# UNITED STATES
# SECURITIES AND EXCHANGE COMMISSION

**Washington, DC 20549**

# Form 10-Q

**(Mark One)**

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

**For the Quarterly Period Ended March 31, 2011**

**OR**

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

**For the transition period from to**

**Commission file number 0-19125**

# Isis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

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

**1896 Rutherford Road, Carlsbad, CA 92008**
(Address of principal executive offices, including zip code)

**760-931-9200**
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **None**

Securities registered pursuant to Section 12(g) of the Act:

**Common Stock, $.001 Par Value**

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes x No o

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

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

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

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

The number of shares of voting common stock outstanding as of May 2, 2011 was 99,594,202.

**ISIS PHARMACEUTICALS, INC.**
**FORM 10-Q**

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**TRADEMARKS**

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

**Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc.**

**Ibis T5000™ is a trademark of Ibis Biosciences, Inc.**

**Vitravene® is a registered trademark of Novartis AG.**



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

| | March 31, 2011 (Unaudited) | December 31, 2010 |
|---|---|---|
| **ASSETS** | | |
| Current assets: | | |
| Cash and cash equivalents | $ 86,200 | $ 70,052 |
| Short-term investments | 340,622 | 402,301 |
| Contracts receivable | 591 | 1,242 |
| Inventories | 2,606 | 2,484 |
| Other current assets | 7,376 | 7,058 |
| Total current assets | 437,395 | 483,137 |
| Property, plant and equipment, net | 37,680 | 35,703 |

| | | |
|---|---|---|
| Licenses, net | 11,696 | 12,288 |
| Patents, net | 15,773 | 15,821 |
| Deposits and other assets | 3,398 | 3,528 |
| Total assets | $ 505,942 | $ 550,477 |
| **LIABILITIES AND STOCKHOLDERS' EQUITY** | | |
| Current liabilities: | | |
| Accounts payable | $ 4,652 | $ 6,523 |
| Accrued compensation | 3,076 | 6,831 |
| Accrued liabilities | 8,134 | 12,389 |
| Current portion of long-term obligations | 5,145 | 5,645 |
| Current portion of deferred contract revenue | 73,392 | 74,502 |
| Total current liabilities | 94,399 | 105,890 |
| Long-term deferred contract revenue | 32,065 | 50,413 |
| $2^5/_8$ percent convertible subordinated notes | 134,964 | 132,895 |
| Long-term obligations, less current portion | 4,938 | 5,720 |
| Long-term financing obligation | 10,147 | 10,147 |
| Investment in Regulus Therapeutics Inc. | 1,726 | 870 |
| Total liabilities | 278,239 | 305,935 |
| Stockholders' equity: | | |
| Common stock, $0.001 par value; 200,000,000 shares authorized, 99,580,093 and 99,393,780 shares issued and outstanding at March 31, 2011 and December 31, 2010, respectively | 100 | 99 |
| Additional paid-in capital | 1,003,595 | 1,000,181 |
| Accumulated other comprehensive income | 689 | 949 |
| Accumulated deficit | (776,681) | (756,687) |
| Total stockholders' equity | 227,703 | 244,542 |
| Total liabilities and stockholders' equity | $ 505,942 | $ 550,477 |

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 March 31, | |
|---|---|---|
| | 2011 | 2010 |
| Revenue: | | |
| Research and development revenue under collaborative agreements | $ 20,014 | $ 28,556 |
| Licensing and royalty revenue | 1,133 | 1,370 |
| Total revenue | 21,147 | 29,926 |
| | | |
| Expenses: | | |
| Research and development | 34,245 | 31,987 |
| General and administrative | 3,010 | 2,819 |
| Total operating expenses | 37,255 | 34,806 |
| | | |
| Loss from operations | (16,108) | (4,880) |
| | | |
| Other income (expense): | | |
| Equity in net loss of Regulus Therapeutics Inc. | (856) | (1,486) |
| Investment income | 705 | 955 |
| Interest expense | (3,415) | (3,237) |
| Loss on investments | (318) | (1,010) |
| | | |
| Loss before income tax expense | (19,992) | (9,658) |
| | | |
| Income tax expense | (2) | — |
| | | |
| Net loss | $ (19,994) | $ (9,658) |
| | | |
| Basic and diluted net loss | $ (0.20) | $ (0.10) |
| Shares used in computing basic and diluted net loss per share | 99,569 | 99,013 |

See accompanying notes.

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

| | Three Months Ended March 31, | |
|---|---|---|
| | 2011 | 2010 |
| Net cash used in operating activities | $ (39,842) | $ (21,691) |
| **Investing activities:** | | |
| Purchases of short-term investments | (110,164) | (125,598) |
| Proceeds from the sale of short-term investments | 170,328 | 158,621 |
| Purchases of property, plant and equipment | (2,576) | (11,009) |
| Proceeds from land sold to BioMed | — | 10,147 |
| Reduction of cash due to deconsolidation of Regulus Therapeutics Inc. upon adoption of a new accounting standard | — | (16,228) |
| Acquisition of licenses and other assets | (511) | (516) |
| Purchases of strategic investments | (359) | (459) |
| Net cash provided by investing activities | 56,718 | 14,958 |
| **Financing activities:** | | |
| Net proceeds from issuance of equity | 683 | 1,031 |
| Principal payments on debt and capital lease obligations | (1,411) | (963) |
| Net cash (used in) provided by financing activities | (728) | 68 |
| Net increase (decrease) in cash and cash equivalents | 16,148 | (6,665) |
| Cash and cash equivalents at beginning of period | 70,052 | 105,255 |
| Cash and cash equivalents at end of period | $ 86,200 | $ 98,590 |
| **Supplemental disclosures of cash flow information:** | | |
| Interest paid | $ 2,275 | $ 2,281 |
| Income taxes paid | $ 2 | $ 7,700 |
| **Supplemental disclosures of non-cash investing activities:** | | |
| Amounts accrued for capital and patent expenditures | $ 1,222 | $ 836 |

See accompanying notes.





**ISIS PHARMACEUTICALS, INC.**
**NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS**
**March 31, 2011**
**(Unaudited)**

## 1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three month periods ended March 31, 2011 and 2010 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2010. 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, 2010 included in our Annual Report on Form 10-K filed with the Securities and Exchange Commission ("SEC").

The condensed consolidated financial statements include the accounts of Isis Pharmaceuticals, Inc. ("we", "us" or "our") and our wholly owned subsidiaries, Isis USA Ltd. and Symphony GenIsis, Inc. We use the equity method of accounting to account for our investment in Regulus Therapeutics Inc. (formerly Regulus Therapeutics LLC).

## 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 under current accounting rules. 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 condensed consolidated balance sheet.

*Research and development revenue under collaborative agreements*

We often enter into collaborations under which we receive non-refundable upfront payments. We recognize revenue related to upfront payments ratably over our period of performance relating to the term of the contractual arrangements. Occasionally, we must estimate our period of performance when the agreements we enter into do not clearly define such information. The revenue we recognize could be materially different if different estimates prevail. We have made estimates of our continuing obligations on several agreements. To date, we have not had to make material adjustments to our estimates. Our collaborative agreements typically include a research and/or development project plan that includes the activities the agreement requires each party to perform during the collaboration and the party responsible for performing them. We estimate the period of time over which we will complete the activities for which we are responsible and use that period of time as our period of performance for purposes of revenue recognition and amortize revenue over such period. 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. Adjustments to performance periods and related adjustments to revenue amortization periods have had a material impact on our revenue on only one occasion. When Alnylam Pharmaceuticals, Inc. terminated the single-stranded RNAi, or ssRNAi, research program in November 2010, we recognized as revenue $4.9 million, which was the remaining deferred revenue from the upfront fee that we were amortizing into revenue over the research term.

Our collaborations often include contractual milestones, which typically relate to the achievement of pre-specified development, regulatory and commercialization events. When we achieve these milestones, we are entitled to payment, according to the underlying agreements. We assess whether a substantive milestone exists at the inception of our agreements. When a substantive milestone is achieved, we recognize revenue related to milestone payments upon completion of the milestone's performance requirement. In evaluating if a payment represents a milestone which is substantive we considered whether:

- Substantive uncertainty exists as to the achievement of the milestone event at the inception of the arrangement;
- Substantive effort is involved to achieve the milestone event;
- The amount of the milestone payment appeared 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 January 2011 OncoGenex Pharmaceuticals Inc., initiated a Phase 2 trial of OGX-427 in men with metastatic prostate cancer. We considered the initiation of a Phase 2 trial under our collaboration with OncoGenex to be a substantive milestone because the level of effort and inherent risk associated with successfully moving a drug into Phase 2 clinical development is high. Therefore, we recognized the entire $750,000 milestone payment in the first quarter of 2011. Further information about our collaborative arrangements can be found in Note 8 of our audited financial statements for the year ended December 31, 2010 included in our Annual Report on Form 10-K filed with the SEC.



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On January 1, 2011, we adopted an accounting standard on a prospective basis, which amended the criteria to identify separate units of accounting for revenue arrangements with multiple deliverables. The new guidance replaces the concept of allocating revenue among deliverables in a multiple-element revenue arrangement according to fair value with an allocation based on selling price. The adoption of the standard did not impact our financial position or results of operations as of and for the three month period ended March 31, 2011 as we did not enter into or materially modify any multiple-element arrangements during that period. However, the adoption of this standard may result in revenue recognition for future agreements that is different from our existing multiple-element arrangements.

Prior to the adoption of the revised multiple element guidance, we recognized revenue from arrangements that contained multiple deliverables from each element of the arrangement as long as we could determine a standalone value for the delivered element and fair value for the undelivered elements, we had completed our obligation to deliver or perform on that element and we were reasonably assured of collecting the resulting receivable.

As part of our Genzyme Corporation, or Genzyme, strategic alliance, in February 2008 Genzyme made a $150 million equity investment in us by purchasing five million shares of our common stock at $30 per share. The price Genzyme paid for our common stock represented a significant premium over the fair value of our stock. We accounted for this premium as deferred revenue and are amortizing it along with the $175 million licensing fee that we received in June 2008 ratably into revenue until June 2012, which represents the end of our performance obligation based on the current research and development plan.

*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.

**Short-term investments**

We consider all liquid investments with maturities of 90 days or less when purchased 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. We hold ownership interests of less than 20 percent in each of the respective companies except Regulus, our jointly owned subsidiary. 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. We record unrealized gains and losses related to temporary declines in the publicly-held companies as a separate component of stockholders' equity and account for securities in the privately-held companies, except for Regulus, under the cost method of accounting because we own less than 20 percent and do not have significant influence in 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.

When 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-off for the first three months of 2011 and 2010. Total inventory, which consisted of raw materials, was $2.6 million and $2.5 million as of March 31, 2011 and December 31, 2010, 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



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over their estimated useful lives of 10 years, beginning with the date the United States Patent and Trademark Office, or foreign equivalent, issues the patent. For the first three months of 2011 and 2010, we recorded a non-cash charge of $582,000 and $68,000, respectively, which we included in research and development expenses, related to the write-down of our patent costs to their estimated net realizable values.

**Long-lived assets**

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

**Equity method of accounting**

We account for our ownership interest in Regulus using the equity method of accounting. We include 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 present our investment in Regulus on a separate line in the non-current liabilities section called "Investment in Regulus Therapeutics Inc." Under the equity method of accounting, we are required 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. Since we and Alnylam are guarantors of both of the convertible notes that Regulus issued to GlaxoSmithKline, or GSK, we will continue to recognize losses in excess of our net investment in Regulus up to the principal plus accrued interest we guaranteed, which was $5.4 million at March 31, 2011.

**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. Adjustments to our estimates have had a material impact to our actual results on only one occasion. When Alnylam terminated the ssRNAi research program in November 2010, we recognized as revenue $4.9 million, which was the remaining deferred revenue from the upfront fee that we were amortizing into revenue over the research term.

**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 loss from continuing operations for the three months ended March 31, 2011 and 2010, we did not include the following diluted common equivalent shares in the computation of diluted net loss from continuing operations per share because the effect would have been anti-dilutive:

- $2^5/_8$ percent convertible subordinated notes;
- GlaxoSmithKline convertible promissory notes;
- Dilutive stock options; and
- Warrants issued to Symphony GenIsis Holdings LLC

In April 2011, the remaining warrants issued to Symphony GenIsis Holdings LLC were exercised.

**Consolidation of variable interest entities**

We identify entities as variable interest entities either: (1) that do not have sufficient equity investment at risk to permit the entity to finance its activities without additional subordinated financial support, or (2) in which the equity investors lack an essential characteristic of a controlling financial interest. We perform ongoing qualitative assessments of our variable interest entities to determine whether we have a controlling financial interest in the variable interest entity and therefore are the primary beneficiary. As of March 31, 2011 and December 31, 2010, we had collaborative arrangements with eight entities that we consider 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 right to

receive benefits from our variable interest entities that could potentially be significant to the variable interest entities. In the case of Regulus, since we and Alnylam share the ability to impact Regulus' economic performance, we are not the primary beneficiary of Regulus.



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**Comprehensive loss**

We report, in addition to net loss, comprehensive loss and its components as follows (in thousands):

| | Three Months Ended March 31, | |
|---|---|---|
| | 2011 | 2010 |
| Comprehensive loss: | | |
| Unrealized holding gains (losses) | $ (260) | $ 151 |
| Reclassification adjustment for realized loss included in net loss | — | (925) |
| Net loss | (19,994) | (9,658) |
| Comprehensive loss | $ (20,254) | $ (10,432) |

**Convertible debt**

We account for our $2^5/_8$ percent convertible notes by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate when we recognize interest expense in subsequent periods. As a result, we assigned a value to the debt component of our $2^5/_8$ percent convertible notes equal to the estimated fair value of a similar debt instrument without the conversion feature, which resulted in us recording the debt at a discount. We are amortizing the resulting debt discount over the life of the debt as additional non-cash interest expense utilizing the effective interest method.

**Segment information**

Prior to 2011 we reported our results in two separate segments; Drug Discovery and Development and Regulus. Beginning in the first quarter of 2011, we no longer consider Regulus as an operating segment because our chief decision making officer no longer reviews Regulus' operating results for purposes of making resource allocations. Therefore we only provide financial information and results for our Drug Discovery and Development operations.

**Stock-based compensation expense**

We account for our stock-based compensation expense related to employee stock options and employee stock purchases by estimating the fair value of each employee stock option grant and the employee stock purchase plan ("ESPP") purchase rights on the date of grant using the Black-Scholes model. The expected term of stock options granted represents the period of time that they are expected to be outstanding. We estimated the expected term of options granted based on historical exercise patterns.

For the three months ended March 31, 2011 and 2010, we used the following weighted-average assumptions in our Black-Scholes calculations:

*Employee Stock Options:*

| | Three Months Ended March 31, | |
|---|---|---|
| | 2011 | 2010 |
| Risk-free interest rate | 2.3% | 2.8% |
| Dividend yield | 0.0% | 0.0% |
| Volatility | 52.5% | 55.7% |
| Expected Life | 5.3 years | 5.1 years |

*ESPP:*

| | Three Months Ended March 31, | |
|---|---|---|
| | 2011 | 2010 |
| Risk-free interest rate | 0.2% | 0.2% |
| Dividend yield | 0.0% | 0.0% |
| Volatility | 26.5% | 54.8% |
| Expected Life | 6 months | 6 months |



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The following table summarizes stock-based compensation expense related to employee and non-employee stock options and the ESPP for the three months ended March 31, 2011 and 2010 (in thousands, except per share data), which was allocated as follows:

| | Three Months Ended March 31, | |
|---|---|---|
| | 2011 | 2010 |
| Research and development | $ 2,292 | $ 2,826 |
| General and administrative | 440 | 530 |
| Total | $ 2,732 | $ 3,356 |

As of March 31, 2011, total unrecognized compensation cost related to non-vested stock-based compensation plans was $14.3 million. We will adjust total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize this cost over a weighted average period of 1.5 years.

**3. Investments**

As of March 31, 2011, our excess cash was primarily invested in commercial paper and debt instruments with strong credit ratings of financial institutions, corporations, U.S. government agencies and the U.S. Treasury with an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's (S&P) or Fitch, respectively. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

The following table summarizes the contract maturity of the available-for-sale securities we held as of March 31, 2011:

| | |
|---|---|
| One year or less | 79% |
| After one year but within two years | 18% |
| After two years but within three years | 3% |
| Total | 100% |

In April 2011, S&P affirmed the 'AAA/A-1+' rating on the sovereign credit rating of the United States. At the same time, however, S&P lowered the outlook of the long-term rating to 'Negative' from 'Stable.' The action taken by S&P pertains primarily to the long-term challenges associated with the United States' budget deficits and rising indebtedness. As illustrated above, our excess cash is invested primarily in short-term instruments with 97 percent of our available-for-sale securities having a maturity of less than two years. Therefore, we do not believe the action taken by S&P impacts the carrying value of our available-for-sale securities at March 31, 2011.

At March 31, 2011, we had an ownership interest of less than 20 percent in each of five private companies and two public companies with which we conduct business. The companies are Santaris Pharma A/S (formerly Pantheco A/S), Achaogen, Inc., Atlantic Pharmaceuticals Limited, Altair Therapeutics Inc. and Excaliard Pharmaceuticals, Inc., which are privately-held and Antisense Therapeutics Limited, or ATL, and iCo Therapeutics Inc., which are publicly-traded. We account for securities in the privately-held companies under the cost method of accounting and we classify the securities in the publicly-traded companies as available-for-sale. In the first quarter of 2011, we recognized a $318,000 loss on investments primarily consisting of a $359,000 valuation allowance we recorded related to our investment in Excaliard. Because realization of our Excaliard investment is uncertain we recorded a full valuation allowance.



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

| March 31, 2011 | Amortized Cost | Unrealized Gains | Unrealized Losses | Other-Than-Temporary Impairment Loss | Estimated Fair Value |
|---|---|---|---|---|---|
| Short-term investments: | | | | | |
| Corporate debt securities | $ 169,701 | $ 211 | $ (32) | $ — | $ 169,880 |
| Debt securities issued by U.S. government agencies | 85,846 | 20 | (54) | — | 85,812 |
| Debt securities issued by the U.S. Treasury | 9,015 | 5 | — | — | 9,020 |
| Debt securities issued by states of the United States and political subdivisions of the states | 6,025 | — | — | — | 6,025 |
| Total securities with a maturity of one year or less | 270,587 | 236 | (86) | — | 270,737 |
| | | | | | |
| Corporate debt securities | 48,387 | 210 | (78) | — | 48,519 |
| Debt securities issued by U.S. government agencies | 18,282 | 5 | (57) | — | 18,230 |
| Debt securities issued by the U.S. Treasury | 2,508 | 3 | — | — | 2,511 |
| Debt securities issued by states of the United States and political subdivisions of the states | 619 | 6 | — | — | 625 |
| Total securities with a maturity of more than one year | 69,796 | 224 | (135) | — | 69,885 |
| | | | | | |
| Subtotal | $ 340,383 | $ 460 | $ (221) | $ — | $ 340,622 |
| | | | | | |
| Equity securities: | | | | | |
| Current portion (included in Other current assets) | $ 1,538 | $ 1,255 | $ — | $ (880) | $ 1,913 |
| Long-term portion (included in Deposits and other assets) | 625 | — | — | — | 625 |
| | | | | | |
| Subtotal | $ 2,163 | $ 1,255 | $ — | $ (880) | $ 2,538 |
| | | | | | |
| | $ 342,546 | $ 1,715 | $ (221) | $ (880) | $ 343,160 |



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| December 31, 2010 | Amortized Cost | Unrealized Gains | Unrealized Losses | Other-Than-Temporary Impairment Loss | Estimated Fair Value |
|---|---|---|---|---|---|
| Short-term investments: | | | | | |
| Corporate debt securities | $ 196,010 | $ 294 | $ (41) | $ — | $ 196,263 |
| Debt securities issued by U.S. government agencies | 119,890 | 53 | (34) | — | 119,909 |
| Debt securities issued by the U.S. Treasury | 24,030 | 10 | — | — | 24,040 |
| Debt securities issued by states of the United States and political subdivisions of the states | 6,989 | 3 | — | — | 6,992 |
| Total securities with a maturity of one year or less | 346,919 | 360 | (75) | — | 347,204 |
| Corporate debt securities | 47,842 | 167 | (44) | — | 47,965 |
| Debt securities issued by U.S. government agencies | 7,139 | 4 | (11) | — | 7,132 |
| Total securities with a maturity of more than one year | 54,981 | 171 | (55) | — | 55,097 |
| Subtotal | $ 401,900 | $ 531 | $ (130) | $ — | $ 402,301 |
| Equity securities: | | | | | |
| Current portion (included in Other current assets) | $ 1,538 | $ 1,353 | $ — | $ (880) | $ 2,011 |
| Long-term portion (included in Deposits and other assets) | 625 | — | — | — | 625 |
| Subtotal | $ 2,163 | $ 1,353 | $ — | $ (880) | $ 2,636 |
| | $ 404,063 | $ 1,884 | $ (130) | $ (880) | $ 404,937 |

Investments we consider to be temporarily impaired at March 31, 2011 are as follows (in thousands):

| | Number of Investments | Less than 12 months of temporary impairment: Estimated Fair Value | Less than 12 months of temporary impairment: Unrealized Losses |
|---|---|---|---|
| Corporate debt securities | 29 | $ 60,495 | $ (110) |
| Debt securities issued by U.S. government agencies | 11 | 38,164 | (111) |
| Total temporarily impaired securities | 40 | $ 98,659 | $ (221) |

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, 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. 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. At March 31, 2011, we had no securities that we classified as Level 3.



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Below is a table of our assets that we measure at fair value on a recurring basis. For the following major security types, we break down the inputs used to measure fair value at March 31, 2011 (in thousands):

| | Total | Quoted Prices in Active Markets for Identical Assets (Level 1) | Significant Other Observable Inputs (Level 2) | Significant Unobservable Inputs (Level 3) |
|---|---|---|---|---|
| Cash equivalents (1) | $ 86,176 | $ 45,071 | $ 41,105 | $ — |
| Corporate debt securities (2) | 218,399 | — | 218,399 | — |
| Debt securities issued by U.S. government agencies (2) | 104,042 | — | 104,042 | — |
| Debt securities issued by the U.S. Treasury (2) | 11,531 | 11,531 | — | — |
| Debt securities issued by states of the United States and political subdivisions of the states (2) | 6,650 | — | 6,650 | — |
| Equity securities (3) | 1,913 | 1,913 | — | — |
| Total | $ 428,711 | $ 58,515 | $ 370,196 | $ — |

(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.

**5. Concentration of Business Risk**

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

| | Three Months Ended March 31, | |
|---|---|---|
| | 2011 | 2010 |
| Partner A | 79% | 56% |
| Partner B | 3% | 33% |

None of our contract receivables at March 31, 2011 represented contract receivables from significant partners. Contract receivables from two significant partners comprised approximately 30 percent and 15 percent of our contract receivables at December 31, 2010. Included in our contract receivables at March 31, 2011 and December 31, 2010 was $535,000 and $544,000, respectively, representing 91 percent and 44 percent, respectively, of our contract receivables, due from Regulus.



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## 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, including Regulus Therapeutics Inc., our jointly owned subsidiary.*

### Forward-Looking Statements

In addition to historical information contained in this Report on Form 10-Q, this Report includes forward-looking statements regarding our business, the therapeutic and commercial potential of our technologies and products in development, and the financial position of Isis Pharmaceuticals, Inc. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause 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, 2010, 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 22 of this Report.

### Overview

We are the leading company in antisense technology, exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Antisense technology is a direct route from genomics to drugs. With our highly efficient and prolific drug discovery platform we can expand our drug pipeline and our partners' pipelines with antisense drugs that address significant unmet medical needs. Our business strategy is to do what we do best—to discover unique antisense drugs and develop these drugs to key clinical value inflection points. In this way, our organization remains small and focused. We discover and conduct early development of new drugs, outlicense our drugs to partners and build a broad base of license fees, milestone payments and royalty income. We maximize the value of the drugs we discover by putting them in the hands of quality partners with late-stage development, commercialization and marketing expertise such as Bristol-Myers Squibb, Genzyme, GSK and Eli Lilly and Company. We also work with a consortium of smaller companies that can exploit our technology outside our primary areas of focus using their expertise in specific disease areas. We call these smaller companies our satellite companies. In addition to our cutting edge antisense programs, we maintain technology leadership through collaborations with Alnylam and Regulus, a company we established and jointly own focused on microRNA therapeutics. We also exploit our inventions with other therapeutic opportunities such as through collaborations with Achaogen and Archemix Corp. Beyond human therapeutics, we benefit from the commercialization of products incorporating our technology by other companies that are better positioned to maximize the commercial potential of these inventions, such as when we sold our subsidiary Ibis Biosciences to Abbott Molecular Inc. All of these different types of relationships are part of our unique business model and create current and future shareholder value.

We protect our proprietary RNA-based technologies and products through our substantial patent estate. As an innovator in RNA-based 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, our patent portfolio continues to grow. The patents not only protect our key assets—our technology and our drugs—they also form the basis for lucrative licensing and partnering arrangements. To date, we have generated nearly $400 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

The clinical success of mipomersen, the lead drug in our cardiovascular franchise, is a clear example of the power of our RNA-based technology. We and Genzyme reported positive data from four Phase 3 studies demonstrating consistent and robust lowering of low-density lipoprotein cholesterol, or LDL-C, and other atherogenic lipids. Across these four studies, treatment with mipomersen reduced LDL-C in patients who have persistently high LDL-C levels despite being treated on maximally tolerated lipid-lowering therapy. Mipomersen also reduced many other atherogenic lipids, including triglycerides, lipoprotein a, or Lp(a), and non-high-density lipoprotein cholesterol, or non HDL-C, due to its unique mechanism of action. We believe the safety profile of mipomersen supports our initial market opportunity in patients who cannot currently reach their recommended LDL-C goal. The mipomersen data from all four of our Phase 3 studies support the profile of the drug as a novel treatment to reduce LDL-C in patients with very high cholesterol, at high cardiovascular risk and who cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies.

Our clinical experience with mipomersen demonstrates that antisense drugs work in man. With mipomersen we have additional evidence, as we have shown with other antisense drugs, that we can predict the activity of our drugs in man from the preclinical successes we observe in animals. We believe mipomersen's success has validated our technology platform and increased the value of our drugs.

In addition to mipomersen, many of the other drugs in our pipeline are demonstrating encouraging therapeutic activity in a variety of diseases. Over the past couple of years, we and our partners have reported positive data from five Phase 2 studies and seven Phase 1 studies. For example, we reported data from a positive Phase 2 study from our protein tyrosine phosphatase 1B, or PTP-1B, drug showing consistent and statistically significant reductions in short and intermediate measures of glucose control, reductions in LDL-C and a tendency toward weight loss. We believe these characteristics create an encouraging profile for a new therapy to treat type 2 diabetics. Many of our partnered drugs are also showing encouraging activity in numerous diseases. Our partner Excaliard reported data from three Phase 2 studies showing that treatment with EXC 001, a locally administered antisense drug, significantly reduced scarring in patients. These data highlight the broad therapeutic activity of antisense drugs and the power of our antisense technology platform to generate drugs that address significant medical needs.

The clinical successes of the drugs in our pipeline continue to result in new partnering opportunities. Since 2007, our partnerships have generated an aggregate of more than $832 million in payments from licensing fees, equity purchase payments, milestone payments and research and development funding. In addition, for our currently partnered programs we have the potential to earn more than $3.5 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, and/or royalty arrangements. Our strong financial position is a result of the persistent execution of our business strategy as well as our inventive and focused research and development capabilities.

**Recent Events**

***Drug Development and Corporate Highlights***

- We and Genzyme successfully completed four Phase 3 studies that the companies plan to include in the initial United States and European filings for marketing approval of mipomersen. These filings will seek approval for the treatment of patients with homozygous familial hypercholesterolemia (FH) and severe heterozygous FH in Europe, and homozygous FH in the United States. Genzyme is also preparing for filings in markets beyond the United States and Europe.
- We initiated a Phase 1 study on ISIS-$FXI_{Rx}$.
- We received Orphan Drug Status for ISIS-$SMN_{Rx}$ for the treatment of spinal muscular atrophy.
- We reported data from a Phase 1 study of ISIS-$CRP_{Rx}$ showing that ISIS-$CRP_{Rx}$ produced statistically significant reductions in CRP.

**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, adjustments to our estimates have had a material impact to our actual results on only one occasion. When Alnylam terminated the ssRNAi research program in November 2010, we recognized as revenue $4.9 million, which was the remaining deferred revenue from the upfront fee that we were amortizing into revenue over the research term. 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, 2010.

**Results of Operations**

*Revenue*

Total revenue for the three months ended March 31, 2011 was $21.1 million, compared to $29.9 million for the same period in 2010. 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, we earned from OncoGenex a $750,000 milestone payment in the first quarter of 2011 related to the initiation of a Phase 2 study for OGX-427, compared to a $6 million milestone payment we earned from Bristol-Myers Squibb in the first quarter of 2010 related to the initiation of a Phase 1 study for BMS-PCSK9$_{Rx}$. In the first quarter of 2011, we recognized revenue from our collaboration with GSK, which began in the second quarter of 2010. However, first quarter revenue did not include any revenue from BMS and Alnylam because amortization of upfront fees from those collaborations ended.

Collaborations with GSK and Genzyme include ongoing research and development activities. Therefore, we will continue to recognize significant amounts of revenue from these collaborations in the future from the amortization of the upfront fees we received.

*Research and Development Revenue Under Collaborative Agreements*

Research and development revenue under collaborative agreements for the three months ended March 31, 2011 was $20.0 million, compared to $28.6 million for the same period in 2010. The decrease was primarily due to a $750,000 milestone payment we earned from OncoGenex in the first quarter of 2011, compared to a $6 million milestone payment we earned from Bristol-Myers Squibb in the first quarter of 2010 as described above. In the first quarter of 2011, we recognized revenue from our collaboration with GSK, which began in the second quarter of 2010. However, first quarter revenue did not include any revenue from BMS and Alnylam because amortization of upfront fees from those collaborations ended.

*Licensing and Royalty Revenue*

Our revenue from licensing activities and royalties for the three months ended March 31, 2011 was $1.1 million and was slightly lower compared to $1.4 million for the three months ended March 31, 2010.

*Operating Expenses*

Operating expenses for the three months ended March 31, 2011 were $37.3 million, compared to $34.8 million for the same period in 2010. The higher expenses in 2011 were primarily due to an increase in costs associated with our maturing pipeline of drugs, including increases in manufacturing costs as we prepare to begin clinical studies on several of our drugs.

In order to analyze and compare our results of operations to other similar companies, we believe it is important to exclude non-cash compensation expense related to stock options 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.



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***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 March 31, | |
|---|---|---|
| | 2011 | 2010 |
| Research and development expenses | $ 31,953 | $ 29,161 |
| Non-cash compensation expense related to stock options | 2,292 | 2,826 |
| Total research and development | $ 34,245 | $ 31,987 |

For the three months ended March 31, 2011, we incurred total research and development expenses of $32.0 million, compared to $29.2 million for the same period in 2010. The higher expenses in the first quarter of 2011 were primarily due to an increase in costs associated with our maturing pipeline of drugs. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the costs of development increase. All amounts discussed exclude non-cash compensation expense related to stock options.

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 March 31, |
|---|---|

| | 2011 | 2010 |
|---|---|---|
| Antisense drug discovery | $ 7,182 | $ 7,746 |
| Non-cash compensation expense related to stock options | 642 | 803 |
| Total antisense drug discovery | $ 7,824 | $ 8,549 |

Antisense drug discovery costs for the three months ended March 31, 2011 were $7.2 million, compared to $7.7 million for the same period in 2010, all amounts exclude non-cash compensation expense related to stock options. The lower expenses in the first quarter of 2011 were primarily due to the timing of expenses related to ongoing research activities. We expect our 2011 antisense drug discovery costs to be comparable to 2010.



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Antisense Drug Development

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

| | Three Months Ended March 31, | |
|---|---|---|
| | 2011 | 2010 |
| Mipomersen | $ 3,543 | $ 6,503 |
| Other antisense development products | 8,555 | 3,865 |
| Development overhead costs | 1,611 | 1,415 |
| Non-cash compensation expense related to stock options | 774 | 906 |
| Total antisense drug development | $ 14,483 | $ 12,689 |

Antisense drug development expenditures were $13.7 million for the three months ended March 31, 2011, compared to $11.8 million for the same period in 2010, all amounts exclude non-cash compensation expense related to stock options. The higher expenses in the first quarter of 2011 were primarily due to an increase in costs associated with our maturing pipeline of drugs. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the costs of development increase.

We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Our Phase 1 and Phase 2 programs are clinical research programs that fuel our Phase 3 pipeline. When our products are in Phase 1 or Phase 2 clinical trials, they are in a dynamic state where we continually adjust the development strategy for each product. Although we may characterize a product as “in Phase 1” or “in Phase 2,” it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product’s particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous products in preclinical and early stage clinical research, the fluctuations in expenses from product to product, in large part, offset one another. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related cost. Our partners are developing, with our support, 11 of our 24 drug candidates, which substantially reduces our development costs. As part of our collaboration with Genzyme, we are over time transitioning the development responsibility to Genzyme and Genzyme will be responsible for the commercialization of mipomersen. We are contributing up to the first $125 million in funding for the development costs of mipomersen. We anticipate that we will reach $125 million in spending in the second half of 2011, thereafter we and Genzyme will share development costs equally. Our initial development funding commitment and the shared funding will end when the program is profitable.

Manufacturing and Operations

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

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

| | Three Months Ended March 31, | |
|---|---|---|
| | 2011 | 2010 |
| Manufacturing and operations | $ 4,551 | $ 4,133 |
| Non-cash compensation expense related to stock options | 306 | 404 |
| Total manufacturing and operations | $ 4,857 | $ 4,537 |

Manufacturing and operations expenses for the three months ended March 31, 2011 were $4.6 million, compared to $4.1 million for the same period in 2010, all amounts exclude non-cash compensation expense related to stock options. The increase in expenses was primarily a result of costs to manufacture the drug we need to begin clinical studies on several of our drugs.



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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 March 31, | |
|---|---|---|
| | 2011 | 2010 |
| Personnel costs | $ 2,064 | $ 1,984 |
| Occupancy | 1,785 | 1,542 |
| Depreciation and amortization | 1,816 | 1,239 |
| Insurance | 213 | 228 |
| Other | 633 | 505 |
| Non-cash compensation expense related to stock options | 570 | 713 |
| Total R&D support costs | $ 7,081 | $ 6,211 |

R&D support costs for the three months ended March 31, 2011 were $6.5 million, compared to $5.5 million for the same period in 2010, all amounts exclude non-cash compensation expense related to stock options. The increase in expenses in 2011 compared to 2010 primarily relates to the timing of non-cash charges related to patents and patent applications that we are no longer pursuing and a reduction in the costs we allocated to Regulus. When Regulus moved to a separate facility in the second half of 2010, we significantly reduced the costs for facilities and support we were charging them.

***General and Administrative Expenses***

General and administrative expenses include corporate costs required to support our company, our employees and our stockholders. These costs include personnel and outside costs in the areas of legal, human resources, investor relations, and finance. Additionally, we include in general and administrative expenses such costs as rent, repair and maintenance of buildings and equipment, depreciation, utilities, information technology and procurement costs that we need to support the corporate functions listed above.

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

| | Three Months Ended March 31, | |
|---|---|---|
| | 2011 | 2010 |
| General and administrative expenses | $ 2,570 | $ 2,289 |
| Non-cash compensation expense related to stock options | 440 | 530 |
| Total general and administrative expenses | $ 3,010 | $ 2,819 |

General and administrative expenses for the three months ended March 31, 2011 were $2.6 million, and increased slightly compared to $2.3 million for the same period in 2010.

*Equity in Net Loss of Regulus Therapeutics Inc.*

Our equity in net loss of Regulus for the three months ended March 31, 2011 was $856,000, compared to $1.5 million for the same period in 2010. The decrease in our equity in net loss of Regulus reflects the decrease in Regulus' net loss in the first quarter of 2011 compared to the same period in 2010 resulting from the additional revenue Regulus earned from its collaboration with sanofi-aventis, which began in June 2010.

*Investment Income*

Investment income for the three months ended March 31, 2011 was $705,000, compared to $955,000 for the same period in 2010. The decrease in investment income was primarily due to a lower average return on our investments resulting from a lower average cash balance and current market conditions.



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*Interest Expense*

Interest expense for the three months ended March 31, 2011 was $3.4 million and was slightly higher compared to $3.2 million for the same period in 2010.

*Loss on Investments*

Loss on investments for the three months ended March 31, 2011 was $318,000, compared to a loss on investments of $1.0 million for the same period in 2010. The loss on investments for the first three months of 2011 was primarily due to a $359,000 valuation allowance we recorded related to our investment in Excaliard offset by nominal gains on our available for sale securities. The loss on investments for the first three months of 2010 consists of an $880,000 non-cash loss related to the other-than-temporary impairment of our equity investment in ATL and a $149,000 valuation allowance we recorded related to our investment in Excaliard slightly offset by realized gains on sales of our available-for-sale securities. Because realization of our Excaliard investment is uncertain we recorded a full valuation allowance.

*Net Loss and Net Loss per Share*

Net loss for the three months ended March 31, 2011 was $20.0 million, compared to a net loss of $9.7 million for the three months ended March 31, 2010. Basic and diluted net loss per share for the three months ended March 31, 2011 was $0.20 per share, compared to $0.10 per share for the three months

ended March 31, 2010. Net loss for the first three months of 2011 was higher than the same period in 2010 primarily due to the increase in our net operating loss in 2011, which is discussed above.

**Liquidity and Capital Resources**

We have financed our operations with revenue primarily from research and development under collaborative agreements. Additionally, we have earned licensing and royalty revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through March 31, 2011, we have earned approximately $948.3 million in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through March 31, 2011, we have raised net proceeds of approximately $821.2 million from the sale of our equity securities and we have borrowed approximately $566.9 million under long-term debt arrangements to finance a portion of our operations.

As of March 31, 2011, we had cash, cash equivalents and short-term investments of $426.8 million and stockholders' equity of $227.7 million. In comparison, we had cash, cash equivalents and short-term investments of $472.4 million and stockholders' equity of $244.5 million at December 31, 2010. At March 31, 2011, we had consolidated working capital of $343.0 million, compared to $377.2 million at December 31, 2010. The decrease in cash and working capital primarily relates to cash used for our operations.

As of March 31, 2011, our debt and other obligations totaled $145.0 million, compared to $144.3 million at December 31, 2010. The slight increase was primarily related to $2.1 million of non-cash amortization of the debt discount we recorded in the first three months of 2011, which increased the carrying value of our $2^5/_8$ percent convertible notes, offset by $1.4 million of principal payments we made in the first three months of 2011 on our equipment financing arrangement.

The following table summarizes our contractual obligations as of March 31, 2011. 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** |
| $2^5/_8$ percent Convertible Subordinated Notes (principal and interest payable) | $ 175.3 | $ 4.3 | $ 8.5 | $ 162.5 | $ — |
| Equipment Financing Arrangements (principal and interest payable) | $ 8.5 | $ 5.3 | $ 3.2 | $ — | $ — |
| Other Obligations (principal and interest payable) | $ 1.5 | $ 0.1 | $ 0.1 | $ 0.1 | $ 1.2 |
| Capital Leases | $ 0.9 | $ 0.2 | $ 0.4 | $ 0.3 | $ — |
| Operating Leases | $ 31.5 | $ 3.0 | $ 2.8 | $ 2.7 | $ 23.0 |
| Total | $ 217.7 | $ 12.9 | $ 15.0 | $ 165.6 | $ 24.2 |



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

In January 2007, we completed a $162.5 million convertible debt offering, which raised proceeds of approximately $157.1 million, net of $5.4 million in issuance costs. We included the issuance costs in our balance sheet and are amortizing these costs to interest expense over the life of the debt. The $162.5 million convertible subordinated notes mature in 2027 and bear interest at $2^5/_8$ percent, which is payable semi-annually. The $2^5/_8$ percent notes are convertible, at the option of the note holders, into approximately 11.1 million shares of our common stock at a conversion price of $14.63 per share. We can redeem these notes at a redemption price equal to 100.75 percent of the principal amount between February 15, 2012 and February 14, 2013; 100.375 percent of the principal amount between February 15, 2013 and February 14, 2014; and 100 percent of the principal amount thereafter. Holders of the $2^5/_8$ percent notes may also require us to repurchase the $2^5/_8$ percent notes on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100 percent of the principal amount of the $2^5/_8$ percent notes being repurchased plus unpaid interest.

In October 2008, we entered into a loan agreement related to an equipment financing and in September 2009, we amended the loan agreement to increase the aggregate maximum amount of principal we can draw under the agreement. Under the loan agreement, we can borrow up to $18.4 million in principal to finance the purchase of equipment until the end of the draw down period. Each draw down under the loan agreement has a term of three years, with principal and interest payable monthly. We calculate interest on amounts we borrow under the loan agreement based upon the three year interest rate swap at the time we make each draw down plus four percent. We are using the equipment purchased under the loan agreement as collateral. As of March 31, 2011, we have drawn down $16.7 million in principal under this loan agreement at a weighted average interest rate of 6.31 percent. The carrying balance under this loan agreement at March 31, 2011 and December 31, 2010 was $8.0 million and $9.4 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 new lease agreement with an affiliate of BioMed Realty, L.P. Under the lease, BioMed is constructing a new 176,000 square foot research facility in Carlsbad, California. Upon completion of construction, we will lease the new facility and consolidate the majority of our operations in the new facility. 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 the new lease is based on a percentage of the total construction costs spent by BioMed to acquire the land and build the new facility. We will begin paying rent on January 1, 2012. Once the new facility is complete, we will be responsible for the costs associated with maintaining the facility. Since our rent is based on a percentage of total construction costs spent by BioMed to acquire the land and build the new facility, and the construction of the facility is not complete, it is difficult for us to calculate our future payment obligations under the lease. However, as of March 31, 2011, we estimate that the maximum potential future payments we may be required to make over the 20 year term of the lease are $154.8 million.

In addition to contractual obligations, we had outstanding purchase orders as of March 31, 2011 for the purchase of services, capital equipment and materials as part of our normal course of business.

We plan to continue to enter into collaborations with partners to provide for additional revenue to us and we may be required to incur additional cash expenditures related to our obligations under any of the new agreements we may enter into. We currently intend to use our cash, 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.



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**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, 2010.*

**Risks Associated with our Drug Discovery and Development Business**

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

We cannot guarantee that any of our drugs, including mipomersen, 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 mipomersen, before a drug can be approved for sale. We must conduct these studies in compliance with 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 mipomersen. Even though we have completed the Phase 3 program to support our initial market for mipomersen, and Genzyme plans to file for marketing approval for mipomersen in Europe early in the third quarter of 2011 and in the United States in 2011, it is possible that regulatory agencies will not approve mipomersen 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 mipomersen, 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 mipomersen, 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 mipomersen, 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 mipomersen, are safe and effective for human use, we may need to abandon one or more of our drug development programs.

In the past, we have invested in clinical studies of drugs that have not met the primary clinical end points in their Phase 3 studies. Similar results could occur with any additional clinical studies for mipomersen and in clinical studies for our other drugs. If any of our drugs in clinical studies, including mipomersen, 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 mipomersen 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 mipomersen. There are a number of factors that could cause a clinical study to fail or be delayed, including:

- the clinical study may produce negative or inconclusive results;
- regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;
- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical study due to adverse side effects of a drug on subjects in the trial;
- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical studies;
- enrollment in our clinical studies may be slower than we anticipate;
- the cost of our clinical studies may be greater than we anticipate; and



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- 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 mipomersen, could reduce the commercial potential or viability of our drugs.

**Even if approved, mipomersen 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 mipomersen. The FDA has 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 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 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 mipomersen.

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

If mipomersen 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 agencies approve mipomersen 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 mipomersen, 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 mipomersen or our other drugs or increase patient coinsurance to a level that makes mipomersen or our other drugs unaffordable.

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

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

We entered into this collaboration primarily to:

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



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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 mipomersen, 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 mipomersen. Our collaboration with Genzyme may not continue or result in the successful commercialization of mipomersen. Genzyme can terminate our collaboration at any time. If Genzyme stopped developing or commercializing mipomersen, we would have to seek additional sources for funding and may have to delay or reduce our development and commercialization programs for mipomersen. If Genzyme does not successfully commercialize mipomersen, we may receive limited or no revenues for mipomersen. In addition, sanofi-aventis recently acquired Genzyme which could disrupt Genzyme or distract it from performing its obligations under our collaboration.

**If Genzyme cannot manufacture finished drug product for mipomersen or the post-launch supply of the active drug substance for mipomersen, mipomersen 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 mipomersen, if approved. However, we rely on Genzyme to manufacture the finished drug product for mipomersen, including the initial commercial launch supply. In addition, if approved, Genzyme will be responsible for the long term supply of both mipomersen drug substance and finished drug product. Genzyme may not be able to reliably manufacture mipomersen drug substance and drug product to support mipomersen's long term commercialization. If

Genzyme cannot reliably manufacture mipomersen drug substance and drug product, mipomersen 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 mipomersen, or result in enforcement action after approval that could limit the commercial success of our drugs, including mipomersen.

**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 mipomersen, 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



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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 mipomersen.

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 mipomersen, some competitors are pursuing a development strategy that competes with our strategy for mipomersen. Other companies are currently developing products that could compete with mipomersen. 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 mipomersen. For example, Aegerion is currently evaluating its MTP inhibitor in a Phase 3 study in homozygous FH patients. Our revenues and financial position will suffer if mipomersen 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 mipomersen. 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 mipomersen.

## Risks Associated with our Businesses as a Whole

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

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of March 31, 2011, we had an accumulated deficit of approximately $776.7 million and stockholders' equity of approximately $227.7 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, Bristol-Myers Squibb, iCo, Eli Lilly and Company, Genzyme, GSK, OncoGenex, 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.



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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 Bristol-Myers Squibb, 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 Bristol-Myers Squibb, 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 mipomersen.

**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 mipomersen, the price of our securities would likely decrease.

For example, in April 2008 the FDA provided guidance regarding approval requirements for mipomersen. The FDA indicated that reduction of LDL-C is an acceptable surrogate endpoint for accelerated approval of mipomersen for use in patients with HoFH. The FDA required us to include data from two preclinical studies for carcinogenicity in the HoFH filing, which studies we have now completed. 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 Genzyme's initial regulatory filings for mipomersen will seek marketing approval for the treatment of patients with HoFH in Europe early in the third quarter of 2011 and in the United States in 2011. The European filing may also include patients with severe HeFH.

**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.



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

It is possible that in the future we may have to defend our intellectual property rights. In the event of an intellectual property dispute, we may need to litigate to defend our rights or assert them against others. Disputes could involve arbitration, litigation or proceedings declared by the United States Patent and Trademark Office or the International Trade Commission or foreign patent authorities. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business.

For example, in December 2006 the European Patent Office, or EPO, Technical Board of Appeal reinstated with amended claims our Patent EP0618925 which claims a class of antisense compounds. Prior to its reinstatement, several parties originally opposed this patent and the EPO Opposition Division revoked it in December of 2003. We intend to fully exercise our rights under this patent by pursuing licensing arrangements, but if licensing efforts are unsuccessful we may choose to assert our rights through litigation, which may be costly and which 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 a commitment of significant additional resources prior to their commercialization. As of March 31, 2011, we had cash, cash equivalents and short-term investments equal to $426.8 million. If we do not meet our goals to commercialize mipomersen 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 launch of mipomersen;
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements;
- continued scientific progress in our research, drug discovery and development programs;
- the size of our programs and progress with preclinical and clinical studies;
- the time and costs involved in obtaining regulatory approvals;
- competing technological and market developments, including the introduction by others of new therapies that address our markets; and
- the profile and launch timing of our drugs.

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 decided to terminate the development of two lower priority drugs, ISIS 14803 and ISIS 104838. Alternatively, we may obtain funds through arrangements with collaborative partners or others, which could require us to give up rights to certain of our technologies or drugs.



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**The loss of key personnel, or the inability to attract and retain highly skilled personnel, could make it more difficult to run our business and reduce our likelihood of success.**

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our executive officers that would prevent them from leaving us. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. In addition, failure to succeed in clinical studies may make it more challenging to recruit and retain qualified scientific personnel.

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding March 31, 2011, the market price of our common stock ranged from $7.59 to $11.27 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. These materials and various wastes resulting from their use are stored at our facilities in Carlsbad, California pending ultimate use and disposal. We cannot completely eliminate the risk of contamination, which could cause:

- interruption of our research, development and manufacturing efforts;
- injury to our employees and others;
- environmental damage resulting in costly clean up; and
- liabilities under federal, state and local laws and regulations governing health and human safety, as well as the use, storage, handling and disposal of these materials and resultant waste products.

In such an event, we may be held liable for any resulting damages, and any liability could exceed our resources. Although we carry insurance in amounts and 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. In the event 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 jointly owned company that we and Alnylam established to focus on discovery, developing, and commercializing of microRNA therapeutics. We exclusively licensed to Regulus our intellectual property rights covering microRNA



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technology. Regulus operates as an independent company, governed by a board of directors. We and Alnylam can elect an equal number of directors to serve on the Regulus Board. Regulus researches and develops microRNA projects and programs pursuant to an operating plan that its board approves. However, 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.

**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 in the event they are affected by a disaster, our development and commercialization efforts would be delayed. Although we possess insurance for damage to our property and the disruption of our business from casualties, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all.

**Provisions in our certificate of incorporation, other agreements and Delaware law may prevent stockholders from receiving a premium for their shares.**

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least $66^{2}¤_{3}$ 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. Our stockholders' rights plan expired in December 2010. These provisions, as well as Delaware law and other of our agreements, may discourage certain types of transactions in which our

stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests. In addition, our board of directors has the authority to fix the rights and preferences of, 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 subordinated notes could make it more difficult or more expensive for a third party to acquire us. Upon the occurrence of certain transactions constituting a fundamental change, holders of the notes will have the right, at their option, to require us to repurchase all of their notes or a portion of their notes, which may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over the then current market prices.

In addition, our collaboration agreement with Genzyme regarding mipomersen provides that if we are acquired, Genzyme may elect to purchase all of our rights to receive payments under the mipomersen collaboration agreement for a purchase price to be mutually 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.

**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 have registered for resale our $2^{5}/_{8}$ percent convertible subordinated notes, including the approximately 11.1 million shares issuable upon conversion of the notes. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.



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**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 Select 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 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 is 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 invest our excess cash in highly liquid short-term investments that we typically hold 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 March 31, 2011. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 2011.

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

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



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**PART II — OTHER INFORMATION**

**ITEM 1. LEGAL PROCEEDINGS**

In February 2008, we notified Bruker Daltonics, Ibis' manufacturing and commercialization partner for the T5000 System, that we were initiating the formal dispute resolution process under Ibis' agreement with them. We asserted that Bruker's performance of its manufacturing, commercialization and product service obligations are unsatisfactory and fail to meet their obligations under this agreement. In May 2008, Bruker filed a complaint against Isis Pharmaceuticals, Inc. and Ibis Biosciences, Inc. in Superior Court of Middlesex County, Massachusetts alleging monetary damages due to breach of contract by us and Ibis. We and Ibis filed an Answer, Affirmative Defenses and Counterclaim in July 2008 alleging breach of contract by Bruker. In April 2011, we, Bruker, and Ibis signed a mutual release in this matter and the litigation has been formally dismissed. We will not make or receive any payment in connection with the release.

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

Not applicable

**ITEM 3. DEFAULT UPON SENIOR SECURITIES**

Not applicable

**ITEM 4. (REMOVED AND RESERVED)**

Not applicable

**ITEM 5. OTHER INFORMATION**

Not applicable

**ITEM 6. EXHIBITS**

a. Exhibits

| Exhibit Number | Description of Document |
|---|---|
| 31.1 | Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002. |
| 31.2 | Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002. |
| 32.1 | Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002. |
| 101 | The following financial statements from the Isis Pharmaceuticals, Inc. Quarterly Report on Form 10-Q for the quarter ended March 31, 2011, formatted in Extensive Business Reporting Language (XBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of cash flows, and (iv) notes to condensed consolidated financial statements (tagged as blocks of text). |

**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<br>Stanley T. Crooke, M.D., Ph.D. | Chairman of the Board, President, and Chief Executive Officer (Principal executive officer) | May 5, 2011 |
| /s/ B. Lynne Parshall<br>B. Lynne Parshall, J.D. | Director, Chief Operating Officer, Chief Financial Officer and Secretary (Principal financial and accounting officer) | May 5, 2011 |

**EXHIBIT 31.1**

**CERTIFICATION**

I, Stanley T. Crooke, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: May 5, 2011

/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: May 5, 2011

/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 March 31, 2011, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: May 5, 2011

| | |
|---|---|
| /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.