment income was primarily due to a higher average cash balance and market conditions during the first quarter of 2014.

Interest Expense

Interest expense for the three months ended March 31, 2014 was $4.9 million, and was essentially flat compared to $4.8 million for the same period in 2013.

Gain on Investments, net

Gain on investments for the three months ended March 31, 2014 was $397,000, compared to $1.1 million for the same period in 2013. The gain on investments in the first quarter of 2014 was primarily due to the $341,000 we realized when we sold a portion of the stock we hold in iCo Therapeutics Inc. The gain on investments in the first quarter of 2013 was due to the $1.1 million we realized when we sold the stock we held in Sarepta Therapeutics. These gains demonstrate the value that we are realizing from our satellite company strategy.

Income Tax Benefit

We recorded a tax benefit of $2.3 million for the three months ended March 31, 2014, compared to $64,000 for the same period in 2013. The tax benefit we recorded in 2014 is primarily related to the unrealized gain associated with our investment in Regulus and Achaogen.

Net Loss and Net Loss per Share

Net loss for the three months ended March 31, 2014 was $31.3 million, compared to $1.7 million for the same period in 2013. Basic and diluted net loss per share for the three months ended March 31, 2014 was $0.27 per share, compared to $0.02 per share for the same period in 2013. Our net loss increased in the first quarter of 2014 primarily due to variations in the timing of revenue from milestone payments and an 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 March 31, 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 March 31, 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 March 31, 2014, we had cash, cash equivalents and short-term investments of $631.3 million and stockholders' equity of $374.1 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. Our cash declined slightly in the first quarter of 2014 due to cash used in operations offset by more than $30 million in cash received from our partners and from stock option exercises. At March 31, 2014, we had consolidated working capital of $621.2 million, compared to $637.7 million at December 31, 2013. Our working capital decreased in the first quarter of 2014 primarily due to the decrease in cash.

As of March 31, 2014, our debt and other obligations totaled $282.5 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 quarter of 2014 on our lease obligations and notes payable.

The following table summarizes our contractual obligations as of March 31, 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:

	Payments Due by Period (in millions)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
2¾ percent Convertible Senior Notes (principal and interest payable)	$ 234.5	$ 5.5	$ 11.1	$ 11.1	$ 206.8
Facility Rent Payments	$ 136.4	$ 6.2	$ 12.8	$ 13.6	$ 103.8
Equipment Financing Arrangements (principal and interest payable)	$ 6.6	$ 4.3	$ 2.3	$ —	$ —
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	$ 26.2	$ 1.5	$ 3.1	$ 2.9	$ 18.7
Total	$ 405.3	$ 17.8	$ 29.5	$ 27.7	$ 330.3

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

In October 2008, we entered into an equipment financing loan agreement and in September 2009 and June 2012, we amended the loan agreement to increase the aggregate maximum amount of principal we could draw under the agreement. Each draw down under the loan agreement has a term of three years, with principal and interest payable monthly. Interest on amounts we borrow under the loan agreement is based upon the three year interest rate swap at the time we make each draw down plus 3.5 or four percent, depending on the date of the draw. We are using the equipment purchased under the loan agreement as collateral. As of March 31, 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 March 31, 2014 and December 31, 2013 was $6.4 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 March 31, 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 March 31, 2014, we had an accumulated deficit of approximately $998.9 million and stockholders' equity of approximately $374.1 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 March 31, 2014, we had cash, cash equivalents and short-term investments equal to $631.3 million. If we do not meet our goals to successfully commercialize KYNAMRO or our other drugs, including ISIS-APOCIII$_{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 March 31, 2014, the market price of our common stock ranged from $15.92 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 March 31, 2014. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 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 activities related to a sale of Isis' patented methods are not actionable as a matter of law. In addition, in March 2014 Santaris filed another motion asking the court to reconsider the courts' February 2014 denial of Santaris' previous motion for summary judgment or in the alternative to permit Santaris to immediately appeal to the Court of Appeals for the Federal Circuit. Both motions are briefed and awaiting the court's decision.

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

On January 27, 2014, we entered into a Letter Agreement Amendment with Biogen Idec, which amended the clinical development plan for ISIS-SMN_{Rx} to add a new open-label extension study for those children with SMA who have completed dosing in our previous studies, to expand the dosing in the Phase 2 study in infants with SMA, and to increase the number of patients to be included in the infant Phase 3 study. As a result of these changes, we and Biogen Idec agreed to increase the payments that we are eligible to receive under this collaboration.

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Letter Agreement Amendment between the Registrant and Biogen Idec International Holding Ltd dated January 27, 2014. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
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 March 31, 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)	May 6, 2014
/s/ Elizabeth L. Hougen Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	May 6, 2014

CONFIDENTIAL TREATMENT REQUESTED

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

EXHIBIT 10.1

January 27, 2014

Richard Brudnick
Vice President, Co-Head Business Development/M&A
Biogen Idec MA Inc.
14 Cambridge Center
Cambridge, MA 02142

M Tonesan Naa-Lamle Amissah
Biogen Idec International Holding Ltd.
Appleby (Bermuda) Ltd.
Canon's Court, 22 Victoria Street
Hamilton HM 12
Bermuda

Dear Richard,

Isis and Biogen Idec are parties to the Development, Option and License Agreement dated January 3, 2012 (the ***"SMA Agreement"***), which grants the JDC authority to amend the ISIS-SMN_{Rx} Development Plan upon unanimous written consent, pursuant to Section 1.2.2 of the SMA Agreement. This letter agreement is intended to memorialize the parties' mutual understanding of certain changes to the ISIS-SMN_{Rx} Development Plan as approved by the JDC on August 5 and December 6, 2013.

Isis and Biogen Idec hereby agree that, effective as of January 27, 2014, the ISIS-SMN_{Rx} Development Plan is amended as follows:

1. CS2 Study. A new 12mg cohort of [***] patients is added. A new milestone payment of $[***] is added to cover the costs for such new cohort and will be payable to Isis upon [***].

CS2 Study Variable	As of March 13, 2013	As Amended Herein
	3mg cohort/[***] patients	3mg cohort/[***] patients
Cohort/Number of	6mg cohort/[***] patients	6mg cohort/[***] patients
Patients	9mg cohort/[***] patients	9mg cohort/[***] patients
	n/a	12mg cohort/[***] patients

2. CS3A Study. The CS3A Study is expanded from [***] patients to up to [***] patients and extended from 3 doses to [***] doses per patient. A new milestone payment of $[***] is added to cover the costs for [***] patients to receive [***] doses and will be payable to Isis upon the earlier of (i) [***], or (ii) [***]. In the event that more than [***] patients are enrolled in the CS3A Study, Biogen Idec will pay Isis a milestone payment of $[***] upon [***] and $[***] upon [***].

CS3A Study Variable	As of March 13, 2013	As Amended Herein
Cohort/Number of	6mg cohort/[***] patients	6mg cohort/[***] patients
Patients	9mg cohort/[***] patients	12mg cohort/[***] patients
Number of Doses	3 doses each patient	[***] doses each patient

3. CS3B Study. To reflect the addition of [***] patients and [***] sites to the CS3B Study, the CS3B Study milestone payment structure is revised to (i) [***] milestone payment set forth in the letter agreement between the Parties dated March 13, 2013, due upon [***], to $[***]; and (ii) to provide an additional milestone payments of $[***] due upon [***], $[***], due upon [***], and $[***] upon [***] in the CS3B Study.

CS3B Study Variable	As of March 13, 2013	As Amended Herein
Number of Patients	[***]	[***]
Number of Sites	[***]	[***]

4. CS12 Study. A new open label extension study and related milestone payment of $[***] is added. This new CS12 Study will provide for an additional single 12mg dose for the [***] patients in the CS2 Study and CS10 Study who are expected to roll over to the CS12 Study. The CS12 Study milestone payment of $[***] will be due upon [***].

All invoices referenced in this letter agreement will be due within [***] of receipt.

Except as set forth above, all other provisions of the SMA Agreement will remain in full force and effect. Capitalized terms used but not defined herein will have the meaning ascribed to such terms in the SMA Agreement.

This letter agreement may be signed in counterparts, each of which will be deemed an original. Facsimile signatures and signatures transmitted via electronic mail in PDF format will be treated as original signatures.

IN WITNESS WHEREOF, Isis and Biogen Idec have caused this letter agreement to be executed by their representatives as of the date hereof.

BIOGEN IDEC INTERNATIONAL HOLDING LTD

/s/ M. Tonesan N. Amissah
M. Tonesan N. Amissah

Director, Biogen Idec International Holding Ltd.

ISIS PHARMACEUTICALS, INC.

/s/ B. Lynne Parshall
B. Lynne Parshall
Chief Operating Officer

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: May 6, 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: May 6, 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 March 31, 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: May 6, 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.