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 September 30, 2012

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 November 1, 2012 was 101,210,828.

ISIS PHARMACEUTICALS, INC.
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TRADEMARKS

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

Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc.

Vitravene® is a registered trademark of Novartis AG.

KYNAMRO™ is a trademark of Genzyme Corporation.

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

	September 30, 2012 (Unaudited)	December 31, 2011
ASSETS		
Current assets:		
Cash and cash equivalents	$ 84,563	$ 65,477
Short-term investments	259,010	278,187
Contracts receivable	3,476	6,921
Inventories	6,737	4,139

Other current assets	7,800	5,415
Total current assets	361,586	360,139
Property, plant and equipment, net	92,598	96,615
Licenses, net	7,191	9,036
Patents, net	18,180	16,259
Deposits and other assets	6,126	2,845
Total assets	$ 485,681	$ 484,894
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 5,256	$ 8,300
Accrued compensation	5,836	9,183
Accrued liabilities	11,900	18,655
Current portion of long-term obligations	5,182	3,390
Current portion of deferred contract revenue	23,427	36,584
Total current liabilities	51,601	76,112
Long-term deferred contract revenue	36,961	17,474
$2^{3}/_{4}$ percent convertible senior notes	142,500	—
$2^{5}/_{8}$ percent convertible subordinated notes	—	141,448
Long-term obligations, less current portion	8,404	4,125
Long-term financing liability for leased facility	70,375	69,877
Investment in Regulus Therapeutics Inc.	5,563	4,424
Total liabilities	315,404	313,460
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 101,193,132 and 100,042,976 shares issued and outstanding at September 30, 2012 and December 31, 2011, respectively	102	100
Additional paid-in capital	1,073,658	1,013,592
Accumulated other comprehensive gain (loss)	846	(770)
Accumulated deficit	(904,329)	(841,488)
Total stockholders' equity	170,277	171,434
Total liabilities and stockholders' equity	$ 485,681	$ 484,894

See accompanying notes.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2012	2011	2012	2011
Revenue:				
Research and development revenue under collaborative agreements	$ 11,127	$ 20,189	$ 80,085	$ 64,508
Licensing and royalty revenue	474	524	2,091	2,175
Total revenue	11,601	20,713	82,176	66,683
Expenses:				
Research and development	36,551	39,924	115,700	110,178
General and administrative	3,096	3,105	9,281	8,989
Total operating expenses	39,647	43,029	124,981	119,167
Loss from operations	(28,046)	(22,316)	(42,805)	(52,484)
Other income (expense):				
Equity in net loss of Regulus Therapeutics Inc.	—	(386)	(1,139)	(2,275)
Investment income	408	575	1,485	1,896
Interest expense	(5,937)	(4,773)	(16,335)	(11,624)
Gain (loss) on investments, net	—	18	19	(267)
Loss on early retirement of debt	(4,770)	—	(4,770)	—
Loss before income tax benefit (expense)	(38,345)	(26,882)	(63,545)	(64,754)
Income tax benefit (expense)	706	—	704	(11)
Net loss	$ (37,639)	$ (26,882)	$ (62,841)	$ (64,765)
Basic and diluted net loss per share	$ (0.37)	$ (0.27)	$ (0.63)	$ (0.65)
Shares used in computing basic and diluted net loss per share	100,680	99,687	100,351	99,620

See accompanying notes.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2012	2011	2012	2011
Net loss	$ (37,639)	$ (26,882)	$ (62,841)	$ (64,765)
Unrealized gains (losses) on securities, net	(122)	(1,552)	1,616	(2,102)
Comprehensive loss	$ (37,761)	$ (28,434)	$ (61,225)	$ (66,867)

See accompanying notes.

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

	Nine Months Ended September 30,	
	2012	2011
Net cash used in operating activities	$ (34,159)	$ (89,188)
Investing activities:		
Purchases of short-term investments	(172,581)	(284,379)
Proceeds from the sale of short-term investments	189,397	371,872
Purchases of property, plant and equipment	(1,033)	(8,934)
Acquisition of licenses and other assets, net	(2,779)	(2,544)
Purchases of strategic investments	(40)	(359)
Net cash provided by investing activities	12,964	75,656
Financing activities:		
Proceeds from issuance of equity	7,789	1,554
Proceeds from issuance of 2¾ percent convertible senior notes, net of issuance costs	194,689	—
Principal and premium payment on redemption of the 2⅝ percent convertible subordinated notes	(163,718)	—
Proceeds from equipment financing arrangement	9,100	1,625
Principal payments on debt and capital lease obligations	(7,579)	(4,436)
Net cash provided by (used in) financing activities	40,281	(1,257)
Net increase (decrease) in cash and cash equivalents	19,086	(14,789)
Cash and cash equivalents at beginning of period	65,477	70,052
Cash and cash equivalents at end of period	$ 84,563	$ 55,263
Supplemental disclosures of cash flow information:		
Interest paid	$ 5,584	$ 4,647
Income taxes paid	$ —	$ 2
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 839	$ 1,378
Capitalized costs and financing liability associated with leased facility	$ —	$ 58,748

See accompanying notes.

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ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
September 30, 2012

(Unaudited)

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three and nine month periods ended September 30, 2012 and 2011 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2011. 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, 2011 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. We used the equity method of accounting to account for our investment in Regulus Therapeutics Inc. until October 2012 when Regulus completed an initial public offering (IPO). We now own less than 20 percent of Regulus' common stock and we no longer have significant influence over the operating and financial policies of Regulus. As such, beginning in the fourth quarter we will no longer use the equity method of accounting for our equity investment in Regulus and instead we will account for it at fair value.

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

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. 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 the deliverables as a single unit of accounting, then we recognize the revenue ratably over our estimated period of performance.

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 that includes 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. If our collaborators ask us to continue performing work in a collaboration beyond the initial period of performance, we extend our amortization period to correspond to the new extended period of performance. The revenue we recognize could be materially different if different estimates prevail. We have made estimates of our continuing obligations on several agreements. Adjustments to performance periods and related adjustments to revenue amortization periods have not had a material impact on our revenue.

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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.

In January 2012, we entered into a collaboration agreement with Biogen Idec to develop and commercialize ISIS-SMN_{Rx} for Spinal Muscular Atrophy, or SMA. As part of the collaboration, we received a $29 million upfront payment and we are responsible for global development of ISIS-SMN_{Rx} through completion of Phase 2/3 registrational clinical trials. Biogen Idec has the option to license ISIS-SMN_{Rx} through completion of the first successful Phase 2/3 trial. If Biogen Idec exercises its option, it will pay us a license fee and will assume global development, regulatory and commercialization responsibilities. We evaluated the delivered item, the option to license ISIS-SMN_{Rx}, to determine if it had stand-alone value. We determined that the option did not have stand-alone value because Biogen Idec cannot pursue the development or commercialization of ISIS-SMN_{Rx} until it exercises the option. As such we considered the deliverables in this collaboration to be a single unit of accounting and we are recognizing the upfront payment over the four-year research and development term for ISIS-SMN_{Rx}, which is the estimated period of our performance.

In June 2012, we entered into a 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 Phase 2 clinical trials. Biogen Idec has the option to license the drug through completion of the Phase 2 trial. If Biogen Idec exercises its option, it will pay us a license fee and will assume global development, regulatory and commercialization responsibilities. We evaluated the delivered item, the option to license the drug, to determine if it had stand-alone value. We determined that the option did not have stand-alone value because Biogen Idec cannot pursue the development or commercialization of the drug until it exercises the option. As such we considered the deliverables in this collaboration to be a single unit of accounting and we are recognizing the upfront payment over the five-year research and development term, which is the estimated period of our performance.

We evaluated the SMA and DMPK agreements to determine whether we should account for them as separate agreements or as a single multiple element arrangement. We determined that we should account for the agreements separately because we conducted the negotiations independently of one another, the two agreements cover two different diseases, there are no interrelated or interdependent deliverables, there are no provisions in either agreement that are essential to the other agreement, and the payment terms and fees under each agreement are independent of each other.

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 which 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 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

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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 ongoing access to new technologies we discover, we have determined that all future development, regulatory and commercialization milestones are substantive. For example, for our strategic alliance with GlaxoSmithKline, or GSK, we are using our antisense drug discovery platform to seek out and develop new drugs against targets for rare and serious diseases. Alternatively, we provide on-going access to our technology to Alnylam to develop and commercialize RNA interference, or RNAi, therapeutics. We consider milestones for both of these collaborations to be substantive. For those agreements that do not meet the following criteria, we do not consider the future milestones to be substantive. 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 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 will defer recognition of the milestone payment and recognize it as revenue over the estimated period of performance, if any. In 2012, the FDA accepted the NDA for KYNAMRO. In 2011, we initiated a Phase 1 clinical study on ISIS-TTR$_{Rx}$, the first drug selected as part of our collaboration with GSK, and we selected ISIS-AAT$_{Rx}$ as the second development candidate as part of that collaboration. We consider milestones 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. Therefore, we recognized the entire $25 million milestone payment from Genzyme, a Sanofi Company, in the second quarter of 2012 and the two $5 million milestone payments from GSK in their entirety in 2011. Further information about our collaborative arrangements can be found in Note 7, *Collaborative Arrangements and Licensing Agreements*, below and Note 8 of our audited financial statements for the year ended December 31, 2011 included in our Annual Report on Form 10-K filed with the SEC.

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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.

Cash, cash equivalents and short-term investments

We consider all liquid investments with maturities of 90 days or less when we purchase them to be cash equivalents. Our short-term investments have initial maturities of greater than 90 days 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 stockholders’ equity 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 September 30, 2012 we held ownership interests of less than 20 percent in each of the respective companies except Regulus in which we owned more than 20 percent. In October 2012, Regulus completed an IPO and we now own less than 20 percent of Regulus.

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 stockholders’ equity. 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. Most of the cost method investments we hold are in early stage biotechnology 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 allocated for that drug to manufacture our other drugs. We expense these costs when we deliver the drugs to our partners, or as we provide these drugs for our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf life of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. We did not record any inventory write-offs for the first nine months of 2012 and 2011. Total inventory, which consisted of raw materials, was $6.7 million and $4.1 million as of September 30, 2012 and December 31, 2011, respectively.

Patents

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents. We review our capitalized patent costs regularly to ensure that they include costs for 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. We amortize patent costs over their useful lives, beginning with the date the United States Patent and Trademark Office, or foreign equivalent, issues the patent and ending when the patent expires or is written off. For the first nine months of 2012 and 2011, we recorded non-cash charges of $664,000 and $883,000, respectively, which we included in research and development expenses, related to the write-down of our patent costs to their estimated net realizable values.

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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.

Equity method of accounting

We accounted for our ownership interest in Regulus using the equity method of accounting until Regulus' IPO in October 2012. Under the equity method of accounting, we included our share of Regulus' operating results on a separate line in our condensed consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc." On our condensed consolidated balance sheet, we presented our investment in Regulus on a separate line in the non-current liabilities section called "Investment in Regulus Therapeutics Inc." The equity method of accounting requires us to suspend recognizing losses if the carrying amount of our investment in Regulus exceeds the amount of funding we are required to provide to Regulus. Until the completion of Regulus' IPO, we and Alnylam were guarantors of both of the convertible notes that Regulus issued to GSK. As such, we continued to recognize losses in excess of our net investment in Regulus up to the principal plus accrued interest we guaranteed, which was $5.6 million at September 30, 2012. Because our share of Regulus' net loss exceeded the $5.6 million we guaranteed, in the second quarter of 2012 we suspended recording our portion of Regulus' net loss. As of September 30, 2012, we had $2.7 million of suspended net losses, which we have not recognized.

Subsequent to Regulus' IPO, we own less than 20 percent of Regulus' common stock and we no longer have significant influence over the operating and financial policies of Regulus. As such, beginning in the fourth quarter we will no longer use the equity method of accounting for our investment in Regulus and instead we will account for it at fair value. In the fourth quarter of 2012, we will record a significant gain to reflect the change in our ownership percentage.

Use of estimates

The preparation of condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the amounts reported in the condensed consolidated financial statements and accompanying notes. Actual results could differ from those estimates.

Basic and diluted net loss per share

We compute basic net loss per share by dividing the net loss by the weighted-average number of common shares outstanding during the period. As we incurred a net loss for the three and nine months ended September 30, 2012 and 2011, we did not include the following diluted common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive:

- $2^{3}/_{4}$ percent convertible senior notes;
- $2^{5}/_{8}$ percent convertible subordinated notes;
- GlaxoSmithKline convertible promissory notes;
- Dilutive stock options;
- Restricted stock units; and
- Warrants issued to Symphony GenIsis Holdings LLC.

In April 2011, Symphony GenIsis Holdings LLC exercised the remaining warrants. In September 2012, we redeemed all of our $2^{5}/_{8}$ percent convertible subordinated notes.

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 September 30, 2012 and December 31, 2011, we had collaborative arrangements with six entities that we considered to be variable interest entities. We are not the primary beneficiary for any of these entities as we do not have both the power to direct the activities that most significantly impact the economic performance of our variable interest entities and 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. In the case of Regulus, prior to Regulus' IPO, we and Alnylam shared the ability to impact Regulus' economic performance. As a result, we were not the primary beneficiary of Regulus.

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Comprehensive income (loss)

We report the components of comprehensive income (loss) in our condensed consolidated statements of comprehensive income (loss) in the period in which we recognize them. The components of comprehensive income (loss) include net loss and unrealized gains and losses on investment holdings.

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 $2^{5}¤_{8}$ percent convertible subordinated notes. Consistent with how we accounted for our $2^{5}¤_{8}$ percent 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 a similar debt instrument 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 the Employee Stock Purchase Plan, or ESPP, at the grant date, based on the estimated fair value of the award and we recognize the expense over the employee's requisite service period.

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 estimated the expected term of options granted based on historical exercise patterns. For the nine months ended September 30, 2012 and 2011, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Nine Months Ended September 30,	
	2012	2011
Risk-free interest rate	1.0%	2.3%
Dividend yield	0.0%	0.0%
Volatility	50.65%	52.4%
Expected life	5.1 years	5.3 years

Board of Director Stock Options:

	Nine Months Ended September 30,	
	2012	2011
Risk-free interest rate	1.3%	2.9%
Dividend yield	0.0%	0.0%
Volatility	51.3%	52.8%
Expected Life	7.6 years	7.8 years

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ESPP:

	Nine Months Ended September 30,	
	2012	2011
Risk-free interest rate	0.2%	0.1%
Dividend yield	0.0%	0.0%
Volatility	49.6%	34.9%
Expected life	6 months	6 months

In 2012, we began granting RSUs to our employees and the Board of Directors. The fair value of RSUs is based on the market price of our common stock on the date of grant. The weighted-average grant date fair value of RSUs granted to employees and the Board of Directors for the nine months ended September 30, 2012 was $7.97 and $12.94 per RSU, respectively.

The following table summarizes stock-based compensation expense for the three and nine months ended September 30, 2012 and 2011 (in thousands), which was allocated as follows:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2012	2011	2012	2011
Research and development	$ 1,720	$ 2,017	$ 5,728	$ 6,594
General and administrative	314	347	1,033	1,002
Total	$ 2,034	$ 2,364	$ 6,761	$ 7,596

As of September 30, 2012, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options and RSUs was $7.3 million and $1.2 million, respectively. We will adjust total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize the cost of non-cash, stock-based compensation expense related to non-vested stock options and RSUs over a weighted average amortization period of 1.2 years and 3.3 years, respectively.

Impact of recently issued accounting standards

In May 2011, the FASB amended its authoritative guidance on the measurement and disclosure for fair value measurements. The amendment clarifies the application of certain existing fair value measurement guidance and expands the disclosures for fair value measurements that are estimated using significant unobservable (Level 3) inputs. The guidance is effective prospectively for fiscal years, and interim periods within those years, beginning after December 15, 2011 and was effective for our fiscal year beginning January 1, 2012. The adoption of this guidance did not have a material impact on our financial statements.

In June 2011, the FASB amended its authoritative guidance on the presentation of comprehensive income. Under the amendment, companies have the option to present the components of net income and other comprehensive income either in a single continuous statement of comprehensive income or in separate but consecutive statements. This amendment eliminates the option to present the components of other comprehensive income as part of the statement of changes in stockholders' equity. The amendment does not change the items that companies must report in other comprehensive income or when companies must reclassify an item of other comprehensive income to net income. The guidance is effective retrospectively for fiscal years, and interim periods within those years, beginning after December 15, 2011 and was effective for our fiscal year beginning January 1, 2012. As this guidance relates to presentation only, the adoption of this guidance did not have any other effect on our financial statements.

3. Investments

As of September 30, 2012, we primarily invested our excess cash in commercial paper and 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.

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The following table summarizes the contract maturity of the available-for-sale securities we held as of September 30, 2012:

One year or less	63%
After one year but within two years	24%
After two years but within three years	13%
Total	100%

As illustrated above, we primarily invest our excess cash in short-term instruments with 87 percent of our available-for-sale securities having a maturity of less than two years.

At September 30, 2012, we had an ownership interest of less than 20 percent in each of three private companies and three public companies with which we conduct business. The privately-held companies are Santaris Pharma A/S (formerly Pantheco A/S), Achaogen Inc., and Atlantic Pharmaceuticals Limited. The publicly-traded companies are Antisense Therapeutics Limited, or ATL, iCo Therapeutics Inc., or iCo, and Sarepta Therapeutics, Inc. (formerly AVI BioPharma). 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 and record unrealized gains and losses as a separate component of stockholders' equity and include net realized gains and losses in gain (loss) on investments. In October 2012, Regulus completed an IPO and we now own less than 20 percent of Regulus' common stock. Beginning in the fourth quarter, we will no longer use the equity method to account for our investment in Regulus and instead we will account for our equity investment in Regulus at fair value.

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

September 30, 2012	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Short-term investments:					
Corporate debt securities	$ 135,045	$ 146	$ (7)	$ —	$ 135,184
Debt securities issued by U.S. government agencies	18,015	6	—	—	18,021
Debt securities issued by states of the United States and political subdivisions of the states	11,100	7	—	—	11,107
Total securities with a maturity of one year or less	164,160	159	(7)	—	164,312
Corporate debt securities	55,374	127	(37)	—	55,464
Debt securities issued by U.S. government agencies	13,177	36	(83)	—	13,130
Debt securities issued by the U.S. Treasury	13,455	31	—	—	13,486
Debt securities issued by states of the United States and political subdivisions of the states	12,572	49	(3)	—	12,618
Total securities with a maturity of more than one year	94,578	243	(123)	—	94,698
Subtotal	$ 258,738	$ 402	$ (130)	$ —	$ 259,010
Equity securities:					
Current portion (included in Other current assets)	$ 1,579	$ 2,491	$ —	$ (880)	$ 3,190
Long-term portion (included in Deposits and other assets)	625	—	—	—	625
Subtotal	$ 2,204	$ 2,491	$ —	$ (880)	$ 3,815
	$ 260,942	$ 2,893	$ (130)	$ (880)	$ 262,825

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December 31, 2011	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Short-term investments:					
Corporate debt securities	$ 109,842	$ 13	$ (255)	$ —	$ 109,600
Debt securities issued by U.S. government agencies	53,723	35	(5)	—	53,753
Debt securities issued by the U.S. Treasury	2,353	3	—	—	2,356

Debt securities issued by states of the United States and political subdivisions of the states	16,141	4	(3)	—	16,142
Total securities with a maturity of one year or less	182,059	55	(263)	—	181,851
Corporate debt securities	57,632	21	(331)	—	57,322
Debt securities issued by U.S. government agencies	26,754	—	(67)	—	26,687
Debt securities issued by states of the United States and political subdivisions of the states	12,331	19	(23)	—	12,327
Total securities with a maturity of more than one year	96,717	40	(421)	—	96,336
Subtotal	$ 278,776	$ 95	$ (684)	$ —	$ 278,187
Equity securities:					
Current portion (included in Other current assets)	$ 1,538	$ 624	$ —	$ (880)	$ 1,282
Long-term portion (included in Deposits and other assets)	625	—	—	—	625
Subtotal	$ 2,163	$ 624	$ —	$ (880)	$ 1,907
	$ 280,939	$ 719	$ (684)	$ (880)	$ 280,094

Investments we considered to be temporarily impaired at September 30, 2012 were as follows (in thousands):

		Less than 12 months of temporary impairment	
	Number of Investments	Estimated Fair Value	Unrealized Losses
Corporate debt securities	24	$ 37,348	$ (44)
Debt securities issued by U.S. government agencies	2	7,056	(83)
Debt securities issued by the U.S. Treasury			
Debt securities issued by states of the United States and political subdivisions of the states	1	5,200	(3)
Total temporarily impaired securities	27	$ 49,604	$ (130)

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 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. The majority of our securities have been classified as Level 2. To estimate the fair value of securities classified as Level 2, we utilize the services of a fixed income pricing provider that uses an industry standard valuation model, which is based on a market approach. The significant inputs for the valuation model include reported trades, broker/dealer quotes, benchmark securities and bids. We validate the fair value of securities from our pricing provider by understanding the pricing model they used and comparing their assessment of the fair value of our Level 2 investments to the fair value provided by the custodians of our Level 2 investments. Our pricing provider and custodians use similar techniques to derive fair value for Level 2 securities. During the three and nine months ended September 30, 2012 and 2011 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. At September 30, 2012 and December 31, 2011, we had no securities that we classified as Level 3.

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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 September 30, 2012 and December 31, 2011 as follows (in thousands):

	At September 30, 2012	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 82,863	$ 73,064	$ 9,799	$ —
Corporate debt securities (2)	190,648	—	190,648	—
Debt securities issued by U.S. government agencies (2)	31,151	—	31,151	—
Debt securities issued by the U.S. Treasury (2)	13,486	13,486	—	—
Debt securities issued by states of the United States and political subdivisions of the states (2)	23,725	—	23,725	—
Equity securities (3)	3,190	3,190	—	—
Total	$ 345,063	$ 89,740	$ 255,323	$ —

	At December 31, 2011	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 58,892	$ 55,893	$ 2,999	$ —
Corporate debt securities (2)	166,922	—	166,922	—
Debt securities issued by U.S. government agencies (2)	80,440	—	80,440	—
Debt securities issued by the U.S. Treasury (2)	2,356	2,356	—	—
Debt securities issued by states of the United States and political subdivisions of the states (2)	28,469	—	28,469	—

Equity securities (3)	1,282	1,282	—	—
Total	$ 338,361	$ 59,531	$ 278,830	$ —

(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.

Other Fair Value Disclosures

Our 2¾ percent convertible notes had a fair value of $230.4 million at September 30, 2012. 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. Long-Term Obligations

Convertible Notes

In August 2012, we completed a $201.3 million convertible debt offering, which raised net proceeds of approximately $194.7 million, after deducting $6.6 million in issuance costs. The $201.3 million convertible senior notes mature in 2019 and bear interest at 2¾ percent, which is payable semi-annually in arrears on April 1 and October 1 of each year. We are amortizing the debt issuance costs to interest expense over the life of the debt, or seven years.

The 2¾ percent notes are convertible, at the option of the note holders prior to July 1, 2019 only under certain conditions. On or after July 1, 2019, the notes are initially convertible into approximately 12.1 million shares of common stock at a conversion price of approximately $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 these notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest.

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We account for the 2¾ percent notes using an accounting standard that requires us to assign a value to our convertible debt equal to the estimated fair value of a similar debt instrument without the conversion feature, which results in us recording our convertible debt at a discount. We are amortizing the resulting debt discount over the expected life of the debt, or seven years, as additional non-cash interest expense. Using a combination of the present value of the debt's cash flows and a Black-Scholes valuation model, we determined that our nonconvertible debt borrowing rate for the 2¾ percent notes was 8 percent. Interest expense for the nine months ended September 30, 2012 included $894,000 of non-cash interest expense related to the amortization of the debt discount and debt issuance costs.

We used a substantial portion of the net proceeds from the issuance of the 2¾ percent notes to repurchase our 2⅝ percent convertible subordinated notes. In September 2012, we redeemed the entire $162.5 million in principal of our 2⅝ percent notes at a price of $164.0 million including accrued interest. As a result of the redemption, we recognized a $4.8 million loss. A significant portion of the loss, or $3.6 million, was non-cash and related to the unamortized debt discount and debt issuance costs and the remainder was related to a $1.2 million early redemption premium we paid to the holders of the 2⅝ percent notes.

Equipment Financing Arrangement

In October 2008, we entered into a loan agreement related to an equipment financing 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. In June 2012, we drew down $9.1 million in principal under the loan agreement at an interest rate of 4.12 percent. As of September 30, 2012, we had drawn down $27.4 million in principal under this loan agreement at a weighted average interest rate of 5.51 percent and we can borrow up to an additional $6.0 million in principal to finance the purchase of equipment until April 2014. The carrying balance under this loan agreement at September 30, 2012 and December 31, 2011 was $11.3 million and $5.3 million, respectively. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

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 nine months ended September 30, 2012, we recorded unrealized gains on our investments in available-for-sale securities in other comprehensive income. As a result, we recorded a $706,000 tax benefit in the third quarter of 2012.

7. Collaborative Arrangements and Licensing Agreements

Traditional Pharmaceutical Alliances and Licensing

Biogen Idec

In January 2012, we entered into a global collaboration agreement with Biogen Idec valued at up to $299 million to develop and commercialize ISIS-SMN$_{Rx}$ for the treatment of SMA. Under the terms of the agreement, we received an upfront payment of $29 million and are eligible to receive up to $45 million in substantive milestone payments associated with the clinical development of ISIS-SMN$_{Rx}$ prior to licensing. We are responsible for global development of ISIS-SMN$_{Rx}$ through the completion of Phase 2/3 registrational clinical trials. Biogen Idec has the option to license ISIS-SMN$_{Rx}$ through completion of the first successful Phase 2/3 trial. If Biogen Idec exercises its option, it will pay us a license fee and will assume global development, regulatory and commercialization responsibilities. We may also receive up to $150 million in substantive milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we will receive up to double-digit royalties on sales of ISIS-SMN$_{Rx}$ if Biogen Idec successfully develops and commercializes ISIS-SMN$_{Rx}$ after option exercise. We will earn the next milestone payment of $18 million if we initiate the first Phase 2/3 study for ISIS-SMN$_{Rx}$.

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In June 2012, we and Biogen Idec entered into a separate collaboration and license agreement valued at up to $271 million to develop and commercialize a novel antisense drug targeting DMPK for the treatment of myotonic dystrophy type 1, or DM1. Under the terms of the agreement, in July 2012 we received an upfront payment of $12 million and are eligible to receive up to $59 million in substantive milestone payments associated with the development of the DMPK-targeting drug prior to licensing. We are responsible for global development of the drug through the completion of Phase 2 clinical trials. Biogen Idec has the option to license the drug through the completion of the Phase 2 trial. We may also receive up to $130 million in substantive milestone payments if Biogen Idec achieves pre-specified regulatory milestones. In addition, we will receive up to double-digit royalties on future product sales of the drug. We will earn the next milestone payment of $10 million if we initiate an IND-enabling toxicology study for our DMPK program

During the three and nine months ended September 30, 2012, we earned revenue of $2.4 million and $6.0 million, respectively, from our relationships with Biogen Idec which represented 21 percent and seven percent, respectively, of our total revenue for those periods. Our balance sheet at September 30, 2012 included deferred revenue of $35.0 million related to the upfront payments.

Eli Lilly and Company

In August 2001, we formed a broad strategic relationship with Eli Lilly and Company, which included a joint research collaboration. As part of the collaboration, Eli Lilly and Company licensed LY2181308, an antisense inhibitor of survivin. In the second quarter of 2012, Eli Lilly and Company decided not to continue the development of LY2181308. Therefore we will not earn future milestone payments from Eli Lilly and Company associated with LY2181308.

Genzyme Corporation, a Sanofi company

In January 2008, we entered into a strategic alliance with Genzyme focused on the licensing and co-development of KYNAMRO and a research relationship. The license and co-development agreement provides Genzyme with exclusive worldwide rights for all therapeutic purposes to our patents and know-how related to KYNAMRO, including the key product related patents, and their foreign equivalents pending or granted in various countries outside the United States, including in the European Union via the European Patent Convention, Japan, Canada, Australia, South Africa and India. In addition, we agreed that we would not develop or commercialize another oligonucleotide-based compound designed to modulate apolipoprotein-B, or apo-B, by binding to the mRNA encoding apo-B, throughout the world.

The transaction, which closed in June 2008, included a $175 million licensing fee, a $150 million equity investment in our stock in which we issued Genzyme five million shares of our common stock, and a share of worldwide profits on KYNAMRO and follow-on drugs ranging from 30 percent to 50 percent of all commercial sales. In May 2012, we earned a $25 million milestone payment from Genzyme when the FDA accepted the NDA for KYNAMRO. We may also receive over $1.5 billion in substantive milestone payments if Genzyme achieves pre-specified events, including up to $725 million for the achievement of regulatory milestones and up to $825 million for the achievement of commercialization milestones. The next milestone payment we could earn under our agreement with Genzyme is $25 million if the FDA approves the NDA for KYNAMRO.

Under this alliance, Genzyme is responsible for the continued development and commercialization of KYNAMRO. We agreed to supply the drug substance for KYNAMRO for the Phase 3 clinical trials and initial commercial launch. Genzyme is responsible for manufacturing the finished drug product for KYNAMRO, including the initial commercial launch supply, and, if approved, Genzyme will be responsible for the long term supply of KYNAMRO drug substance and finished drug product. As part of the agreement, we contributed the first $125 million in funding for the development costs of KYNAMRO. Genzyme is now sharing these expenses equally with us until KYNAMRO is profitable.

The license and co-development agreement for KYNAMRO will continue in perpetuity unless we or Genzyme terminate it earlier under the following situations:

- Genzyme may terminate the license and co-development agreement at any time by providing written notice to Isis;
- We may terminate the license and co-development agreement on a country-by-country basis or in its entirety upon Genzyme's uncured failure to use commercially reasonable efforts to develop and commercialize KYNAMRO in the United States, France, Germany, Italy, Spain, the United Kingdom, Japan and Canada; and
- Either we or Genzyme may terminate the license and co-development agreement upon the other party's uncured failure to perform a material obligation under the agreement.

Upon termination of the license and co-development agreement, the license we granted to Genzyme for KYNAMRO will terminate and Genzyme will stop selling the product. In addition, if Genzyme voluntarily terminates the agreement or we terminate the agreement in a country or countries for Genzyme's failure to develop and commercialize KYNAMRO, then the rights to KYNAMRO will revert back to us and we may develop and commercialize KYNAMRO in the countries that are the subject of the termination, subject to a royalty payable to Genzyme.

If we are the subject of an acquisition, then within 180 days following the acquisition, Genzyme may elect to purchase all of our rights to receive payments under the KYNAMRO license and co-development 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.

Genzyme has agreed to monthly limits on the number of shares it can sell of the Company's stock that it purchased in February 2008. In addition, Genzyme has agreed that until the earlier of the 10 year anniversary of the KYNAMRO license and co-development agreement or the date Genzyme holds less than two percent of our issued and outstanding common stock, Genzyme will not acquire any additional shares of our common stock without our consent.

The price Genzyme paid for our common stock represented a significant premium over the then fair value of our common stock. In May 2012, we finished amortizing this $100 million premium along with the $175 million licensing fee that we received in the second quarter of 2008. During the three and nine months ended September 30, 2012, we earned revenue of $4.7 million and $63.9 million, respectively, from our relationship with Genzyme, which represented 41 percent and 78 percent, respectively, of our total revenue for those periods compared to $16.6 million and $49.9 million for the same periods in 2011. Our balance sheets at September 30, 2012 and December 31, 2011 included deferred revenue of $5.6 million and $27.7 million, respectively.

GlaxoSmithKline

In March 2010, we entered into a strategic alliance with GSK, which covers up to six programs, in which we use 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 rapid development of drugs while still being eligible to receive milestone payments as we advance these drugs in clinical development.

In October 2012, we and GSK amended the original agreement to reflect an accelerated clinical development plan for ISIS-TTR_{Rx}. Under the terms of the original agreement, which includes five programs in addition to the transthyretin, or TTR, program, we are eligible to receive on average up to $20 million in milestone payments per program up to Phase 2 proof-of-concept. GSK has the option to license drugs from these programs at Phase 2 proof-of-concept, and will be responsible for all further development and commercialization. We have already received $10 million in milestone payments from GSK related to the development of ISIS-TTR_{Rx}. Under the amended terms of the agreement, we will receive a $2.5 million upfront payment and we will earn a $7.5 million payment upon initiation of the Phase 2/3, registration-directed, clinical study for ISIS-TTR_{Rx}. We are also eligible to earn an additional $50 million in pre-licensing milestone payments associated with the ISIS-TTR_{Rx} Phase 2/3 study. In addition, GSK has increased the regulatory and commercial milestone payments we can earn should ISIS-TTR_{Rx} achieve registration and meet certain sales thresholds.

Under the terms of the amended agreement, if GSK successfully develops all six programs for one or more indications and achieves pre-agreed sales targets, we could receive license fees and substantive milestone payments of more than $1.3 billion, including up to $239 million for the achievement of development milestones, up to $594.5 million for the achievement of regulatory milestones and up to $545 million for the achievement of commercialization milestones. We will earn the next milestone payment of $7.5 million if we initiate a Phase 2/3 clinical study for ISIS-TTR_{Rx}. In addition, we will receive up to double-digit royalties on sales from any product that GSK successfully commercializes under this alliance.

As of September 30, 2012, we have received $53 million from GSK, including the $35 million upfront payment, $15 million in development milestone payments and $3 million we received when GSK expanded the collaboration to include a sixth program.

During the three and nine months ended September 30, 2012, we earned revenue of $2.1 million and $6.0 million, respectively, from our relationship with GSK, which represented 18 percent and seven percent, respectively, of our total revenue for those periods compared to $2.0 million and $10.7 million for the same periods in 2011. Our balance sheets at September 30, 2012 and December 31, 2011 included deferred revenue of $19.4 million and $25.3 million, respectively, related to the upfront and expansion payments.

Satellite Company Collaborations

Alnylam Pharmaceuticals, Inc.

In March 2004, we entered into a strategic alliance with Alnylam to develop and commercialize RNA interference, or RNAi, 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 for 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. We will earn the next milestone payment of $750,000 if Alnylam initiates a Phase 3 study for its TTR program. 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. As of September 30, 2012, we did 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.

In the third quarter of 2012, we earned $1.6 million in sublicense revenue from Alnylam primarily as a result of earning our portion of the upfront fees in Alnylam's recently announced collaboration with Monsanto Company. In October 2012, we earned $1.1 million in sublicense revenue from Alnylam as our portion of the upfront fees in Alnylam's recently announced collaboration with Genzyme. In addition, we have the potential to receive royalty

payments and a portion of future milestone payments. Including the $1.1 million we earned in October, we have earned a total of $39.8 million from Alnylam resulting from sublicenses of our technology for the development of RNAi therapeutics and technology that Alnylam has granted to its partners.

During the three and nine months ended September 30, 2012, we earned revenue of $1.6 million from our relationship with Alnylam, which represented 13 percent and two percent, respectively, of our total revenue for those periods. During the three and nine months ended September 30, 2011, we did not recognize any revenue from our relationship with Alnylam.

Xenon Pharmaceuticals Inc.

In November 2010, we established a collaboration with Xenon to discover and develop antisense drugs as novel treatments for the common disease anemia of inflammation, or AI. AI is the second most common form of anemia worldwide and physicians associate a wide variety of conditions including infection, cancer and chronic inflammation with AI. We received an upfront payment in the form of a convertible promissory note from Xenon to discover and develop antisense drugs to the targets hemojuvelin and hepcidin. In addition to license and option fees, we are eligible to receive development and commercial milestone payments and royalties on sales of drugs licensed to Xenon under the collaboration and a portion of sublicense revenue.

In May 2012, Xenon selected XEN701, a drug targeting the hepcidin-hemojuvelin pathway, as a development candidate. Xenon may take an exclusive license for the development and worldwide commercialization of XEN701. Under our collaboration agreement with Xenon we may receive up to $296 million in substantive milestone payments for multiple indications upon the achievement of pre-specified events, including up to $26 million for the achievement of development milestones, up to $150 million for the achievement of regulatory milestones and up to $120 million for the achievement of commercialization milestones. We will earn the next milestone payment of $3 million if Xenon initiates a phase 2 clinical trial for XEN701. During the three and nine months ended September 30, 2012, we earned $84,000 in revenue from our relationship with Xenon. During the three and nine months ended September 30, 2011, we did not earn any revenue from our relationship with Xenon.

8. 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 September 30,		Nine Months Ended September 30,	
	2012	2011	2012	2011
Partner A	41%	80%	78%	75%
Partner B	18%	10%	7%	16%
Partner C	21%	0%	7%	0%
Partner D	13%	0%	2%	0%

Contract receivables from one significant partner comprised approximately 82 percent of our contract receivables at September 30, 2012. Contract receivables from one significant partner comprised approximately 85 percent of our contract receivables at December 31, 2011.

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9. Subsequent Events

In October 2012, Regulus Therapeutics, Inc. completed an IPO of approximately 12.7 million shares of its common stock at $4.00 per share. As part of the offering, we purchased $3.0 million of Regulus' common stock at the offering price. Upon the close of the offering, our investment in Regulus' preferred shares converted into common stock and we received one share of Regulus' Class A common stock for every two shares of Preferred Series A stock that we held at the date of the offering. We now own approximately 7 million shares of Regulus' common stock. Subsequent to Regulus' IPO, we own less than 20 percent of Regulus' common stock and we no longer have significant influence over the operating and financial policies of Regulus. As such, beginning in the fourth quarter we will no longer use the equity method of accounting for our equity investment in Regulus and instead we will account for it at fair value. In the fourth quarter of 2012, we will record a significant gain to reflect the change in our ownership percentage.

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

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

Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, this Report includes forward-looking statements regarding our business, the therapeutic and commercial potential of our technologies and products in development, and the financial position of Isis Pharmaceuticals, Inc. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, including the planned commercialization of KYNAMRO, 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 its 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, 2011, 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 30 of this Report.

Overview

We are the leading company in antisense drug discovery and development, exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Antisense technology provides a direct route from genomics to drugs. With our highly efficient and prolific drug discovery

platform we can expand our pipeline and our partners' pipelines with antisense drugs that address significant medical needs. Our strategy is to do what we do best—to discover unique antisense drugs and develop these drugs to key clinical value inflection points. We discover and conduct early development of new drugs and, at the key clinical value inflection points, outlicense our drugs to partners. We maximize the value of the drugs we discover by putting them in the hands of leading pharmaceutical companies with late-stage development, commercialization and marketing expertise, such as Biogen Idec, Genzyme, a Sanofi company, and GlaxoSmithKline, or GSK. For instance, our partner, Genzyme, plans to commercialize our lead product, KYNAMRO, following planned regulatory approval in Europe and in the United States. We also work with a consortium of smaller companies that can exploit our drugs and technologies in areas that are outside of our core focus. As a result of our unique strategy, we can keep our organization small and focused. Our strong financial position is a result of the successful execution of our business strategy as well as our inventive and focused research and development capabilities.

Our flagship product, KYNAMRO (formerly mipomersen), is moving closer to the market for patients with severe forms of familial hypercholesterolemia, or FH, at high cardiovascular risk, who cannot reduce their low-density lipoprotein cholesterol, or LDL-C, sufficiently with currently available lipid-lowering therapies. In July 2011, Genzyme submitted a marketing application in Europe for KYNAMRO for patients with homozygous familial hypercholesterolemia, or hoFH, and severe heterozygous familial hypercholesterolemia, or severe heFH. In May 2012, the U.S. Food and Drug Administration, or FDA, accepted the marketing application for KYNAMRO for patients with hoFH. Genzyme is actively preparing to launch KYNAMRO subject to marketing approval. Genzyme is also preparing to commercialize KYNAMRO in other major markets.

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To maximize the value of our drugs and technologies, we have a multifaceted partnering strategy. 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 broad base of license fees, milestone payments and royalty income. We also form preferred partner transactions that provide us with a vested partner, such as Biogen Idec and GSK, early in the development of a drug. In this way, we benefit in the short term from upfront option fees and development milestone payments while we maintain control over the early development of the drug. We benefit in the long term by having a knowledgeable and committed partner to license the drug at clinical proof-of-concept and by receiving regulatory milestone payments and royalties as our partner moves the drug to the market. In all of our partnerships, we benefit from the expertise our partners bring to our drugs. We also work with a consortium of smaller companies that can exploit our drugs and technologies. We call these smaller companies our satellite companies. In this way, 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. In addition, we can maintain our broad RNA technology leadership through collaborations with companies such as Alnylam Pharmaceuticals, Inc., or Alnylam, and Regulus Therapeutics Inc., or Regulus, a company we co-founded with Alnylam focused on microRNA therapeutics. In October 2012 Regulus completed an IPO, which we supported, bringing our ownership in Regulus to approximately seven million shares of Regulus' common stock, which is currently valued at $35 million. All of these different types of relationships are part of our unique business model and create near and long-term shareholder value.

The clinical successes of the drugs in our pipeline continue to create new partnering opportunities. For example, in January 2012, we formed a strategic alliance with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ to treat spinal muscular atrophy. We received a $29 million upfront payment and are eligible to receive up to $270 million in payments as well as double-digit royalties on sales from ISIS-SMN$_{Rx}$. Since 2007, our partnerships have generated an aggregate of more than $880 million in payments from upfront and licensing fees, equity purchase payments, milestone payments and research and development funding, including the $12 million upfront payment we received from Biogen Idec in July 2012 related to our new alliance valued at up to $271 million to develop and commercialize a drug targeting dystrophia myotonica-protein kinase, or DMPK. In addition, for our current partnered programs we have the potential to earn $3.6 billion in future milestone payments. We also will share in the future commercial success of our inventions and drugs resulting from these partnerships through earn out, profit sharing, or royalty arrangements. Our strong financial position is a result of the successful execution of our business strategy as well as our inventive and focused research and development capabilities.

We protect our proprietary technologies and products through our substantial patent estate. 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. The 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 over $400 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

Recent Events

Drug Development and Corporate Highlights

- KYNAMRO continues to advance in development and move closer to the market for patients with severe forms of familial hypercholesterolemia (FH; homozygous FH and severe heterozygous FH) through regulatory approval and with the focus FH study.
  - The FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 9 to 6 that Genzyme had provided sufficient efficacy and safety data to support the marketing of KYNAMRO for the treatment of patients with homozygous FH.
  - Dr. Klaus Parhofer, a clinical investigator, presented an analysis of data from the KYNAMRO Phase 3 study in patients with severe heterozygous FH at the European Society of Cardiology. These data highlighted the potential of KYNAMRO to reduce the need for apheresis by lowering LDL-C values below the thresholds for apheresis eligibility in patients with severe heterozygous FH.
  - We received European GMP certification of our manufacturing facility for production of drug substance to support KYNAMRO commercial launch.
- We initiated a Phase 2 study on ISIS-FXI$_{Rx}$ in patients undergoing total knee replacement surgery and a Phase 1b/2a study on ISIS-SMN$_{Rx}$ in children with spinal muscular atrophy.
- We and GSK amended the clinical development plan and financial terms relating to ISIS-TTR$_{Rx}$ to support an accelerated development plan for the drug. As a result of the revised agreement, we will receive a $2.5 million upfront payment and we will receive $7.5 million upon initiation of the Phase 2/3 study for ISIS-TTR$_{Rx}$. We are also eligible to earn an additional $50 million in pre-licensing milestone payments to support the ISIS-TTR$_{Rx}$ Phase 2/3 study.
- We reported preliminary Phase 1 data on ISIS-STAT3$_{Rx}$ in patients with cancer and initiated a Phase 2 study evaluating ISIS-STAT3$_{Rx}$ in patients with advanced lymphoma.
- We and collaborators published a paper in Nature demonstrating that an antisense compound selectively and rapidly reduced target RNA in skeletal muscle and alleviated disease in animal models of muscular dystrophy type 1 (DM1).

- We and collaborators published two papers in the journal Cell demonstrating that single-stranded RNA-like antisense technology can activate the RNAi pathway and inhibit the expression of targeted genes.
- We benefit from our partners as they advance RNA-based technologies and products that incorporate our technology resulting in financial benefits as these assets mature.
  - We earned $2.7 million from Alnylam as a result of Alnylam's licenses that included our patents.
  - Regulus formed a strategic alliance with AstraZeneca for the discovery, development and commercialization of microRNA therapeutics.
  - Regulus formed a strategic alliance with Biogen Idec to identify microRNAs as biomarkers for multiple sclerosis.
  - We received a $1.25 million payment from Pfizer triggered by Pfizer's decision to advance EXC 001 into a Phase 2 study.
  - Regulus Therapeutics completed an initial public offering and is now traded on The NASDAQ Global Market under the ticker RGLS. We purchased $3 million of Regulus' common stock at the offering price and remain a significant shareholder with approximately 17 percent ownership on a fully diluted basis.
- We completed a successful offering of $201.3 million of 2¾ percent convertible senior notes. We used the proceeds of this offering to redeem the entire $162.5 million of 2⅝ percent convertible subordinated notes.

Critical Accounting Policies

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

Historically, our estimates have been accurate as we have not experienced any material differences between our estimates and our actual results. The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, require the following:

- 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 proper valuation of inventory;
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimating our net deferred income tax asset valuation allowance;
- Determining when we are the primary beneficiary for entities that we identify as variable interest entities;
- Determining the fair value of convertible debt without the conversion feature; and
- Determining the fair value of stock-based compensation, including the expected life of the option, the expected stock price volatility over the term of the expected life and estimated forfeitures.

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, 2011.

Results of Operations

Revenue

Total revenue for the three and nine months ended September 30, 2012 was $11.6 million and $82.2 million, respectively, compared to $20.7 million and $66.7 million for the same periods in 2011. 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, our revenue in the first nine months of 2012 was significantly higher than in 2011 primarily due to the $25 million milestone payment we earned from Genzyme for FDA acceptance of the KYNAMRO NDA. Also in the first nine months of 2012, we sold $10.9 million of drug substance to Genzyme to support the planned commercial launch of KYNAMRO and began recognizing revenue from the $41 million in upfront payments we received from the partnerships we entered into with Biogen Idec this year. These increases were partially offset by a decrease in revenue because amortization of the upfront payments associated with our Genzyme collaboration ended in May 2012.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the three and nine months ended September 30, 2012 was $11.1 million and $80.1 million, respectively, compared to $20.2 million and $64.5 million for the same periods in 2011. The increase in the first nine months of 2012 was primarily due to the $25 million milestone payment from Genzyme and the $10.9 million from sales of drug substance that we earned from Genzyme and

revenue we earned from Biogen Idec partially offset by a decrease in revenue because amortization of the upfront payments associated with our Genzyme collaboration ended in May 2012.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the three and nine months ended September 30, 2012 was $474,000 and $2.1 million, respectively, and was essentially flat when compared to $524,000 and $2.2 million for the same periods in 2011.

Operating Expenses

Operating expenses for the three and nine months ended September 30, 2012 were $39.6 million and $125.0 million, respectively, compared to $43.0 million and $119.2 million for the same periods in 2011. The moderately higher expenses in the first nine months of 2012 were primarily due to higher development costs associated with our maturing pipeline of drugs offset by lower development expenses related to KYNAMRO because Genzyme is now sharing these expenses equally with us until KYNAMRO is profitable. In addition, Genzyme is paying all of the marketing and selling expenses until KYNAMRO is profitable.

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.

Research and Development Expenses

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

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2012	2011	2012	2011
Research and development expenses	$ 34,831	$ 37,907	$ 109,972	$ 103,584
Non-cash compensation expense related to equity awards	1,720	2,017	5,728	6,594
Total research and development	$ 36,551	$ 39,924	$ 115,700	$ 110,178

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For the three and nine months ended September 30, 2012, we incurred total research and development expenses of $34.8 million and $110.0 million, respectively, compared to $37.9 million and $103.6 million for the same periods in 2011. Our expenses in the third quarter of 2012 were less than the same period in 2011 primarily as a result of lower development expenses related to KYNAMRO and lower development expenses for our other antisense projects due to the timing of when studies were initiated. The higher expenses in the first nine months of 2012 were primarily due to higher development costs associated with our maturing pipeline of drugs offset, in part, by lower development expenses related to KYNAMRO. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the costs of development increase. All amounts exclude non-cash compensation expense related to equity awards.

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

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2012	2011	2012	2011
Antisense drug discovery	$ 8,250	$ 7,662	$ 25,044	$ 22,863
Non-cash compensation expense related to equity awards	499	581	1,663	1,893
Total antisense drug discovery	$ 8,749	$ 8,243	$ 26,707	$ 24,756

Antisense drug discovery costs for the three and nine months ended September 30, 2012 were $8.3 million and $25.0 million, respectively, compared to $7.7 million and $22.9 million for the same periods in 2011. The higher expenses in 2012 compared to 2011 were primarily due to increased research services provided by third parties to support our partnered research programs and higher expense for personnel and laboratory supplies required to support our collaborative research efforts. 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 September 30,		Nine Months Ended September 30,	
	2012	2011	2012	2011
KYNAMRO	$ 2,593	$ 4,409	$ 8,060	$ 10,386
Other antisense development products	10,976	12,470	37,669	31,767
Development overhead costs	1,555	1,635	5,005	4,744
Non-cash compensation expense related to equity awards	589	697	1,970	2,217
Total antisense drug development	$ 15,713	$ 19,211	$ 52,704	$ 49,114

Antisense drug development expenditures were $15.1 million and $50.7 million, respectively, for the three and nine months ended September 30, 2012, compared to $18.5 million and $46.9 million for the same periods in 2011. Lower expenses in the third quarter of 2012 compared to the same period in 2011 were primarily a result of lower development expenses related to KYNAMRO and lower development expenses for other antisense projects due to the timing of when studies were initiated. Overall, the increase in the first nine months of 2012 was primarily due to an increase in development costs associated with our maturing pipeline of drugs offset, in part, by lower development expenses related to KYNAMRO. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the costs of development increase. All amounts exclude non-cash compensation expense related to equity awards.

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We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Our Phase 1 and Phase 2 programs are clinical research programs that fuel our Phase 3 pipeline. When our products are in Phase 1 or Phase 2 clinical trials, they are in a dynamic state where we continually adjust the development strategy for each product. Although we may characterize a product as “in Phase 1” or “in Phase 2,” it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product’s particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous products in preclinical and early stage clinical research, the fluctuations in expenses from product to product, in large part, offset one another. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related cost. We have partnered 13 of our 25 drug candidates, which substantially reduces our development costs. As part of our collaboration with Genzyme, we have transitioned development responsibility for KYNAMRO to Genzyme. In 2011, we satisfied our $125 million development funding obligation. We and Genzyme now share development costs equally. Our shared funding will end when the program is profitable.

Manufacturing and Operations

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

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2012	2011	2012	2011
Manufacturing and operations	$ 4,624	$ 4,258	$ 14,309	$ 13,543
Non-cash compensation expense related to equity awards	232	226	797	837
Total manufacturing and operations	$ 4,856	$ 4,484	$ 15,106	$ 14,380

Manufacturing and operations expenses increased slightly for the three and nine months ended September 30, 2012 with $4.6 million and $14.3 million, respectively, compared to $4.3 million and $13.5 million for the same periods in 2011. The increase in 2012 was due to higher personnel costs and supplies required to support our maturing pipeline of drugs. All amounts exclude non-cash compensation expense related to equity awards.

R&D Support

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

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2012	2011	2012	2011
Personnel costs	$ 2,252	$ 2,176	$ 6,792	6,357
Occupancy	1,767	2,921	5,170	6,569
Depreciation and amortization	1,467	1,372	3,927	4,666
Insurance	286	216	866	643
Other	1,061	788	3,130	2,046
Non-cash compensation expense related to	400	513	1,298	1,647

equity awards				
Total R&D support costs	$ 7,233	$ 7,986	$ 21,183	$ 21,928

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R&D support costs for the three and nine months ended September 30, 2012 were $6.8 million and $19.9 million, respectively, compared to $7.5 million and $20.3 million for the same periods in 2011. Expenses in the first nine months of 2012 compared to the same period in 2011 are essentially flat. The increase in Other costs primarily relates to litigation costs for our patent infringement lawsuit against Santaris Pharma A/S. The increase in Other costs is offset, in part, by a reduction in Occupancy costs because the leases on our former primary research and development facilities expired at the end of 2011. 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 September 30,		Nine Months Ended September 30,	
	2012	2011	2012	2011
General and administrative expenses	$ 2,782	$ 2,758	$ 8,248	$ 7,987
Non-cash compensation expense related to equity awards	314	347	1,033	1,002
Total general and administrative expenses	$ 3,096	$ 3,105	$ 9,281	$ 8,989

General and administrative expenses are essentially flat for the three and nine months ended September 30, 2012 with $2.8 million and $8.2 million, respectively, compared to $2.8 million and $8.0 million for the same periods in 2011. All amounts exclude non-cash compensation expense related to equity awards.

Equity in Net Loss of Regulus Therapeutics Inc.

Our equity in net loss of Regulus for the nine months ended September 30, 2012 was $1.1 million, compared to equity in net loss of Regulus of $2.3 million for the nine months ended September 30, 2011. We did not recognize any equity in net loss of Regulus for the three months ended September 30, 2012, compared to equity in net loss of Regulus of $386,000 for the three months ended September 30, 2011. Under the equity method of accounting, we are required to suspend recognizing losses if our share of Regulus' net loss exceeds the amount of funding we are required to provide to Regulus. Until the completion of Regulus' IPO, we and Alnylam were guarantors of both of the convertible notes that Regulus issued to GSK. Therefore, we continued to recognize losses in excess of our net investment in Regulus up to the principal plus accrued interest we guaranteed, which was $5.6 million at September 30, 2012. In the second quarter of 2012, we suspended recording our portion of Regulus' net loss because our share of Regulus' net loss exceeded the $5.6 million we guaranteed. As of September 30, 2012, we had $2.7 million of suspended net losses, which we have not recognized.

In October 2012, Regulus completed an IPO and we now own less than 20 percent of Regulus' common stock and we no longer have significant influence over the operating and financial policies of Regulus. As such, beginning in the fourth quarter we will no longer use the equity method of accounting for our equity investment in Regulus and instead we will account for it at fair value. In the fourth quarter of 2012, we will record a gain of approximately $15 million to $20 million to reflect the change in our ownership percentage.

Investment Income

Investment income for the three and nine months ended September 30, 2012 was $408,000 and $1.5 million, respectively, compared to $575,000 and $1.9 million for the same periods in 2011. The decrease in investment income was primarily due to a lower average cash balance.

Interest Expense

Interest expense for the three and nine months ended September 30, 2012 was $5.9 million and $16.3 million, respectively, compared to $4.8 million and $11.6 million for the same periods in 2011. The increase in interest expense in 2012 is primarily a result of additional non-cash interest expense we recorded for the long-term liability associated with our primary research and development facility. Assuming no other changes, our interest expense over the next twelve months will decrease by approximately $2.6 million because the debt discount we are amortizing as additional non-cash interest expense for the 2³¤₄ convertible senior notes is less than the amount we were amortizing for the 2⁵¤₈ percent convertible subordinated notes we redeemed in September 2012.

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Gain (Loss) on Investments, Net

We did not record any gain or loss on investments for the three months ended September 30, 2012, compared to a net gain of $18,000 for the three months ended September 30, 2011. We recorded a net gain on investments for the nine months ended September 30, 2012 of $19,000, compared to a net loss of $267,000 for the nine months ended September 30, 2011. The loss on investments for the first nine months of 2011 was primarily due to a $359,000 valuation allowance we recorded related to an investment we made in Excaliard Pharmaceuticals, Inc. offset by nominal gains on our available-for-sale securities.

Early Retirement of Debt

In September 2012, we redeemed our 2⅝ percent convertible subordinated notes. The carrying value of the 2⅝ percent notes on our balance sheet included a discount based on the estimated fair value of a similar debt instrument without the conversion feature. We were amortizing this discount over the expected life of the debt as additional non-cash interest expense. As a result of our early redemption of the 2⅝ percent notes, we recognized a $4.8 million loss in the third quarter of 2012. A significant portion of the loss, or $3.6 million, was non-cash and related to the unamortized debt discount and debt issuance costs while the remainder of the loss was related to a $1.2 million early redemption premium we paid to the holders of the 2⅝ percent notes.

Income Tax Benefit

In the third quarter of 2012, we recorded a tax benefit of $706,000, which reflected our application of the intraperiod tax allocation rules under which a tax benefit is recorded in continuing operations to offset a tax provision recorded directly to other comprehensive income related to current unrealized gains on our investments in available-for-sale securities.

Net Loss and Net Loss per Share

Net loss for the three and nine months ended September 30, 2012 was $37.6 million and $62.8 million, respectively, compared to a net loss of $26.9 million and $64.8 million for the same periods in 2011. Basic and diluted net loss per share for the three and nine months ended September 30, 2012 was $0.37 per share and $0.63 per share, respectively, compared to $0.27 per share and $0.65 per share for the same periods in 2011. Our net loss for the first nine months of 2012 decreased slightly compared to the same period in 2011 primarily due to a decrease in our net operating loss offset, in part, by the $4.8 million loss on the early retirement of our 2⅝ percent convertible subordinated notes and additional non-cash interest expense we recorded for the long-term liability associated with our primary research and development facility.

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 September 30, 2012, we have earned approximately $1.1 billion in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through September 30, 2012, we have raised net proceeds of approximately $831.9 million from the sale of our equity securities and we have borrowed approximately $784.3 million under long-term debt arrangements to finance a portion of our operations.

As of September 30, 2012, we had cash, cash equivalents and short-term investments of $343.6 million, which was essentially flat compared to December 31, 2011. In addition, as of September 30, 2012 our stockholders' equity was $170.3 million compared to $171.4 million at December 31, 2011. At September 30, 2012, we had consolidated working capital of $310.0 million, compared to $284.0 million at December 31, 2011. Our September 30, 2012 cash balance was bolstered by the over $140 million we received in the first nine months of 2012, including the $41 million in upfront payments we received from Biogen Idec, a $25 million milestone payment we received from Genzyme for FDA acceptance of the KYNAMRO NDA, and approximately $30 million in net proceeds remaining from the issuance of the 2¾ percent convertible notes after deducting offering fees and expenses and the redemption of the 2⅝ percent notes.

As of September 30, 2012, our debt and other obligations totaled $285.2 million, compared to $239.9 million at December 31, 2011. The increase was primarily related to our 2⅝ percent convertible notes we refinanced with the issuance of the 2¾ percent convertible notes in the third quarter of 2012 and additional draw downs on our equipment financing arrangement offset, in part, by the rent and principal payments we made in the first nine months of 2012 on our lease obligations and notes payable.

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The following table summarizes our contractual obligations as of September 30, 2012. 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)	$ 240.0	$ 2.7	$ 11.1	$ 11.1	$ 215.1
Facility Rent Payments	$ 145.1	$ 5.8	$ 12.2	$ 13.0	$ 114.1
Equipment Financing Arrangements (principal and interest payable)	$ 12.0	$ 5.4	$ 6.6	$ —	$ —
Other Obligations (principal and interest payable)	$ 1.4	$ 0.1	$ 0.1	$ 0.1	$ 1.1
Capital Lease	$ 0.6	$ 0.2	$ 0.4	$ —	$ —
Operating Leases	$ 27.8	$ 1.5	$ 2.7	$ 2.8	$ 20.8
Total	$ 426.9	$ 15.7	$ 33.1	$ 27.0	$ 351.1

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 2¾ percent, which is payable semi-annually. We used a substantial portion of the net proceeds from the issuance of these to redeem the entire $162.5 million in principal of our 2⅝ 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 a loan agreement related to an equipment financing 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 September 30, 2012, we had drawn down $27.4 million in principal under this loan agreement at a weighted average interest rate of 5.51 percent and we can borrow up to an additional $6.0 million in principal to finance the purchase of equipment until April 2014. The carrying balance under this loan agreement at September 30, 2012 and December 31, 2011 was $11.3 million and $5.3 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 our rent payments, which began on January 1, 2012, will decrease the liability over the term of the lease.

In addition to contractual obligations, we had outstanding purchase orders as of September 30, 2012 for the purchase of services, capital equipment and materials as part of our normal course of business.

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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, 2011.

Risks Associated with our Drug Discovery and Development Business

If we or our partners fail to obtain regulatory approval for our drugs, including KYNAMRO, we cannot sell them.*

We cannot guarantee that any of our drugs, including KYNAMRO, will be safe and effective, or will be approved for commercialization. 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, before a drug can be approved for sale. We must conduct these studies in compliance with U.S. Food and Drug Administration, or 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, including KYNAMRO. Even though Genzyme has submitted marketing approval applications for KYNAMRO in Europe and the United States, it is possible that regulatory agencies will not approve KYNAMRO 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, the agency will not approve the specific drug or will require additional studies, which can be time consuming and expensive and which will delay commercialization of the drug.

Failure to receive marketing approval for our drugs, including KYNAMRO, 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, including KYNAMRO, 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, including KYNAMRO, are safe and effective for human use, we may need to abandon one or more of our drug development programs. We have ongoing clinical studies for KYNAMRO, adverse events from which could negatively impact our pending marketing approval applications.

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 with any additional clinical studies for KYNAMRO and in clinical studies for our other drugs. If any of our drugs in clinical studies, including

KYNAMRO, does 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. 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;

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- 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 our clinical studies, including any further studies under our development program for KYNAMRO, could reduce the commercial potential or viability of our drugs.

Even if approved, KYNAMRO and any of our other drugs may be subject to regulatory limitations.

Following approval of a drug, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute drug products. Even if approved, we may not obtain the labeling claims necessary or desirable for successfully commercializing our drug products, including KYNAMRO. 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. If 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. In addition, 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 may lose regulatory approval, or we may need to conduct additional clinical studies and/or change the labeling of our drug products including KYNAMRO.

If the market does not accept KYNAMRO or our other drugs, we are not likely to generate revenues or become consistently profitable.

If KYNAMRO or any of our other drugs is approved for marketing, our success will depend upon the medical community, patients and third party payors accepting our drug as medically useful, cost-effective and safe. Even if the FDA or foreign regulatory authorities approve KYNAMRO or our other drugs for commercialization, doctors may not use our drugs to treat patients. For example, we currently have one commercially approved drug, Vitravene, a treatment for CMV retinitis in AIDS patients, which our partner is no longer marketing due to a dramatic decline in the incidence of CMV retinitis in AIDS patients. We and our partners may not successfully commercialize additional drugs.

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, 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 that we receive for KYNAMRO or our other drugs or increase patient coinsurance to a level that makes KYNAMRO or our other drugs unaffordable.

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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 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 believe that our manufacturing facility has sufficient capacity to supply the drug substance necessary for the initial commercial launch of KYNAMRO, if approved. However, we rely on Genzyme to manufacture the finished drug product for KYNAMRO, including the initial commercial launch supply. In addition, if approved, Genzyme will be responsible for the long term supply of both KYNAMRO drug substance and finished drug product. 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 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 our receipt of marketing approval for our drugs, including KYNAMRO, or result in enforcement action after approval that could limit the commercial success of our drugs, including KYNAMRO.

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If our drug discovery and development business fails to compete effectively, our drugs 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, 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.

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 strategy that competes with our strategy for KYNAMRO. Other companies are currently developing products that could compete with KYNAMRO. For example, products such as microsomal triglyceride transfer protein inhibitors, or MTP inhibitors, and other lipid lowering drugs other companies are developing could potentially compete with KYNAMRO. For example, Aegerion has submitted a new drug application to the FDA and a marketing authorization application to the European Medicines Agency seeking approval of its MTP inhibitor, lomitapide, as an adjunct to a low fat diet and other lipid-lowering therapies to reduce cholesterol in patients with HoFH. Our revenues and financial position will suffer if KYNAMRO receives regulatory approval, but cannot compete effectively in the marketplace.

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, Medpace is the primary clinical research organization for clinical studies for KYNAMRO. 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 KYNAMRO.

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Risks Associated with our Businesses as a Whole

We have incurred losses, and our business will suffer if we fail to 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 September 30, 2012, we had an accumulated deficit of approximately $904.3 million and stockholders' equity of approximately $170.3 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 have had only one product, Vitravene, approved for commercial use, but our exclusive distribution partner for this product no longer markets this product. 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, including ATL, Atlantic Pharmaceuticals, Biogen Idec, iCo, Genzyme, GSK, OncoGenex, Pfizer, and Teva Pharmaceutical Industries Ltd. 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 Genzyme, GSK, and Biogen Idec, 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 Genzyme, GSK or Biogen Idec, 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.

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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 approval of KYNAMRO, the price of our securities would likely decrease.

For example, in April 2008 the FDA provided guidance regarding approval requirements for KYNAMRO. The FDA indicated that reduction of LDL-C is an acceptable surrogate endpoint for accelerated approval of KYNAMRO for use in patients with HoFH. The FDA also indicated that for broader indications in high risk, high cholesterol patients the FDA would require an outcome study. This FDA guidance caused us to revise our development plans and timelines such that in July 2011 Genzyme filed for marketing approval in Europe for the treatment of patients with HoFH and patients with severe HeFH and in March 2012 submitted a new drug application (NDA) seeking approval for KYNAMRO for the treatment of patients with HoFH in the United States.

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. This lawsuit 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 commercialization. As of September 30, 2012, we had cash, cash equivalents and short-term investments equal to $343.6 million. If we do not meet our goals to commercialize KYNAMRO or our other drugs, 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:

- marketing approval 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;

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- the time and costs involved in obtaining regulatory approvals;
- competing technological and market developments, including the introduction by others of new therapies that address our markets; and
- the profile and launch timing of our drugs.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and 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 September 30, 2012, the market price of our common stock ranged from $6.25 to $15.61 per share. On November 1, 2012, the closing price of our common stock on the Nasdaq Global Market was $8.92 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. 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;

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- 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, governed by a board of directors, and Regulus and its employees are ultimately 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. In addition, Regulus' directors, executive management team, and strategic partners, including Alnylam, Isis, AstraZeneca, GSK, Biogen Idec and Sanofi have agreed that until October 4, 2013, subject to specified exceptions, not to offer, sell, contract to sell, pledge or otherwise dispose of, directly or indirectly, any shares of Regulus' common stock or securities convertible into or exchangeable or exercisable for any shares of Regulus' common stock.

If a natural or man-made disaster strikes our research, development or manufacturing facilities, it could delay our progress developing and commercializing our drugs.

We manufacture our research and clinical supplies in a 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.

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.

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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

As of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of September 30, 2012. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to September 30, 2012.

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An evaluation was also performed under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of any change in our internal control over financial reporting that occurred during our last fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting. That evaluation did not identify any change in our internal control over financial reporting that occurred during our latest fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

We maintain disclosure controls and procedures that are designed to ensure that information required to be disclosed in our Exchange Act reports is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable and not absolute assurance of achieving the desired control objectives.

PART II — OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

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 January 2012, Alnylam Pharmaceuticals, Inc. filed a patent infringement lawsuit against Tekmira Pharmaceuticals Corporation in the U.S. District Court of the District of Massachusetts. Alnylam's lawsuit alleges Tekmira has infringed a number of issued patents related to siRNA and LNP technologies, including: U.S. Patent No. 7,695,902; U.S. Patent No. 6,858,225; U.S. Patent No. 6,815,432; U.S. Patent No. 6,534,484; U.S. Patent No. 6,586,410; and, U.S. Patent No. 6,858,224. Under Alnylam's contractual right to enforce Isis' patent U.S. Patent No. 7,695,902. Alnylam joined us to the suit as a co-plaintiff.

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

Not applicable

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable

ITEM 5. OTHER INFORMATION

Not applicable

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ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Letter Agreement Amendment dated August 27, 2012 to Strategic Collaboration and License Agreement between the Registrant and Alnylam Pharmaceuticals, Inc. 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 September 30, 2012, 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)

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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)	November 6, 2012
/s/ B. Lynne Parshall B. Lynne Parshall, J.D.	Director, Chief Operating Officer, Chief Financial Officer and Secretary (Principal financial and accounting officer)	November 6, 2012

Isis Pharmaceuticals, Inc.
Requests that the marked portions of the exhibit be granted confidential treatment under Rule 24b-2 of the Securities Exchange Act of 1934.

August 27, 2012

B. Lynne Parshall
Chief Operating Officer and Chief Financial Officer
Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

Re: Letter Agreement Amendment

Dear Lynne:

Reference is made to the Amended and Restated Strategic Collaboration and License Agreement dated April 28, 2009 between Isis Pharmaceuticals, Inc. ("Isis") and Alnylam Pharmaceuticals, Inc. (together with its wholly owned subsidiaries Alnylam US, Inc. and Alnylam Europe AG, "Alnylam") (the "Agreement"). Capitalized terms used herein and not otherwise defined shall have the meanings set forth in the Agreement.

Concurrent with the execution of this letter by the Parties, Alnylam is entering into that certain License and Collaboration Agreement with Monsanto Company dated as of August 27, 2012 ("Agbio License Agreement"), that includes an exclusive sublicense of Alnylam's rights under the Agreement to certain of Isis' intellectual property rights with respect to Double Stranded RNA. Pursuant to Section 7.6 of the Agreement, the CEO of Isis and the CEO of Alnylam have discussed the Agbio License Agreement and simultaneously with the execution of the Agbio License Agreement, the Parties agree to amend the Agreement as follows:

1. Definitions. Exhibit 1.1 of the Agreement is amended as follows:

a. The following definitions are added to Exhibit 1.1:

"Agbio License Agreement" shall mean that certain License and Collaboration Agreement with Monsanto Company dated as of August 27, 2012, as amended from time to time.

"Agricultural Field" shall mean applications in agriculture, horticulture, forestry, aquaculture and/or the residential markets relating to plants, fish, arthropods and/or pests and pathogens thereof (e.g., home, lawn, and/or garden). The Agricultural Field excludes, without limitation, (a) all human and animal (other than fish and arthropods) therapeutic, prophylactic or diagnostic applications; (b) the development, sale and use

of research reagent products for any purpose; and (c) modification of any cells, tissues or organisms for the purpose of manufacturing heterologous proteins, peptides or viruses for any purpose other than the modification of plants, plant cells, or plant tissues for the purpose of manufacturing heterologous proteins, peptides or viruses for application to plants, fish, arthropods and/or pests or pathogens thereof.

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

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

such party's methodologies, which changes are consistently applied by such selling party across of such party's products in the Agricultural Field and which changes are made in the ordinary course of such party's business.

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

b. The definition "Bona Fide Drug Discovery Collaboration" is hereby amended in its entirety as follows, and all references to "Bona Fide Drug Discovery Collaboration" in the Agreement shall be replaced with "Bona Fide Discovery Collaboration":

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

c. The definition "Double Stranded RNA Product" is hereby amended in its entirety as follows:

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

d. The definition of "Net Sales" is hereby amended by adding the following sentence to the end of such definition:

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

e. The definition of "Technology Access Fee" is amended by (i) replacing all references to "Bona Fide Collaboration" in such definition with "Bona Fide Discovery Collaboration" and (ii) replacing clause (iii) thereof with the following:

(iii) payments specifically committed to reimburse Alnylam for the fully-burdened cost of research and development, including without limitation the fully-burdened cost of products transferred by Alnylam in connection with such research and development, and payments received by Alnylam pursuant to the Agbio License Agreement that are specifically committed to reimburse Alnylam for the cost of Patent prosecution, maintenance and/or defense of Patents covering or claiming Agricultural Field Products; *provided*, *however*, that any payments received by Alnylam but not applied to reimburse Alnylam for such expenses will be Technology Access Fees,

2. Isis Retained Rights; Limitations on Licenses.

a. Section 5.2(d). Clause (ii) of Section 5.2(d) is hereby amended in its entirety as follows:

(ii) Isis may continue to grant licenses to Third Parties for the purpose of manufacturing and selling oligonucleotides; provided that, to the extent such licenses cover Double Stranded RNA or Single Stranded RNAi Compounds, Isis will restrict such licenses to [***] and, in the case of Double Stranded RNA, will exclude from such licenses granted after the date of this Letter Agreement Agricultural Field Products.

b. Section 5.3(d). Section 5.3(d) of the Agreement is hereby amended in its entirety as follows:

(d) Licenses to Isis Patent Rights that are subject to contractual obligations between Isis and Third Parties in effect as of the Restatement Date are licensed (i) subject to the restrictions and other terms described in Exhibit 5.3(d) attached hereto, and (ii) with respect to Agricultural Field Products, to the extent Isis has the right under such Third Party agreements to grant such a license for Agricultural Field Products. Alnylam hereby agrees to comply, and to cause its sublicensees to comply, with such restrictions and other terms.

3. Technology Access Fees and Royalties.

a. Royalties. Section 7.2(a) of the Agreement is hereby amended in its entirety as follows:

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

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

b. Milestones. Section 7.3(c) of the Agreement is hereby amended by including the following sentence at the end of such section:

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

c. Technology Access Fee. Section 7.5(b) of the Agreement is hereby amended by including the following sentence at the end of such section:

Notwithstanding the foregoing, the provisions of this Section 7.5(b) shall not apply to any Bona Fide Discovery Collaboration involving solely Agricultural Field Products.

4. Representation and Warranty. Alnylam hereby represents and warrants to Isis that the Agbio License Agreement includes a collaboration involving the discovery and/or development of Double Stranded RNA Products, in which Alnylam plays an integral role in the experimentation and an important, though not necessarily dominant or co-equal, role in the decision-making, relating to the discovery and/or development of such Double Stranded RNA Products.

5. Additional Provisions. The Parties agree that the provisions of Section 10.2 of the Agreement shall not apply to licenses involving solely Agricultural Field Products.

6. No Other Amendments; Entire Agreement. Except as amended, modified and supplemented by the terms of this Letter Agreement, the provisions of the Agreement are and shall remain in full force and effect. This Letter Agreement and the Agreement (as amended by this Letter Agreement) contain the entire understanding of the Parties with respect to the subject matter hereof. All express or implied agreements and understandings, either oral or written, with regard to such subject matter are superseded by the terms of this Letter Agreement and the Agreement (as amended by this Letter Agreement). This Letter Agreement may be amended, or any term hereof modified, only by a written instrument duly-executed by authorized representatives of both Parties hereto.

[*Signature page follows.*]

If Isis is in agreement with the foregoing, please so indicate by signing below.

Sincerely,

ALNYLAM PHARMACEUTICALS, INC.

By: /s/ John Maraganore
Name: John Maraganore
Title: Chief Executive Officer

Agreed to and acknowledged by:

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall
Name: B. Lynne Parshall
Title: Chief Operating Officer and
Chief Financial 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: November 6, 2012

/s/ Stanley T. Crooke

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

EXHIBIT 31.2

CERTIFICATION

I, B. Lynne Parshall, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: November 6, 2012

/s/ B. Lynne Parshall

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

Exhibit 32.1

CERTIFICATION

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

1. The Company's Quarterly Report on Form 10-Q for the period ended September 30, 2012, 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: November 6, 2012

/s/ Stanley T. Crooke	/s/ B. Lynne Parshall
Stanley T. Crooke, M.D., Ph.D.	B. Lynne Parshall, J.D.
Chief Executive Officer	Chief Financial Officer

A signed original of this written statement required by Section 906 has been provided to Isis Pharmaceuticals, Inc. and will be retained by Isis Pharmaceuticals, Inc. and furnished to the Securities and Exchange Commission or its staff upon request.