UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended September 30, 2009

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 o No o

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

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

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

The number of shares of voting common stock outstanding as of November 2, 2009 was 98,380,956.

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)

	September 30, 2009 (Unaudited)	December 31, 2008 (1)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 149,293	$ 217,918
Short-term investments	458,547	273,080
Contracts receivable	586	4,121
Inventories	2,817	2,718
Other current assets	8,004	5,085
Assets from discontinued operations (including cash and cash equivalents of $6.1 million as of December 31, 2008)	—	15,462
Total current assets	619,247	518,384
Property, plant and equipment, net	26,911	17,371

Licenses, net	15,128	16,861
Patents, net	15,851	16,260
Deposits and other assets	3,441	3,900
Total assets	$ 680,578	$ 572,776
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 5,554	$ 5,710
Accrued compensation	4,763	6,835
Income taxes payable	15,864	—
Accrued liabilities	7,491	9,557
Current portion of long-term obligations	4,106	2,065
Current portion of deferred contract revenue	76,941	92,662
Liabilities from discontinued operations	—	7,870
Total current liabilities	114,719	124,699
2 5/8% convertible subordinated notes	123,265	117,993
Long-term obligations, less current portion	12,532	9,938
Long-term deferred contract revenue	125,237	172,766
Total liabilities	375,753	425,396
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 98,376,753 and 97,172,380 shares issued and outstanding at September 30, 2009 and December 31, 2008, respectively	98	97
Additional paid-in capital	978,411	960,361
Accumulated other comprehensive income	3,678	982
Accumulated deficit	(689,192)	(851,216)
Total Isis Pharmaceuticals, Inc. stockholders' equity	292,995	110,224
Noncontrolling interest in Regulus Therapeutics Inc.	11,830	4,737
Noncontrolling interest in Ibis Biosciences, Inc. — discontinued operations	—	32,419
Total stockholders' equity	304,825	147,380
Total liabilities and stockholders' equity	$ 680,578	$ 572,776

(1) The Condensed Consolidated Balance Sheet at December 31, 2008 has been derived from the audited financial statements as adjusted for the required retroactive adoption of accounting standards that became effective in January 2009. See Note 1, *Basis of Presentation*, for additional details.

See accompanying notes.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2009	2008 (1)	2009	2008 (1)
Revenue:				
Research and development revenue under collaborative agreements	$ 25,962	$ 28,488	$ 86,415	$ 69,750
Licensing and royalty revenue	809	975	2,923	7,790
Total revenue	26,771	29,463	89,338	77,540
Expenses:				
Research and development	33,832	26,024	94,520	73,096
General and administrative	3,335	3,263	10,685	9,428
Total operating expenses	37,167	29,287	105,205	82,524
Income (loss) from operations	(10,396)	176	(15,867)	(4,984)
Other income (expense):				
Investment income	1,430	3,468	5,243	8,804
Interest expense	(3,185)	(3,084)	(9,422)	(8,902)
Gain on investments	123	—	2,794	—
Income (loss) from continuing operations, before income tax benefit	(12,028)	560	(17,252)	(5,082)
Income tax benefit	3,968	—	4,625	—
Net income (loss) from continuing operations, net of income tax benefit	(8,060)	560	(12,627)	(5,082)

Discontinued operations:				
Loss from discontinued operations	—	(155)	(29)	(5,884)
Gain on sale of Ibis Biosciences, Inc., net of tax	—	—	171,773	—
Net income (loss) from discontinued operations, net of tax	—	(155)	171,744	(5,884)
Net income (loss)	(8,060)	405	159,117	(10,966)
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	1,136	1,208	2,907	3,056
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (6,924)	$ 1,613	$ 162,024	$ (7,910)
Basic and diluted net income (loss) per share:				
Net income (loss) from continuing operations	$ (0.07)	$ 0.02	$ (0.10)	$ (0.02)
Net income (loss) from discontinued operations	—	—	1.75	(0.06)
Basic and diluted net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.07)	$ 0.02	$ 1.65	$ (0.08)
Shares used in computing basic net income (loss) per share	98,320	95,863	97,988	93,786
Shares used in computing diluted net income (loss) per share	98,320	100,181	97,988	93,786

(1) Adjusted for the required retroactive adoption of accounting standards that became effective in January 2009. See Note 1, *Basis of Presentation*, for additional details.

See accompanying notes.

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

	Nine Months Ended September 30,	
	2009	2008
Net cash (used in) provided by operating activities	$ (76,909)	$ 231,207
Investing activities:		
Purchases of short-term investments	(626,703)	(305,998)
Proceeds from the sale of short-term investments	440,705	112,227
Purchases of property, plant and equipment	(11,662)	(7,050)
Acquisition of licenses and other assets	(1,915)	(2,585)
Purchases of strategic investments	(349)	—
Proceeds from the sale of strategic investments	2,848	—
Net cash used in investing activities	(197,076)	(203,406)
Financing activities:		
Net proceeds from issuance of equity	9,795	10,543
Proceeds from equipment financing arrangement	6,394	—
Proceeds from issuance of convertible promissory note to GSK	—	5,000
Principal payments on debt and capital lease obligations	(1,896)	(7,238)
Proceeds from stock purchase by Genzyme Corporation, net of fees	—	49,962
Proceeds from sale of Ibis Biosciences, Inc. to Abbott Molecular Inc.	175,000	40,000
Proceeds from Alnylam's capital contribution to Regulus Therapeutics Inc.	10,000	—
Net cash provided by financing activities	199,293	98,267
Net (decrease) increase in cash and cash equivalents	(74,692)	126,068
Cash and cash equivalents at beginning of period	223,985	138,614
Cash and cash equivalents at end of period	$ 149,293	$ 264,682
Supplemental disclosures of cash flow information:		
Interest paid	$ 4,666	$ 4,482
Income taxes paid	$ 10,205	$ —
Supplemental disclosures of non-cash investing and financing activities:		
Amounts accrued for capital and patent expenditures	$ 1,240	$ 2,657

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
September 30, 2009
(Unaudited)

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three and nine month periods ended September 30, 2009 and 2008 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2008. The financial statements include all normal recurring adjustments, which we consider necessary for a fair presentation of the financial position at such dates and the operating results and cash flows for those periods. The condensed consolidated financial statements have been adjusted for the required retroactive adoption of the accounting standards for convertible debt instruments that may be settled in cash upon conversion and for reclassification of noncontrolling interests that became effective in January 2009. See Note 2, *Significant Accounting Policies*, and Note 6, *Long-Term Obligations*, for additional information about these accounting standards. 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, 2008 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. In addition to our wholly owned subsidiaries, our condensed consolidated financial statements include one variable interest entity, Regulus Therapeutics Inc., for which we are the primary beneficiary. As a result of completing the sale of Ibis Biosciences, Inc. to Abbott Molecular Inc., or AMI, in January 2009, we have presented Ibis' financial position and results of operations separately as discontinued operations in our condensed consolidated financial statements. We have reclassified amounts in the prior period financial statements to conform to the current period presentation. Prior to the sale of Ibis, we identified Ibis as a variable interest entity that we consolidated. All significant intercompany balances and transactions have been eliminated.

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

Research and development revenue under collaborative agreements

We often enter into collaborations where we receive non-refundable upfront payments for prior or future expenditures. We recognize revenue related to upfront payments ratably over our period of performance relating to the term of the contractual arrangements. Occasionally, we are required to 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. To date, we have not had to make material adjustments to our estimates. We have made estimates of our continuing obligations on several agreements. 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. When our collaborators have asked us to continue performing work in a collaboration beyond the initial period of performance, we have extended our amortization period to correspond to the new extended period of performance. In no case have adjustments to performance periods and related adjustments to revenue amortization periods had a material impact on our revenue.

Our collaborations often include contractual milestones. When we achieve these milestones, we are entitled to payment, according to the underlying agreements. We generally recognize revenue related to milestone payments upon completion of the milestone's substantive performance requirement, as long as we are reasonably assured of collecting the resulting receivable and we have no future performance obligations related to the achievement of the milestone.

We generally recognize revenue related to the sale of our drug inventory as we ship or deliver drugs to our partners. In several instances, we completed the manufacturing of the drugs, but our partners asked us to deliver the drugs on a later date. Under these circumstances, we ensured that revenue is realized or realizable and earned before we recognized the related revenue. Revenue is realized or realizable and earned when all of the following criteria are met, persuasive evidence of an arrangement exists, the delivery has occurred or services rendered, the fee is fixed and determinable, and collectibility is reasonably assured.

We often enter into revenue arrangements that contain multiple deliverables. In these cases, we recognize revenue from each element of the arrangement as long as we are able to determine a separate fair value for each element, we have completed our obligation to deliver or perform on that element and we are reasonably assured of collecting the resulting receivable.

As part of our Genzyme strategic alliance, in February 2008 Genzyme Corporation made a $150 million equity investment in us by purchasing 5 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. Using a Black-Scholes option valuation model, we determined that the value of the premium was $100 million, which represents value Genzyme gave to us to help fund the companies' research collaboration, which began in January 2008. 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 research and development plan included in the agreement.

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 future significant performance obligations and are reasonably assured of collecting the resulting receivable.

Short-term investments

We consider all liquid investments with maturities of ninety days or less when purchased to be cash equivalents. Our short-term investments have initial maturities of greater than ninety 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 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% in each of the respective entities except Regulus, our majority owned subsidiary, which we consolidate with our financial results. 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 issuer, near term prospects of the issuer 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 under the cost method of accounting because we own less than 20% and do not have significant influence in their operations. When we determine that a decline in value is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs. We determined that there were no other-than-temporary declines in value of our investments during the first nine months of 2009 and 2008. During the first nine months of 2009, we sold all of the common stock of OncoGenex Pharmaceuticals Inc. that we owned resulting in a realized gain of $2.5 million.

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

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estimating the net realizable value, including shelf life of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. We did not record any inventory write-offs during the first nine months of 2009 and 2008. Total inventory, which consisted of raw materials, was $2.8 million and $2.7 million as of September 30, 2009 and December 31, 2008, 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 patent applications that have future value. We evaluate costs related to patents that we are not actively pursuing and write off any of these costs, if appropriate. We amortize patent costs over their estimated useful lives of ten years, beginning with the date the United States Patent and Trademark Office issues the patent. For the first nine months of 2009 and 2008, we recorded a non-cash charge of $497,000 and $1.6 million, respectively, which we included in research and development expenses, related to the assignment of patents to certain of our partners and 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.

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. Historically, our estimates have been accurate as we have not experienced any material differences between our estimates and our actual results.

Basic and diluted net income (loss) per share

We compute basic net income (loss) per share by dividing the net income (loss) by the weighted-average number of common shares outstanding during the period. Diluted net income (loss) per share reflects the potential dilution that could occur from the following items:

- $2^5/_8$% convertible subordinated notes;
- GlaxoSmithKline convertible promissory note;
- Dilutive stock options;
- Warrants issued to Symphony GenIsis Holdings LLC; and
- Warrants issued for the Private Placement Financing

Computations for basic and diluted net income (loss) per share are as follows: (in thousands, except per share amounts)

As we incurred a loss from continuing operations for the three and nine months ended September 30, 2009, we did not include diluted common equivalent shares in the computation of diluted net loss and diluted net income per share because the effect would be anti-dilutive.

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	Numerator: Net Income (Loss)	Denominator: Shares	Amount
For the three months ended September 30, 2009			
Basic and diluted net loss per share:			
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (6,924)		
Net income (loss) from discontinued operations	—		
Total basic and diluted net loss	$ (6,924)	98,320	$ (0.07)
For the nine months ended September 30, 2009			
Basic and diluted net income per share:			
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (9,720)		
Net income from discontinued operations, net of taxes	171,744		
Total basic and diluted net income	$ 162,024	97,988	$ 1.65

As we incurred a net loss for the nine months ended September 30, 2008, we did not include diluted common equivalent shares in the computation of diluted net loss per share because the effect would be anti-dilutive.

	Numerator: Net Income (Loss)	Denominator: Shares	Amount
For the three months ended September 30, 2008			
Basic net income per share:			
Net income from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ 1,768		
Net loss from discontinued operations	(155)		
Total basic net income	$ 1,613	95,863	$ 0.02
Diluted net income per share:			
Dilutive stock options	—	3,266	
Warrants issued for the Private Placement Financing	—	829	
Warrants issued to Symphony GenIsis Holdings LLC	—	223	
Net income from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders plus assumed conversions	1,768		
Net loss from discontinued operations, net of taxes	(155)		
Total diluted net income	$ 1,613	100,181	$ 0.02
Potentially dilutive securities not included above since they are anti-dilutive:			
Anti-dilutive stock options		2,863	
For the nine months ended September 30, 2008			
Basic and diluted net loss per share:			
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (2,026)		
Net loss from discontinued operations	(5,884)		
Total basic and diluted net loss	$ (7,910)	93,786	$ (0.08)

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. As of September 30, 2009, we had collaborative arrangements with eight entities that we consider to be variable interest entities. For the nine months ended September 30, 2009, our condensed consolidated financial statements included one variable interest entity, Regulus, for which we were the primary beneficiary. For the nine months ended September 30, 2008, our condensed consolidated financial statements included two variable interest entities, Ibis and Regulus, for which we were the primary beneficiary. Prior to completing the sale of Ibis to AMI in January 2009, we identified Ibis as a variable interest entity that we consolidated.

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Noncontrolling Interests

On January 1, 2009, we adopted an accounting standard that became effective in January 2009, which recharacterizes the accounting and reporting for minority interests as noncontrolling interests and classifies them as a component of stockholders' equity. Although the adoption of this accounting standard did not impact our results of operations and financial position, it required us to reclassify noncontrolling interests as stockholders' equity, include the net loss attributable to noncontrolling interests as part of our consolidated net income (loss) and provide additional disclosures as part of our financial statements. At adoption, we retrospectively implemented the presentation and disclosure requirements to all periods presented in our condensed consolidated financial statements.

The following table presents the statement of changes in stockholders' equity for the nine months ended September 30, 2009 (in thousands):

	Isis Pharmaceuticals, Inc. Stockholders' Equity					Noncontrolling Interests		
	Common stock		Additional paid in capital	Accumulated other comprehensive income	Accumulated deficit	Regulus	Ibis	Total stockholders' equity
Description	Shares	Amount						
Balance at December 31, 2008	97,172	$ 97	$ 960,361	$ 982	$ (851,216)	$ 4,737	$ 32,419	$ 147,380
Comprehensive income:								
Net income (loss)	—	—	—	—	162,024	(2,907)	—	159,117
Change in unrealized gains	—	—	—	4,344	—	—	—	4,344
Reclassification adjustment for realized gains included in net income	—	—	—	(1,648)	—	—	—	(1,648)
Comprehensive income	—	—	—	—	—	—	—	161,813
Options exercised and employee stock purchase plan issuances	1,205	1	9,794	—	—	—	—	9,795
Share-based compensation expense	—	—	8,256	—	—	—	—	8,256
Sale of Ibis to AMI	—	—	—	—	—	—	(32,419)	(32,419)
Alnylam's capital contribution to noncontrolling interest	—	—	—	—	—	10,000	—	10,000
Balance at September 30, 2009	98,377	$ 98	$ 978,411	$ 3,678	$ (689,192)	$ 11,830	$ —	$ 304,825

The following table presents the statement of changes in stockholders' equity for the nine months ended September 30, 2008 (in thousands):

	Isis Pharmaceuticals, Inc. Stockholders' Equity					Noncontrolling Interests		
	Common stock		Additional paid in capital	Accumulated other comprehensive income	Accumulated deficit	Regulus	Ibis	Total stockholders' equity
Description	Shares	Amount						
Balance at December 31, 2007	87,239	$ 87	$ 882,633	$ 538	$ (833,044)	$ 9,371	$ —	$ 59,585
Comprehensive loss:								
Net loss	—	—	—	—	(7,910)	(3,056)	(1,163)	(12,129)
Change in unrealized gains	—	—	—	(1,809)	—	—	—	(1,809)
Comprehensive loss	—	—	—	—	—	—	—	(13,938)
Options exercised and employee stock purchase plan issuances	1,329	1	10,543	—	—	—	—	10,544
Warrants exercised	2,580	3	(3)	—	—	—	—	—
Share-based compensation expense	—	—	11,815	—	—	—	—	11,815
Issuance of common stock to Genzyme	5,000	5	49,956	—	—	—	—	49,961
AMI's capital contribution to noncontrolling interest	—	—	—	—	—	—	34,522	34,522
Balance at September 30, 2008	96,148	$ 96	$ 954,944	$ (1,271)	$ (840,954)	$ 6,315	$ 33,359	$ 152,489

Convertible debt

On January 1, 2009, we adopted an accounting standard that became effective in January 2009, which requires us to account for convertible debt instruments that may be settled in cash upon conversion (including partial cash settlement) by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing

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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% 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. At adoption, we retrospectively implemented the presentation and disclosure requirements to all periods presented in our condensed consolidated financial statements. For additional information, see Note 6, *Long-Term Obligations*.

Subsequent Events

We have evaluated subsequent events occurring through November 5, 2009, which represents the date we issued our financial statements, for potential recognition or disclosure in our financial statements.

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 nine months ended September 30, 2009 and 2008, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Nine Months Ended September 30,	
	2009	2008
Risk-free interest rate	1.9%	3.1%
Dividend yield	0.0%	0.0%
Volatility	56.9%	55.1%
Expected Life	4.9 years	4.6 years

Board of Director Stock Options:

	Nine Months Ended September 30,	
	2009	2008
Risk-free interest rate	3.4%	3.8%
Dividend yield	0.0%	0.0%
Volatility	61.5%	62.2%
Expected Life	7.7 years	7.6 years

ESPP:

	Nine Months Ended September 30,	
	2009	2008
Risk-free interest rate	0.3%	2.8%
Dividend yield	0.0%	0.0%
Volatility	56.5%	61.4%
Expected Life	6 months	6 months

We account for stock options granted to non-employees, which consist primarily of options granted to Regulus' Scientific Advisory Board, by estimating their fair value. Until the stock option is vested, we remeasure the fair value at each reporting period. We recognize the expense over the period of time the non-employee is required to perform services.

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Stock-based compensation expense for the three and nine months ended September 30, 2009 and 2008 (in thousands, except per share data) was allocated as follows:

	Three Months Ended September 30,		Nine Months Ended September 30	
	2009	2008	2009	2008
Research and development	$ 2,893	$ 2,796	$ 8,031	$ 8,378
General and administrative	653	815	1,783	2,056
Non-cash compensation expense related to stock options included in continuing operations	3,546	3,611	9,814	10,434
Non-cash compensation expense (benefit) related to stock options included in discontinued operations	—	439	(1,558)	1,381
Total	$ 3,546	$ 4,050	$ 8,256	$ 11,815
Basic and diluted stock-based compensation expense, per share:				
Net loss per share included in continuing operations	$ (0.04)	$ (0.04)	$ (0.10)	$ (0.11)
Net income (loss) per share included in discontinued operations	—	—	0.02	(0.02)
Total	$ (0.04)	$ (0.04)	$ (0.08)	$ (0.13)

As part of our Regulus joint venture, both we and Alnylam Pharmaceuticals, Inc. issued our own company's stock options to members of Regulus' Board of Directors and Scientific Advisory Board. In addition, we and Alnylam issued our own company's stock options to those employees of each company who were seconded to Regulus under the three companies' limited liability agreement. The seconded employees of Isis became Regulus employees in January 2009 as part of Regulus' conversion to a C-Corporation. As part of the conversion, both we and Alnylam modified our own company's stock options issued to Regulus' employees, members of Regulus' Board of Directors and Scientific Advisory Board to stop vesting in these stock awards before the awards were fully vested. Additionally, in February 2009, Regulus issued options to purchase its own common stock to Regulus' employees, members of Regulus' Board of Directors and members of Regulus' Scientific Advisory Board. Regulus records the expenses associated with these options on its books.

As of September 30, 2009, total unrecognized compensation cost related to Isis' and Regulus' non-vested stock-based compensation plans was $13.7 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 1.25 years.

Impact of recently issued accounting standards

In June 2009, the Financial Accounting Standards Board issued a new accounting standard to replace the quantitative-based risks and rewards calculation for determining which enterprise, if any, has a controlling financial interest in a variable interest entity. The new approach focuses on identifying which enterprise has the power to direct the activities of a variable interest entity that most significantly impact the entity's economic performance and (1) the obligation to absorb losses of the entity or (2) the right to receive benefits from the entity. We do not expect this new standard to have a material impact on our condensed consolidated financial statements when we are required to adopt it in 2010.

3. Discontinued Operations

In 2008, AMI purchased approximately 18.6% of the issued and outstanding common stock of Ibis for a total purchase price of $40 million. In December 2008, we, Ibis and AMI executed a stock purchase agreement (the "Stock Purchase Agreement"). Under the Stock Purchase Agreement, AMI purchased the remaining equity in Ibis from us for $175 million. We, Ibis and AMI completed the acquisition on January 6, 2009.

Since we sold Ibis to AMI and Ibis met the criteria for a component of an entity, we reflect Ibis as a discontinued operation. Accordingly, we have presented the operating results of Ibis in our Condensed Consolidated Statements of Operations as discontinued operations and we have reclassified all prior periods. Net income from discontinued operations for the first nine months of 2009 primarily consisted of the $202.5 million gain related to the sale of Ibis to AMI less $30.7 million of income tax expense. The components of discontinued operations for the periods presented are as follows (in thousands):

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	Three Months Ended September 30,		Nine Months Ended September 30,	
	2009	2008	2009	2008
Revenue	$ —	$ 2,752	$ —	$ 8,989
Total operating expenses	—	7,252	35	20,293
Loss from operations	—	(4,500)	(35)	(11,304)
Other income, net	—	4,078	—	4,257
Loss attributed to noncontrolling interest in Ibis Biosciences, Inc.	—	267	6	1,163
Loss from discontinued operations	—	(155)	(29)	(5,884)
Gain on sale of Ibis Biosciences, Inc., net of tax	—	—	171,773	—
Net income (loss) from discontinued operations, net of tax	$ —	$ (155)	$ 171,744	$ (5,884)

At December 31, 2008, we had the following assets and liabilities classified as assets and liabilities from discontinued operations in our accompanying Condensed Consolidated Balance Sheets (in thousands):

Cash and cash equivalents	$ 6,067
Contracts receivable	818
Inventories	1,422
Property, plant and equipment, net	2,792
Patents, net	2,001
Other assets	2,362
Assets from discontinued operations	$ 15,462
Accounts payable	2,632
Accrued compensation	371
Accrued liabilities	1,982
Notes payable	585
Deferred contract revenue	2,300
Liabilities from discontinued operations	$ 7,870
Noncontrolling interest in Ibis Biosciences, Inc. — discontinued operations	$ 32,419

We have not separately classified cash flows from discontinued operations in our Condensed Consolidated Statement of Cash Flows.

4. Investments

As of September 30, 2009, 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. 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 September 30, 2009:

One year or less	73%
After one year but within five years	27%
Total	100%

At September 30, 2009, we had an ownership interest of less than 20% in each of five private companies and two public companies with which we conduct business. The companies are Antisense Therapeutics Limited and iCo Therapeutics Inc., which are publicly-traded, and Santaris Pharma A/S, formerly Pantheco A/S, Achaogen, Inc., Atlantic Pharmaceuticals Limited, Altair Therapeutics Inc. and Excaliard Pharmaceuticals, Inc., which are privately-held. We account for securities in the privately-held companies under the cost method of accounting. During the first nine months of 2009, we sold all of the common stock of OncoGenex that we owned resulting in a realized gain of $2.5 million.

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

September 30, 2009	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value
Short-term investments:				
Corporate debt securities	$ 119,529	$ 293	$ (60)	$ 119,762
Debt securities issued by U.S. government agencies	165,058	305	—	165,363
Debt securities issued by the U.S. Treasury	48,970	71	—	49,041
Debt securities issued by states of the United States and political subdivisions of the states	275	—	—	275
Total securities with a maturity of one year or less	333,832	669	(60)	334,441
Corporate debt securities	27,975	259	(22)	28,212
Debt securities issued by U.S. government agencies	74,717	112	(35)	74,794
Debt securities issued by U.S. Treasury	21,063	37	—	21,100
Total securities with a maturity of more than one year	123,755	408	(57)	124,106
Subtotal	$ 457,587	$ 1,077	$ (117)	$ 458,547
Equity securities:				
Current portion	$ 1,229	$ 2718	$ —	$ 3,947
Long-term portion	625	—	—	625
Subtotal	$ 1,854	$ 2,718	$ —	$ 4,572
	$ 459,441	$ 3,795	$ (117)	$ 463,119

December 31, 2008	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Short-term investments:					
Corporate debt securities	$ 111,569	$ 150	$ (307)	$ —	$ 111,412
Debt securities issued by U.S. government agencies	111,112	838	(19)	—	111,931
Debt securities issued by the U.S. Treasury	12,939	44	—	—	12,983
Debt securities issued by states of the United States and political subdivisions of the states	275	—	—	—	275
Total securities with a maturity of one year or less	235,895	1,032	(326)	—	236,601
Corporate debt securities	13,608	5	(371)	—	13,242
Debt securities issued by U.S. government agencies	23,199	56	(18)	—	23,237
Total securities with a maturity of more than one year	36,807	61	(389)	—	36,479
Subtotal	$ 272,702	$ 1,093	$ (715)	$ —	$ 273,080
Equity securities:					
Current portion	$ 2,380	$ 604	$ —	$ (1,163)	$ 1,821
Long-term portion	625	—	—	—	625
Subtotal	$ 3,005	$ 604	$ —	$ (1,163)	$ 2,446
	$ 275,707	$ 1,697	$ (715)	$ (1,163)	$ 275,526

Investments we consider to be temporarily impaired at September 30, 2009 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	More than 12 months of temporary impairment: Estimated Fair Value	More than 12 months of temporary impairment: Unrealized Losses	Total temporary impairment: Estimated Fair Value	Total temporary impairment: Unrealized Losses
Corporate debt securities	20	$ 34,114	$ (48)	$ 1,627	$ (34)	$ 35,741	$ (82)
Debt securities issued by U.S. government agencies	8	25,300	(35)	—	—	25,300	(35)
Total temporarily impaired securities	28	$ 59,414	$ (83)	$ 1,627	$ (34)	$ 61,041	$ (117)

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 intend to hold these securities to maturity and anticipate full recovery of amortized cost with respect to these securities at maturity.

5. 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.

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 September 30, 2009 (in thousands):

	Total	Quoted Prices in Active Markets for	Significant Other Observable	Significant Unobservable

		Identical Assets (Level 1)	Inputs (Level 2)	Inputs (Level 3)
Cash equivalents (1)	$ 126,352	$ 126,352	$ —	$ —
Corporate debt securities (1)	147,974	—	147,974	—
Debt securities issued by U.S. government agencies (1)	240,157	—	240,157	—
Debt securities issued by the U.S. Treasury (1)	70,141	70,141	—	—
Debt securities issued by states of the United States and political subdivisions of the states (1)	275	—	275	—
Equity securities (2)	3,947	3,947	—	—
Total	$ 588,846	$ 200,440	$ 388,406	$ —

(1) Included in cash and cash equivalents and short-term investments on our Condensed Consolidated Balance Sheet.

(2) Included in other current assets on our Condensed Consolidated Balance Sheet.

6. Long-Term Obligations

Convertible Subordinated Notes

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%, which is payable semi-annually. The 2 5/8% 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. At September 30, 2009, the principal and accrued interest payable on the notes was $162.5 million and $545,000, respectively, and the fair value was $193.1 million. At December 31, 2008, the principal and accrued interest payable on the notes was $162.5 million and $1.6 million, respectively, and the fair value was $162.3 million. For the nine months ended September 30, 2009, we included 11.1 million shares of our common stock in the computation of diluted net income per share for the conversion of the 2 5/8% notes. We did not include the effect of the conversion of the note into our common stock in the computation of diluted net loss and diluted net income per share because the effect would have been anti-dilutive.

We will be able to redeem the 2 5/8% notes at a redemption price equal to 100.75% of the principal amount between February 15, 2012 and February 14, 2013; 100.375% of the principal amount between February 15, 2013 and February 14, 2014; and 100% of the principal amount thereafter. Holders of the 2 5/8% notes also are able to require us to repurchase these notes on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100% of the principal amount of the 2 5/8% notes being repurchased plus accrued and unpaid interest.

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In 2009, we began accounting for the 2 5/8% notes using the accounting standard that became effective in January 2009, which requires us to assign a value to our convertible debt equal to the estimated fair value of a similar debt instrument without the conversion feature, that results in us recording our convertible debt at a discount. The resulting debt discount is amortized over the expected life of the debt as additional non-cash interest expense. We retrospectively applied the standard to all periods presented in our condensed consolidated financial statements. Using a combination of the present value of the debt's cash flows and a Black-Scholes valuation model, we determined that our nonconvertible debt borrowing rate for the 2 5/8% notes was 9.3%. As a result, we retrospectively adjusted the carrying value of the 2 5/8% notes. Below is a table summarizing the changes to our balance sheet as of December 31, 2008 as a result of adopting this accounting standard (in thousands):

	As Originally Reported	As Adjusted	Effect of Change
Debt issuance costs (included in deposits and other assets)	$ 3,943	$ 2,569	$ (1,374)
2 5/8% convertible subordinated notes	$ 162,500	$ 117,993	$ (44,507)
Additional paid-in capital	$ 905,721	$ 960,361	$ 54,640
Accumulated deficit	$ (839,708)	$ (851,216)	$ (11,508)

Additionally, we adjusted interest expense for the three and nine months ended September 30, 2008 to reflect our nonconvertible debt borrowing rate as follows (in thousands):

	As Originally Reported	As Adjusted	Effect of Change	Effect of Change per share (Basic and Diluted)
Interest expense:				
Three months ended September 30, 2008	$ 1,509	$ 3,084	$ 1,575	$ 0.02
Nine months ended September 30, 2008	$ 4,297	$ 8,902	$ 4,605	$ 0.05

As a result of adopting the standard, interest expense for the three months ended September 30, 2009 included $1.7 million, or $0.02 for basic and diluted per share, of non-cash interest expense related to the amortization of the debt discount and $5.1 million, or $0.05 for basic and diluted per share for the nine months ended September 30, 2009.

Equipment Financing Arrangement

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 and Regulus could borrow up to $19.4 million in principal to finance the purchase of equipment. The $19.4 million does not include the $600,000 Ibis borrowed in October 2008 that was fully repaid in the first quarter of 2009. Each loan under the loan agreement will have a term of approximately 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 4%. We are using the equipment purchased under the loan agreement as collateral. We have drawn down $13.0 million in principal under this loan agreement at a weighted average interest rate of 6.65%. The carrying balance under this loan agreement at September 30, 2009 and December 31, 2008 was $11.0 million and $6.5 million, respectively.

7. Income Taxes

Primarily as a result of the significant upfront funding that we received from our strategic alliance with Genzyme in 2008 and the gain we recognized on the sale of Ibis to AMI earlier this year, we will have a substantial amount of taxable income in 2009. To reduce our tax liability, we will offset a portion of the taxable income with our projected 2009 loss from continuing operations. We will also use some of our net operating loss carryforwards (NOL's) to reduce our federal income taxes in 2009. The tax law changes that were enacted with the 2008/2009 California Budget have suspended our ability to use NOL's to offset our California tax expense for 2009. However, we will offset our California income tax liability to the full extent allowed under the tax regulations with our research and development tax credit carryforwards, which California tax regulations limit to 50% of our California liability. After using all of our allowable losses and tax credits to reduce our tax liability, we estimate that our annual tax expense will be approximately $20 million for the entire year of 2009.

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We are required to allocate our 2009 tax expense between discontinued operations and continuing operations in our Consolidated Statement of Operations. Since the sale of Ibis to AMI was a discrete event that occurred in the first quarter of 2009, we recorded the total amount of our estimated income tax expense for discontinued operations in the first quarter of this year. Further, the allocation rules require us to gross up this amount by the projected annual tax benefit we expect to record as part of our loss from continuing operations in 2009, which we describe below. This means that in addition to the tax expense for the gain on the sale of Ibis, discontinued operations also includes the tax expense for other timing differences, which principally consists of the timing difference associated with the upfront funding we received from Genzyme. Accordingly, we have recorded tax expense of $30.7 million in discontinued operations in the first nine months of 2009.

We included an income tax benefit in continuing operations because we will be using the tax benefits generated from our current year loss from continuing operations to offset a portion of our taxable income. We calculated this benefit by applying our estimated effective tax rate to our loss from continuing operations for the first nine months of 2009. As a result we recorded an income tax benefit of $4.6 million for the first nine months of 2009.

At September 30, 2009, our balance sheet included an income tax payable of $15.9 million. In the fourth quarter of 2009, as our loss from continuing operations increases, we will record additional income tax benefit using the calculation above. The income tax benefit we record will reduce our overall tax expense and income tax payable until we reach our estimated annual amount of $20 million at the end of 2009.

Pursuant to Internal Revenue Code Sections 382 and 383, annual usage of our NOL's and credit carryforwards to offset future taxable income may be limited due to changes in ownership of more than 50%. We completed a Section 382 analysis and determined that we have not experienced a change in ownership that limits our ability to use our NOL's and credit carryforwards that we had accumulated through December 31, 2008. At December 31, 2008, we had federal, California and foreign tax net operating loss carryforwards of approximately $591.1 million, $180.6 million and $1.1 million, respectively. The Federal and California tax loss carryforwards will continue to expire in 2010 and 2013, respectively, unless previously utilized. We also had federal and California research and development tax credit carryforwards of approximately $31.3 million and $22.2 million, respectively. The Federal research and development tax credit carryforwards began expiring in 2004 and will continue to expire unless utilized. The California research and development tax credit carryforwards are available indefinitely. The difference between the tax loss carryforwards for federal and California purposes is attributable to the capitalization of research and development expenses for California tax purposes and a required 50% to 60% limitation on the utilization of prior years' California loss carryforwards. The foreign tax losses may be carried forward indefinitely and used to offset future taxable profits, provided there is no substantial change in ownership.

8. Collaborative Arrangements and Licensing Agreements

The information discussed below represents material changes to partnerships entered into prior to 2009. There are no other material changes from the information provided in Note 7—*Collaborative Arrangements and Licensing Agreements* of the Consolidated Financial Statements section, included in our Annual Report on Form 10-K for the year ended December 31, 2008.

Technology Development Satellite Company Collaborations

Alnylam Pharmaceuticals, Inc.

In April 2009, we and Alnylam amended our strategic collaboration and license agreement to form a new collaboration focused on the development of single-stranded RNAi (ssRNAi) technology. As part of the collaboration, we have co-exclusively licensed our ssRNAi technology to Alnylam in exchange for upfront payments, research and development milestone payments, and royalties. The alliance provides Alnylam with access to our intellectual property and expertise regarding the development of ssRNAi antisense drugs, while both companies will have the opportunity to discover and develop drugs employing the new technology. In addition to the new collaboration, we and Alnylam also extended our broad cross-licensing arrangement regarding double-stranded RNAi that was established in 2004.

Under the terms of the amended collaboration and license agreement, Alnylam paid us an upfront license fee of $11 million, which we are amortizing over the three year period of our performance obligation based on the research plan included in the agreement. Alnylam will also pay us up to $20 million in additional license fees, which Alnylam will pay in three tranches that include $10 million in 18 months or earlier if *in vivo* efficacy in rodents is demonstrated sooner, $5 million upon achievement of *in vivo* efficacy in non-human primates, and $5 million upon initiation of the first clinical trial with an ssRNAi drug. Alnylam is funding research activities at a minimum of $3 million each year for three years with research and development activities conducted both at Isis and Alnylam. If Alnylam develops and commercializes drugs utilizing ssRNAi technology on its own or with a partner, we could potentially receive milestones, totaling up to $18.5 million per product, together with royalty payments. Also, initially we are eligible to receive up to 50 percent of any sublicense payments due to Alnylam based on Alnylam's partnering of ssRNAi products, which will decline over time as Alnylam's investment in the

technology and drugs increases. In turn, Alnylam is eligible to receive up to 5 percent of any sublicense payments due to us based on our partnering of ssRNAi products. Both we and Alnylam are eligible to receive royalties from each other on any ssRNAi products developed by the other company.

Our Condensed Consolidated Balance Sheets at September 30, 2009 included deferred revenue of $9.5 million related to our agreement with Alnylam and none at December 31, 2008. During the three and nine months ended September 30, 2009, we generated revenue from our relationship with Alnylam totaling $1.4 million and $3.7 million, respectively, compared to $4.6 million for the nine months ended September 30, 2008. We did not recognize any revenue for the three months ended September 30, 2008.

Regulus Collaboration

In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development, and commercialization of microRNA-based therapeutics. We and Alnylam each granted Regulus exclusive rights to our respective intellectual property for microRNA therapeutic applications, including a portfolio of over 900 patents and patent applications (including over 600 issued patents) owned by us and Alnylam pertaining to chemical modifications as well as certain early fundamental patents in the microRNA field, including the "Tuschl III", "Sarnow" and "Esau" patent series. Alnylam made an initial investment of $10 million in Regulus to balance venture ownership. Thereafter, we and Alnylam share funding of Regulus. We own 51% of Regulus and Alnylam owns the remaining 49%. Regulus operates as an independent company with a separate board of directors, scientific advisory board and management team. We and Alnylam retain rights to develop and commercialize on pre-negotiated terms microRNA therapeutic products that Regulus decides not to develop either itself or with a partner.

We and Alnylam provide Regulus research and development and general and administrative services under the terms of a services agreement.

In January 2009, Regulus completed a legal reorganization from an LLC to a C-Corporation. In March 2009, Regulus raised $20 million in a Series A preferred equity financing. We and Alnylam were the sole and equal investors in the financing. Since we are consolidating the financial results of Regulus, our cash and cash equivalents balance increased by the $10 million Alnylam contributed.

9. Segment Information and Concentration of Business Risk

Segment information

Prior to AMI's acquisition of our Ibis business, we reported our financial results in three segments. We currently report our financial results in two segments, Drug Discovery and Development and Regulus. Segment loss from operations includes revenue less research and development expenses and general and administrative expenses attributable to each segment. See the Business Segments discussion within the "Management's Discussion and Analysis of Financial Condition and Results of Operations" in Item 2 below for additional information on the segments.

Our Drug Discovery and Development segment generates revenue from collaborations with corporate partners and from licensing proprietary patent rights. Revenue from collaborations with corporate partners may consist of upfront payments, funding for research and development activities, milestone payments and royalties or profit sharing payments. This segment's proprietary technology to discover and characterize novel antisense inhibitors has enabled our scientists to modify the properties of our antisense drugs for optimal use with particular targets and thus, to produce a broad proprietary portfolio of drugs applicable to many disease targets.

Our Regulus segment generates revenue from research grants and collaborations with corporate partners such as its strategic alliance with GSK.

The following is information for revenue, loss from operations and total assets by segment (in thousands):

	Drug Discovery and Development	Regulus	Total
Three Months Ended September 30, 2009			
Revenue:			
Research and development	$ 25,337	$ 625	$ 25,962
Licensing and royalty	809	—	809
Total segment revenue	$ 26,146	$ 625	$ 26,771
Loss from operations	$ (8,084)	$ (2,312)	$ (10,396)
Three Months Ended September 30, 2008			
Revenue:			
Research and development	$ 27,807	$ 681	$ 28,488
Licensing and royalty	975	—	975
Total segment revenue	$ 28,782	$ 681	$ 29,463
Income (loss) from operations	$ 2,386	$ (2,210)	$ 176

	Drug Discovery and Development	Regulus	Total
Nine Months Ended September 30, 2009			
Revenue:			
Research and development	$ 84,027	$ 2,388	$ 86,415
Licensing and royalty	2,923	—	2,923
Total segment revenue	$ 86,950	$ 2,388	$ 89,338
Loss from operations	$ (9,991)	$ (5,876)	$ (15,867)

Total assets as of September 30, 2009	$ 654,751	$ 25,827	$ 680,578
Nine Months Ended September 30, 2008			
Revenue:			
Research and development	$ 68,321	$ 1,429	$ 69,750
Licensing and royalty	7,790	—	7,790
Total segment revenue	$ 76,111	$ 1,429	$ 77,540
Income (loss) from operations	$ 207	$ (5,191)	$ (4,984)
Total assets as of December 31, 2008 (1)	$ 533,637	$ 23,677	$ 557,314

(1) Total assets do not include $15.5 million of assets from discontinued operations as of December 31, 2008.

Concentrations 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 10% or more of our total revenue, was as follows:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2009	2008	2009	2008
Partner A	62%	56%	56%	41%
Partner B	18%	26%	21%	32%
Partner C	8%	10%	7%	12%

Contract receivables from three significant partners comprised approximately 30%, 23% and 16% of contract receivables at September 30, 2009. Contract receivables from three significant partners comprised approximately 25%, 18% and 14% of contract receivables at December 31, 2008.

10. Subsequent Event

In October 2007, we licensed AIR645 to Altair, a biotechnology company focusing on the discovery, development and commercialization of our antisense drugs to treat asthma and other respiratory conditions. We granted an exclusive worldwide license to Altair for the development and commercialization of AIR645, an antisense drug for the treatment of asthma. In November 2009, we participated in Altair's most recent financing which will fund Altair's Phase 2 development of AIR645. Since the realization of the equity we received from the financing is uncertain, we will recognize a full valuation allowance to offset the $1 million payment we made to Altair in the fourth quarter of 2009. As a result of the financing, our ownership interest in Altair is less than 10%.

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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.

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. and Regulus Therapeutics, our majority-owned subsidiary. 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 products. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning our programs are described in additional detail in our Annual Report on Form 10-K for the year ended December 31, 2008, which is on file with the U.S. Securities and Exchange Commission, and those identified within this Item entitled "Risk Factors" beginning on page 32 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. Our highly efficient and prolific drug discovery platform enables us to 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 value inflection points. In this way, our organization remains small and focused. We discover 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 and commercialization expertise. For example, we partner our drugs with leading pharmaceutical companies with mature development, commercialization and marketing expertise, such as Bristol-Myers Squibb Company, or BMS, Genzyme, Eli Lilly and Company and Ortho-McNeil-Janssen Pharmaceuticals, Inc., or OMJP. Additionally, we created a consortium of smaller companies that can broadly exploit the technology with 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 beyond our core areas of focus through collaborations with Alnylam and Regulus, our jointly owned company focused on microRNA therapeutics. We also exploit our inventions with other therapeutic opportunities through collaborations with Achaogen and Archemix Corp. Beyond human therapeutics, we benefit from the commercialization of products of our inventions by other companies that are better positioned to maximize the commercial potential of these inventions, such as our Ibis

Biosciences subsidiary, which we sold to AMI in the first quarter of 2009. All of these aspects fit into our unique business model and create continued shareholder value.

We protect our proprietary RNA-based technologies and products through our substantial patent estate. We remain one of the most prolific patent holders in the United States, ranked as having one of the highest ratios of issued patents per employee with more than 1,600 issued patents. 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 attractive licensing and partnering arrangements. To date, we have generated more than $345 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 because it demonstrates that antisense drugs can 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, increased the value of our drugs, and created renewed interest from potential partners in antisense technology.

The clinical successes of the drugs in our pipeline continue to result in new partnering opportunities. Since 2007, we have established a number of notable pharmaceutical partnerships, which include Genzyme, BMS and OMJP, to develop and commercialize certain of our key cardiovascular and diabetes drugs. Since 2007, we have also added more than $760

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million in cash from our partnerships. If our current partnerships continue to be successful, we have the opportunity to earn additional 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 and our inventive and focused research and development capabilities.

Business Segments

Prior to AMI's acquisition of our Ibis Biosciences business, we focused on three segments. We currently focus our business on two principal segments:

Drug Discovery and Development Within our primary business segment, we are exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs for us and our partners. Our proprietary drug discovery platform enables us to rapidly identify drugs, providing a wealth of potential targets to treat a broad range of diseases. We focus our efforts in therapeutic areas where our drugs will work best, efficiently screening many targets in parallel and carefully selecting the best drugs. This efficiency combined with our rational approach to selecting disease targets enables us to build a large and diverse portfolio of drugs designed to treat a variety of health conditions including cardiovascular, metabolic, inflammatory, ocular and neurodegenerative diseases, and cancer. We currently have 19 drugs in development. Our partners are licensed to develop, with our support, 15 of these 19 drugs, which substantially reduces our development costs.

Regulus Therapeutics Inc. In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development and commercialization of microRNA therapeutics. Regulus is addressing therapeutic opportunities that arise from alterations in microRNA expression. Since microRNAs may act as master regulators, affecting the expression of multiple genes in a disease pathway, microRNA therapeutics define a new platform for drug discovery and development and microRNAs may also prove to be an attractive new diagnostic tool for disease characterization.

Ibis Biosciences, Inc. In January 2009, we sold our Ibis Biosciences subsidiary to AMI for a total purchase price of $215 million. In 2008, AMI invested $40 million in Ibis, which provided the capital for Ibis to make significant progress in expanding commercial product offerings and building the foundation for Ibis to enter regulated markets, such as clinical diagnostics. When AMI completed the acquisition of Ibis, we received an additional $175 million. We are also eligible to receive an earn out on future sales of Ibis products that will enable us and our shareholders to continue to benefit from Ibis' successes. The earn out payments from AMI are equal to a percentage of Ibis' revenue related to sales of Ibis systems, including instruments, assay kits and successor products, through the end of 2025. The earn out payments will be 5% of net sales over $140 million through net sales of $2.1 billion and 3% of net sales over $2.1 billion, with the percentages subject to reduction in certain circumstances.

As a result of selling Ibis to AMI, Ibis' financial results are considered discontinued operations. Accordingly, we have presented the operating results of Ibis for all prior periods in our financial statements separately as discontinued operations and therefore Ibis is no longer included in our segment reporting. Net income from discontinued operations in the first nine months of 2009 primarily consists of a $202.5 million gain related to the sale of Ibis to AMI less $30.7 million of income taxes.

Recent Events

We reported positive top-line Phase 2 data on ISIS 113715 in patients with type 2 diabetes on stable doses of sulfonylurea.

- Treatment with 200 mg per week of ISIS 113715 for 13 weeks showed consistent and statistically significant reductions in multiple short and intermediate measures of glucose control.
- ISIS 113715 also showed statistically significant and clinically meaningful reductions in LDL-C and a tendency toward weight loss.
- The safety profile of the drug remains positive with no exacerbation of sulfonylurea-induced hypoglycemia or other clinically significant adverse effects.

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Our pipeline matures as antisense drugs continue to advance in development and show promise in clinical studies.

- Altair reported the successful completion of a Phase 1 study that showed AIR645 was safe and well tolerated. Altair intends on initiating Phase 2 studies on AIR645 soon.
- OncoGenex initiated a Phase 1 study evaluating OGX-427 in patients with bladder cancer.
- Achaogen reported the successful completion of a Phase 1 study on ACHN-490.

We support our dominant patent estate and maintain an extensive and broad intellectual property position.

- We received a notice of allowance that expands the scope of our Crooke patents and we, Alnylam and Regulus were granted a key microRNA patent in Japan.

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 are required to 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. There are specific risks associated with these critical accounting policies and we caution that future events rarely develop exactly as expected, and that best estimates routinely require adjustment.

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

- Assessment of the propriety of revenue recognition and associated deferred revenue;
- Determination of the proper valuation of investments in marketable securities and other equity investments;
- Estimations to assess the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determination of the proper valuation of inventory;
- Determination of the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimation of our net deferred income tax asset valuation allowance;
- Determination of the appropriateness of judgments and estimates used in allocating revenue and expenses to operating segments; and
- Estimations to determine 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.

Except as set forth below, 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, 2008.

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Convertible debt

On January 1, 2009, we adopted an accounting standard that became effective in January 2009, which requires us to account for convertible debt instruments that may be settled in cash upon conversion (including partial cash settlement) by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate when we recognize interest expense in subsequent periods. As a result, we assigned a value to the debt component of our $2^5/_8$% 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. At adoption, we retrospectively implemented the presentation and disclosure requirements to all periods presented in our condensed consolidated financial statements. For additional information, see Note 6, *Long-Term Obligations*.

Determining the fair value of the debt component requires the use of accounting estimates and assumptions. These estimates and assumptions are judgmental in nature and could have a significant impact on the determination of the debt component and in effect, the associated non-cash interest expense. The carrying amount of the liability component is determined by measuring the fair value of a similar debt instrument that does not have the conversion feature. If no similar debt instrument exists, estimates of fair value are primarily determined using assumptions that market participants would use in pricing a debt instrument, including market interest rates, credit standing, yield curves and volatilities.

Results of Operations

Revenue

Total revenue for the three and nine months ended September 30, 2009 was $26.8 million and $89.3 million, respectively, compared to $29.5 million and $77.5 million for the same periods in 2008. 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. In August 2009, we finished amortizing the revenue associated with the $50 million upfront payment we received from OMJP in 2007 resulting in less revenue in the third quarter of 2009 compared to the same period in 2008. Our revenue for the first nine months of 2009 increased compared to the same period in 2008 due primarily to an increase in revenue from our collaboration with Genzyme. As part of our strategic relationship with Genzyme, in the first quarter of 2008 Genzyme purchased $150 million of our common stock at $30 per share and in the second quarter paid us a license fee of $175 million. We are amortizing the premium on the stock, $100 million calculated using a Black-Scholes option

valuation model, and the license fee ratably into revenue through June 2012, which represents the end of our performance obligation based on the research and development plan included in the agreement.

Collaborations with Alnylam, BMS, Genzyme and Regulus' strategic alliance with GSK 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 and from research and development funding.

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The following table sets forth information on our revenue by segment (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2009	2008	2009	2008
Drug Discovery and Development:				
Research and development revenue	$ 25,337	$ 27,807	$ 84,027	$ 68,321
Licensing and royalty revenue	809	975	2,923	7,790
	$ 26,146	$ 28,782	$ 86,950	$ 76,111
Regulus Therapeutics:				
Research and development revenue	$ 625	$ 681	$ 2,388	$ 1,429
	$ 625	$ 681	$ 2,388	$ 1,429
Total Revenue:				
Research and development revenue	$ 25,962	$ 28,488	$ 86,415	$ 69,750
Licensing and royalty revenue	809	975	2,923	7,790
	$ 26,771	$ 29,463	$ 89,338	$ 77,540

Drug Discovery & Development

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for the three and nine months ended September 30, 2009 was $25.3 million and $84.0 million, respectively, compared to $27.8 million and $68.3 million for the same periods in 2008. The decrease in our revenue for the three months ended September 30, 2009 compared to the same period in 2008 was primarily due to a decrease in revenue from our collaboration with OMJP that is described above. The increase in our revenue for the first nine months of 2009 compared to the same period in 2008 was primarily due to the increase in revenue from our collaboration with Genzyme.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the three and nine months ended September 30, 2009 was $809,000 and $2.9 million, respectively, compared to $975,000 and $7.8 million for the same periods in 2008. Revenue was higher in 2008 primarily due to the $4.6 million and $1.4 million of sublicensing revenue we earned from Alnylam and ATL, respectively, in the second quarter of 2008 offset, in part, by the $1 million sublicensing revenue received in the first quarter of 2009 from Alnylam when Alnylam entered into a transaction with Cubist that included technology we had licensed to Alnylam.

Regulus Therapeutics

Regulus' revenue for the three and nine months ended September 30, 2009 was $625,000 and $2.4 million, respectively, compared to $681,000 and $1.4 million for the same periods in 2008. The increase in the first nine months of 2009 compared to the same period in 2008 was primarily related to revenue from its collaboration with GSK including the $500,000 discovery milestone payment that Regulus received from GSK for demonstrating a pharmacological effect in immune cells by specific microRNA inhibition. As part of Regulus' strategic alliance with GSK, Regulus received a $15 million upfront fee, which Regulus began amortizing into revenue in the second quarter of 2008 and will continue to amortize over Regulus' six year period of performance under the agreement.

Operating Expenses

Operating expenses for the three and nine months ended September 30, 2009 were $37.2 million and $105.2 million, respectively, compared to $29.3 million and $82.5 million for the same periods of 2008. The higher expenses in 2009 compared to 2008 were primarily due to the expansion of our clinical development programs, including additional expenses associated with the broad Phase 3 clinical program for mipomersen, the lead drug in our cardiovascular franchise, expenses for Regulus as it builds its core team and expenses related to the expansion of our drug discovery activities into new therapeutic areas.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2009	2008	2009	2008
Drug Discovery and Development	$ 34,230	$ 26,396	$ 96,941	$ 75,904
Regulus Therapeutics	2,937	2,891	8,264	6,620

Total operating expenses	$ 37,167	$ 29,287	$ 105,205	$ 82,524

In order to analyze and compare our results of operations to other similar companies, we believe that it is important to exclude non-cash compensation expense related to stock options. We believe non-cash compensation expense is not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding it.

Research and Development Expenses

Our research and development expenses consist of costs for antisense drug discovery, antisense drug development, manufacturing and operations and R&D support costs. In addition, our research and development expenses include costs associated with the research activities Regulus is conducting to advance its microRNA technology.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2009	2008	2009	2008
Research and development expenses	$ 30,939	$ 23,228	$ 86,489	$ 64,718
Non-cash compensation expense related to stock options	2,893	2,796	8,031	8,378
Total research and development expenses	$ 33,832	$ 26,024	$ 94,520	$ 73,096

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2009	2008	2009	2008
Drug Discovery and Development	$ 31,607	$ 23,650	$ 88,238	$ 67,804
Regulus Therapeutics	2,225	2,374	6,282	5,292
Total research and development expenses	$ 33,832	$ 26,024	$ 94,520	$ 73,096

For the three and nine months ended September 30, 2009, we incurred total research and development expenses of $30.9 million and $86.5 million, respectively, compared to $23.2 million and $64.7 million for the same periods in 2008, all amounts excluding non-cash compensation expense related to stock options. We attribute the increase in expenses to the expansion of our clinical development programs, including additional expenses associated with the broad Phase 3 clinical program for mipomersen, the lead drug in our cardiovascular franchise, expenses for Regulus as it builds its core team and expenses related to the expansion of our drug discovery activities into new therapeutic areas. We discuss expenses related to Regulus in a separate section below.

Drug Discovery & Development

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.

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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 by funding core antisense technology research.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2009	2008	2009	2008
Antisense drug discovery	$ 6,987	$ 4,630	$ 18,386	$ 13,355
Non-cash compensation expense related to stock options	771	583	2,281	1,766
Total antisense drug discovery	$ 7,758	$ 5,213	$ 20,667	$ 15,121

Antisense drug discovery costs for the three and nine months ended September 30, 2009 were $7.0 million and $18.4 million, respectively, compared to $4.6 million and $13.4 million for the same periods in 2008, all amounts excluding non-cash compensation expense related to stock options. The higher expenses were primarily due to increased activity levels related to our planned investment to fill our pipeline and additional spending to enhance our platform technology and to support collaborative research efforts for which we earn revenue. These activities resulted in an increase in personnel and laboratory supplies in 2009.

Antisense Drug Development

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

	Three Months Ended September 30,	Nine Months Ended September 30,

	2009	2008	2009	2008
Mipomersen	$ 7,605	$ 2,611	$ 17,894	$ 9,193
Other antisense development products	3,487	3,417	11,766	10,206
Development overhead costs	1,174	910	3,621	2,657
Non-cash compensation expense related to stock options	893	818	2,661	2,596
Total antisense drug development	$ 13,159	$ 7,756	$ 35,942	$ 24,652

Antisense drug development expenditures were $12.3 million and $33.3 million for the three and nine months ended September 30, 2009 compared to $6.9 million and $22.1 million for the same periods in 2008, all amounts excluding non-cash compensation expense related to stock options. We attribute the increase primarily to the development of mipomersen, including the broad Phase 3 program, and increases in our other cardiovascular development projects. Development overhead costs were $1.2 million and $3.6 million for the three and nine months ended September 30, 2009, compared to $910,000 and $2.7 million for the same periods in 2008. The increase in overhead costs was a result of the additional resources needed to support the expansion of our clinical development programs. We expect our drug development expenses to fluctuate based on the timing and size of our clinical trials.

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, 15 of our 19 drug candidates, which

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substantially reduces our development costs. As part of our collaboration with Genzyme, we will over time transition 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. 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 September 30,		Nine Months Ended September 30,	
	2009	2008	2009	2008
Manufacturing and operations	$ 3,467	$ 3,261	$ 10,078	$ 8,694
Non-cash compensation expense related to stock options	353	276	1,052	842
Total manufacturing and operations	$ 3,820	$ 3,537	$ 11,130	$ 9,536

Manufacturing and operations expenses for the three and nine months ended September 30, 2009 were $3.5 million and $10.1 million, respectively, compared to $3.3 million and $8.7 million for the same periods in 2008, all amounts excluding non-cash compensation expense related to stock options. The increase in expenses was primarily a result of an increase in personnel costs to support our expanded clinical development programs including our broad Phase 3 program for mipomersen and an increase in depreciation relating to upgrades made to our manufacturing facility which were completed in the second quarter of 2009.

R&D Support

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

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2009	2008	2009	2008
Personnel costs	$ 1,910	$ 2,678	$ 5,807	5,545
Occupancy	2,242	1,814	5,568	4,911
Depreciation and amortization	1,350	1,961	4,981	4,645
Insurance	224	227	681	680
Other	625	(98)	2,048	938

Non-cash compensation expense related to stock options	761	561	2,276	1,776
Total R&D support costs	$ 7,112	$ 7,143	$ 21,361	$ 18,495

R&D support costs for the three and nine months ended September 30, 2009 were $6.4 million and $19.1 million, respectively, compared to $6.6 million and $16.7 million for the same periods in 2008, all amounts excluding non-cash compensation expense related to stock options. The increase for the first nine months of 2009 compared to the same period in 2008 was primarily a result of an increase in personnel costs, lease modification fees paid in September 2009 and $750,000 we received from Ercole Biotech, Inc. in March 2008 as repayment of a convertible note that we had previously expensed.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2009	2008	2009	2008
Drug Discovery and Development	$ 6,869	$ 7,143	$ 20,498	$ 18,495
Regulus Therapeutics	243	—	863	—
Total R&D support costs	$ 7,112	$ 7,143	$ 21,361	$ 18,495

As part of Regulus' conversion from an LLC to a C-Corporation in January 2009, we began providing Regulus research and development and general and administrative services under the terms of a services agreement. Under the terms of the services agreement, we allocate a portion of our R&D support costs to Regulus and include this allocation in Regulus' research and development expenses.

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

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2009	2008	2009	2008
General and administrative expenses	$ 2,681	$ 2,448	$ 8,902	$ 7,372
Non-cash compensation expense related to stock options	654	815	1,783	2,056
Total general and administrative expenses	$ 3,335	$ 3,263	$ 10,685	$ 9,428

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2009	2008	2009	2008
Drug Discovery and Development	$ 2,623	$ 2,746	$ 8,703	$ 8,100
Regulus Therapeutics	712	517	1,982	1,328
Total general and administrative expenses	$ 3,335	$ 3,263	$ 10,685	$ 9,428

General and administrative expenses for the three and nine months ended September 30, 2009 were $2.7 million and $8.9 million, respectively, compared to $2.4 million and $7.4 million for the same periods in 2008, all amounts excluding non-cash compensation expense related to stock options. The increase was primarily a result of costs associated with our Bruker Daltonics Inc. litigation and the increase in Regulus' general and administrative expenses in 2009. For further information on the Bruker Daltonics litigation, see the Legal Proceedings section below. We discuss expenses related to Regulus in a separate section below.

Regulus Therapeutics

The following table sets forth information on Regulus' operating expenses (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2009	2008	2009	2008
Research and development expenses	$ 2,109	$ 1,816	$ 6,521	$ 3,893
General and administrative expenses	621	192	1,757	610
Non-cash compensation expense/(benefit) related to stock options	207	883	(14)	2,117
Total Regulus' operating expenses	$ 2,937	$ 2,891	$ 8,264	$ 6,620

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Operating expenses for Regulus were $2.7 million and $8.3 million for the three and nine months ended September 30, 2009 compared to $2.0 million and $4.5 million for the same periods in 2008, all amounts excluding non-cash compensation expense related to stock options. The increase was

primarily related to Regulus' continued efforts to build its team to support its internal microRNA programs and the efforts associated with its GSK collaboration, which began in April 2008. With the strategic alliance with GSK, it is anticipated that Regulus' expenses will increase over its run rate going forward as Regulus advances its research and development activities.

Investment Income

Investment income for the three and nine months ended September 30, 2009 totaled $1.4 million and $5.2 million, respectively, compared to $3.5 million and $8.8 million for the same periods in 2008. The decrease in investment income was primarily due to the lower average returns on our investments resulting from the current market conditions offset by significantly higher average cash balances.

Interest Expense

Interest expense for the three and nine months ended September 30, 2009 was $3.2 million and $9.4 million, respectively, and was slightly higher compared to $3.1 million and $8.9 million for the same periods in 2008. In 2009, we adopted the accounting standard related to our 2⁵¤₈% convertible notes that became effective in January 2009. As a result of adopting the standard, the amount of interest expense we recorded in our statement of operations for the three and nine months ended September 30, 2009 increased by $1.7 million and $5.1 million, respectively, compared to an increase of $1.6 million and $4.6 million for the same periods in 2008. For additional information, see *Note 6, Long-Term Obligations*, in the Notes to the Condensed Consolidated Financial Statements.

Gain on Investments

Gain on investments for the three and nine months ended September 30, 2009 was $123,000 and $2.8 million, respectively. The gain on investments for the first nine months of 2009 primarily reflected the gain we realized on the sale of all of the common stock of OncoGenex that we owned. We did not recognize any gain on investments for the first nine months of 2008.

Income Tax Benefit

Even though we finished the first nine months of 2009 with a net loss from continuing operations, we had taxable income, which is primarily a result of the significant upfront payments that we received from our strategic alliance with Genzyme in 2008 and the gain we recognized on the sale of Ibis to AMI earlier this year. We recorded an income tax benefit of $4.0 million and $4.6 million for the three and nine months ended September 30, 2009 on a line called "Income Tax Benefit" as part of our financial results from continuing operations because we will be using the tax benefits generated from our current year loss from continuing operations to offset a portion of our taxable income.

Net Income (Loss) from Continuing Operations attributable to Isis Pharmaceuticals, Inc. Common Stockholders

The following table sets forth computations for our net income (loss) from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2009	2008	2009	2008
Net income (loss) from continuing operations, net of income tax benefit	$ (8,060)	$ 560	$ (12,627)	$ (5,082)
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	1,136	1,208	2,907	3,056
Net income (loss) from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (6,924)	$ 1,768	$ (9,720)	$ (2,026)

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Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders for the three and nine months ended September 30, 2009 was $6.9 million and $9.7 million, respectively, compared to net income of $1.8 million and net loss of $2.0 million for the same periods in 2008. Net loss from continuing operations for the first nine months of 2008 was lower than 2009 primarily due to the increase in operating expenses offset by the increase in revenue and income tax benefit recognized in 2009, all of which are discussed above.

Net Income (Loss) from Discontinued Operations

In 2008, AMI purchased approximately 18.6% of the issued and outstanding common stock of Ibis for a total purchase price of $40 million. In December 2008, we, Ibis and AMI executed a stock purchase agreement. Under this agreement, AMI purchased the remaining equity in Ibis from us for $175 million. We, Ibis and AMI completed the acquisition on January 6, 2009.

Since we sold Ibis to AMI and Ibis met the criteria for a component of an entity, we reflect Ibis as a discontinued operation. Accordingly, we have presented the operating results of Ibis in our Consolidated Statements of Operations as discontinued operations and we have reclassified all prior periods. Net income from discontinued operations for the nine months ended September 30, 2009 was $171.7 million, compared to net loss from discontinued operations of $155,000 and $5.9 million for the three and nine months ended September 30, 2008. We did not recognize any net income (loss) from discontinued operations for the three months ended September 30, 2009. Net income from discontinued operations for the first nine months of 2009 primarily consisted of the $202.5 million gain less income taxes. We are required to allocate our 2009 tax expense between discontinued operations and continuing operations in our Condensed Consolidated Statement of Operations. Since the sale of Ibis to AMI was a discrete event that occurred in the first quarter of 2009, we recorded the total amount of our estimated income tax expense for discontinued operations in the first quarter of this year. Further, we are required to gross up this amount by the projected annual tax benefit we expect to record as part of our loss from continuing operations in 2009, which is described in the *Income Tax Benefit* section above. This means that in addition to the tax expense for the gain on the sale of Ibis, discontinued operations also includes the tax expense for other timing differences, which principally consists of the timing difference associated with the upfront funding we received from Genzyme. Accordingly, we have recorded tax expense of $30.7 million in discontinued operations in the first nine months of 2009.

Net Income (Loss) and Net Income (Loss) Per Share attributable to Isis Pharmaceuticals, Inc. Common Stockholders

Net loss attributable to Isis Pharmaceuticals, Inc. common stockholders for the three months ended September 30, 2009 was $6.9 million and net income for the nine months ended September 30, 2009 was $162.0 million, compared to a net income of $1.6 million and a net loss of $7.9 million for the three and nine months ended September 30, 2008. Basic and diluted net loss per share for the three months ended September 30, 2009 was $0.07 per share compared to basic and diluted net income per share of $0.02 per share for the same period in 2008. Basic and diluted net income per share for the nine months ended September 30, 2009 was $1.65 per share compared to basic and diluted net loss per share of $0.08 for the same period in 2008. In the third quarter of 2008, the discontinued operations line item included $4.1 million of income related to the call option that we granted to AMI in connection with the sale of Ibis. The call option income along with the decrease in revenue and increase in operating expenses that are discussed above contributed to the change in net income/loss from the third quarter of 2008 to the same period in 2009. The improvement in our net income and net income per share for the first nine months of 2009 over the same period in 2008 was primarily due to the gain we recognized when we sold Ibis to AMI.

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 September 30, 2009, we have earned approximately $786.4 million in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through September 30, 2009, we have raised net proceeds of approximately $812.7 million from the sale of our equity securities and we have borrowed approximately $562.2 million under long-term debt arrangements to finance a portion of our operations.

At September 30, 2009, we had cash, cash equivalents and short-term investments of $607.8 million and stockholders' equity of $304.8 million. In comparison, we had cash, cash equivalents and short-term investments of $491.0 million and stockholders' equity of $147.4 million as of December 31, 2008. At September 30, 2009, we had consolidated working capital of $504.5 million, compared to $393.7 million at December 31, 2008. Our cash, cash equivalents and short-term investments, stockholders' equity and consolidated working capital increased primarily as a result of the $175 million we received from AMI in the first quarter of 2009. During the first nine months of 2009, we also received more than $34 million in cash from our corporate partnerships.

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As of September 30, 2009, our debt and other obligations totaled $139.9 million, compared to $130.0 million at December 31, 2008. The increase in our debt and other obligations was primarily due to the $6.4 million additional draw downs on our equipment financing arrangement and $5.3 million of non-cash amortization of the debt discount recorded in the first nine months of 2009 as a result of adopting the accounting standard related to our 2⁵⁄₈% convertible notes that became effective in January 2009. The standard did not impact our cash, cash equivalents and short-term investments but decreased the carrying value of our $162.5 million convertible notes to $123.3 million and $118.0 million at September 30, 2009 and December 31, 2008, respectively, with corresponding increases to shareholders' equity. For additional information, see *Note 6, Long-Term Obligations*, in the Notes to the Condensed Consolidated Financial Statements. We will continue to use equipment lease financing as long as the terms remain commercially attractive.

The following table summarizes our contractual obligations as of September 30, 2009. 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**
2⁵⁄₈% Convertible Subordinated Notes	$ 162.5	$ —	$ —	$ —	$ 162.5
GSK Convertible Promissory Note, including accrued interest	$ 5.3	$ —	$ 5.3	$ —	$ —
Equipment Financing Arrangements	$ 11.0	$ 4.1	$ 6.8	$ 0.1	$ —
Other Obligations	$ 0.4	$ —	$ —	$ —	$ 0.4
Operating Leases	$ 17.8	$ 3.3	$ 5.1	$ 2.4	$ 7.0

Our contractual obligations consist primarily of our publicly traded convertible debt. In addition, we also have a convertible promissory note Regulus issued to GSK, 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 2⁵⁄₈%, which is payable semi-annually. The 2⁵⁄₈% 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 will be able to redeem the 2⁵⁄₈% notes at a redemption price equal to 100.75% of the principal amount between February 15, 2012 and February 14, 2013; 100.375% of the principal amount between February 15, 2013 and February 14, 2014; and 100% of the principal amount thereafter. Holders of the 2⁵⁄₈% notes also are able to require us to repurchase these notes on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100% of the principal amount of the 2⁵⁄₈% notes being repurchased plus accrued and unpaid interest.

In connection with the strategic alliance with GSK in April 2008, Regulus issued a convertible promissory note to GSK in exchange for $5 million in cash. The convertible note bears interest at the prime rate, which was 3.25% at September 30, 2009. The note plus interest will convert into Regulus common stock in the future if Regulus achieves a minimum level of financing with institutional investors. In addition, we and Alnylam are guarantors of the note, and if the note does not convert or Regulus does not repay the note in cash, we, Alnylam and Regulus may elect to repay the note plus interest with shares of each company's common stock.

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 and Regulus could borrow up to $19.4 million in principal to finance the purchase of equipment. The $19.4 million does not include the $600,000 Ibis borrowed in October 2008 that was fully repaid in the first quarter of 2009. Each loan under the loan agreement will have a term of approximately 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 4%. We are using the equipment purchased under the loan agreement as collateral. We have drawn down $13.0 million in principal under this loan agreement at a weighted average interest rate of 6.65%. The carrying balance under this loan agreement at September 30, 2009 and December 31, 2008 was $11.0 million and $6.5 million, respectively.

In addition to contractual obligations, we had outstanding purchase orders as of September 30, 2009 for the purchase of services, capital equipment and materials as part of our normal course of business.

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We plan to continue to enter into collaborations with partners to provide for additional revenue to us and we may 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 and short-term equivalents to finance our activities. However, we may also pursue other financing alternatives, like issuing additional shares of our common stock, issuing debt instruments, refinancing our existing debt, or securing lines of credit. Whether we use our existing capital resources or choose to obtain financing will depend on various factors, including the future success of our business, the prevailing interest rate environment and the condition of financial markets generally.

RISK FACTORS

Investing in our securities involves a high degree of risk. You should consider carefully the following information about the risks described below, together with the other information contained in this report and in our other public filings in evaluating our business. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment. We have marked with an asterisk those risk factors that reflect substantive changes from the risk factors included in our Annual Report on Form 10-K for the year ended December 31, 2008.

Risks Associated with our Businesses as a Whole

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

Because product discovery and development require substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of September 30, 2009, we had accumulated deficit of approximately $689.2 million and stockholders' equity of approximately $304.8 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 currently have only one product, Vitravene, approved for commercial use. This product has limited sales potential, and Novartis, our exclusive distribution partner for this product, no longer markets it. We expect to 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 services, 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 product 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 products, including ISIS 113715. However, we may not be able to negotiate additional attractive collaborative arrangements.

Many of the drugs in our development pipeline are being developed and/or funded by corporate partners, including Altair, ATL, Atlantic Pharmaceuticals, BMS, iCo, Lilly, Merck, OncoGenex, OMJP and Teva. In addition, in January 2008 we entered a major strategic alliance with Genzyme in which Genzyme will develop and commercialize mipomersen. If any of these pharmaceutical companies stop funding and/or developing these products, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these products on our own.

Our collaborators can terminate their relationships with us under certain circumstances, some of which are outside of our control. For example, in November 2004 based on the disappointing results of the Phase 3 clinical trials, Lilly discontinued its investment in Affinitak.

In addition, the disappointing results of the two Affinitak clinical trials, our Phase 3 clinical trials of alicaforsen in patients with active Crohn's disease, or any future clinical trials could impair our ability to attract new collaborative partners. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drugs could suffer.

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 product development programs.

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

- conduct clinical trials;
- seek and obtain regulatory approvals; and
- manufacture, market and sell existing and future products.

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

For example, a collaborator such as Genzyme, OMJP, or BMS, could determine that it is in its financial interest to:

- pursue alternative technologies or develop alternative products that may be competitive with the product 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 under development.

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.

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 trial, 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 investors' expectations, 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-cholesterol is an acceptable surrogate endpoint for accelerated approval of mipomersen for use in patients with homozygous familial hypercholesterolemia, or hoFH. The FDA will require data from two ongoing preclinical studies for carcinogenicity to be included in the hoFH filing, which is now anticipated to take place in 2010. The FDA also indicated that for broader indications in high risk, high cholesterol patients an outcome study would be required for approval. This FDA guidance caused us to revise our development plans and timelines and, as a result, to accelerate our planned outcome trial.

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

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

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 be forced 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.

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For example, in December 2006, the European Patent Office (EPO) Technical Board of Appeal reinstated with amended claims our Patent EP0618925 which claims a class of antisense compounds, any of which is designed to have a sequence of phosphorothioate-linked nucleotides having two regions of chemically modified RNA flanking a region of DNA. Prior to its reinstatement, this patent was originally opposed by several parties and revoked by an EPO Opposition Division 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.

If a third party claims that our products 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 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.*

All of our drugs are undergoing clinical trials or are in the early stages of research and development. All of our drugs under development 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 September 30, 2009, we had cash, cash equivalents and short-term investments equal to $607.8 million. If we do not meet our goals to commercialize our products, 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:

- 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 trials;

- 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 their 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, drugs or products.

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 trials 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.*

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The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding September 30, 2009, the market price of our common stock ranged from $9.90 to $18.81 per share. On November 2, 2009, the closing price of our common stock on the Nasdaq Global Market was $12.38. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial 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.

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 type 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.

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 separate 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% of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15% 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 also have implemented 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. 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.

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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 agree 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 registered for resale 4.25 million shares of our common stock issuable upon the exercise of the warrant we originally issued to Symphony GenIsis Holdings. In addition, we have registered for resale our $2^{5}/_{8}$% convertible subordinated notes, including the approximately 11,111,116 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.

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 will incur additional expenses and will suffer a diversion of management's time. 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 (PCAOB) or the Nasdaq Global Market. Any such action could adversely affect our financial results and the market price of our common stock.

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

The continuing deterioration in the global credit markets, the financial services industry and the U.S. capital markets, 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 current economic crisis is uncertain. It is possible that the current 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.

Risks Associated with our Drug Discovery and Development Business

If we or our partners fail to obtain regulatory approval for our drugs, we will not be able to sell them.

We and our partners must conduct time-consuming, extensive and costly clinical trials to show the safety and efficacy of each of our drugs, including mipomersen and ISIS 113715, before a drug can be approved for sale. We must conduct these trials in compliance with FDA regulations and with comparable regulations in other countries. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of our drugs, including mipomersen and ISIS 113715, it will not approve them or will require additional studies, which can be time consuming and expensive and which will delay commercialization of a drug. We and our partners may not be able to obtain

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necessary regulatory approvals on a timely basis, if at all, for any of our drugs, including mipomersen and ISIS 113715. Failure to receive these approvals or delays in these approvals could prevent or delay commercial introduction of a product, including mipomersen and ISIS 113715, and, as a result, could negatively impact our ability to generate revenue from product sales. In addition, following approval of a drug, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute drug products. If we fail to comply with these regulations, regulators could force us to withdraw a drug from the market or impose other penalties or requirements that also could have a negative impact on our financial results.

We have only introduced one commercial drug product, Vitravene. We cannot guarantee that any of our other drugs, including mipomersen and ISIS 113715, will be safe and effective, will be approved for commercialization or that our partners or we can successfully commercialize these drugs.

If the results of clinical testing indicate that any of our drugs under development 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 technology in particular is relatively new and unproven. If we cannot demonstrate that our drugs, including mipomersen and ISIS 113715, are safe and effective drugs 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. In March 2003, we reported the results of a Phase 3 clinical trial of Affinitak in patients with late-stage non-small cell lung cancer and in October 2004, we reported the results of a second similar Phase 3 clinical trial. In each case, Affinitak failed to demonstrate improved survival sufficient to support an NDA filing. In December 2004, we reported the results of our Phase 3 clinical trials of alicaforsen in patients with active Crohn's disease, in which alicaforsen did not demonstrate statistically significant induction of clinical remissions compared to placebo. Similar results could occur with the clinical trials for our other drugs, including mipomersen and ISIS 113715. If any of our drugs in clinical studies, including mipomersen and ISIS 113715, do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for these and other drugs and our stock price could decline.

Even if our drugs are successful in preclinical and early human clinical studies, these results do not guarantee the drugs will be successful in late-stage clinical trials.

Successful results in preclinical or early human clinical trials, including the Phase 2 results for mipomersen and ISIS 113715, may not predict the results of late-stage clinical trials. There are a number of factors that could cause a clinical trial to fail or be delayed, including:

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

Any failure or delay in one of our clinical trials, including our Phase 2 or Phase 3 development programs for mipomersen and ISIS 113715, could reduce the commercial viability of our drugs, including mipomersen and ISIS 113715.

If the market does not accept our products, we are not likely to generate revenues or become profitable.

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Our success will depend upon the medical community, patients and third-party payors accepting our products as medically useful, cost-effective and safe. We cannot guarantee that, even if approved for commercialization, doctors may not use our products to treat patients. We currently have one commercially approved drug product, Vitravene, a treatment for cytomegalovirus, or CMV, retinitis in AIDS patients, which addresses a small market. Our partners and we may not successfully commercialize additional products.

The degree of market acceptance for any of our products depends upon a number of factors, including:

- the receipt and scope of regulatory approvals;
- the establishment and demonstration in the medical and patient community of the efficacy and safety of our drugs and their potential advantages over competing products;
- the cost and effectiveness of our drugs compared to other available therapies;
- the 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 use any products that we may develop.

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

If we successfully commercialize any of our drugs, we would be required 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 product costs. We may not be able to manufacture 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, which the FDA enforces through its facilities inspection program. We and our contract manufacturers may not be able to comply or maintain compliance with Good Manufacturing Practices regulations. Non-compliance could significantly delay or prevent our receipt of marketing approval for potential products, including mipomersen and ISIS 113715, or result in FDA enforcement action after approval that could limit the commercial success of our potential products, including mipomersen and ISIS 113715.

If our drug discovery and development business fails to compete effectively, our drugs will not contribute significant revenues.

Our competitors are engaged in all areas of drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. Other companies are engaged 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.

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These competitive developments could make our products 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 develop treatments for the same diseases targeted by our own collaborative programs. Competition may negatively impact a partner's focus on and commitment to our drugs and, as a result, could delay or otherwise negatively affect the commercialization of our drugs.

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 trials 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. We will also compete with respect to marketing and sales capabilities, areas in which we have limited or no experience.

Disagreements between Alnylam and us regarding the development of our microRNA technology may cause significant delays and other impediments in the development of this technology, which could negatively affect the value of the technology and our investment in Regulus.

Regulus is a jointly owned company that we and Alnylam established to focus on the discovery, development, and commercialization of microRNA. As part of this joint venture, we exclusively licensed to Regulus our intellectual property rights covering microRNA. Regulus is operated as an independent company and 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 is approved by the board. Any disagreements between Alnylam and us regarding a development decision or any other decision submitted to Regulus' board may cause significant delays in the development and commercialization of our microRNA technology and could negatively affect the value of our investment in Regulus.

We depend on third parties in the conduct of our clinical trials 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 in the conduct of our clinical trials for our drugs and expect to continue to do so in the future. For example, Medpace is the primary clinical research organization for clinical trials for mipomersen. We rely heavily on these parties for successful execution of our clinical trials, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Third parties may not complete activities on schedule, or may not conduct our clinical trials 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.

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 are typically held for the duration of the term of the respective instrument. We do not utilize derivative financial instruments, derivative commodity instruments or other market risk sensitive instruments, positions or transactions to manage exposure to interest rate changes. Accordingly, we believe that, while the securities we hold are subject to changes in the financial standing of the issuer of such securities, we are not subject to any material risks arising from changes in interest rates, foreign currency exchange rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments.

ITEM 4. CONTROLS AND PROCEDURES

As of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended. Based on this

evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of September 30, 2009. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to September 30, 2009.

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

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

PART II – OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

On February 11, 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. Executive level negotiations and formal mediation efforts failed to achieve resolution of this dispute. On May 22, 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 on July 14, 2008, alleging breach of contract by Bruker. Discovery is in its early stage. We will continue to represent and defend Ibis Biosciences in this matter.

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

Not applicable

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

ITEM 4. SUBMISSION OF MATTERS TO A VOTE OF SECURITY HOLDERS

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.

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Isis Pharmaceuticals, Inc.

(Registrant)

SIGNATURES

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

Signatures	Title	Date
/s/ Stanley T. Crooke Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	November 5, 2009
/s/ B. Lynne Parshall B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	November 5, 2009

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: November 5, 2009

/s/ Stanley T. Crooke

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

EXHIBIT 31.2

CERTIFICATION

I, B. Lynne Parshall, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: November 5, 2009

/s/ B. Lynne Parshall

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

Exhibit 32.1

CERTIFICATION

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

1. The Company's Quarterly Report on Form 10-Q for the period ended September 30, 2009, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: November 5, 2009

/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.