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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, 2010

OR

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

For the transition period from to

Commission file number 0-19125

Isis Pharmaceuticals, Inc.
(Exact name of Registrant as specified in its charter)

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

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

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

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

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

Common Stock, $.001 Par Value

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

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

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

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

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

The number of shares of voting common stock outstanding as of November 1, 2010 was 99,231,375.

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ISIS PHARMACEUTICALS, INC.
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TRADEMARKS

Isis Pharmaceuticals® is a registered trademark of Isis Pharmaceuticals, Inc.
Regulus Therapeutics™ is a trademark of Regulus Therapeutics Inc.
Ibis T5000™ is a trademark of Ibis Biosciences, Inc.
Vitravene™ is a trademark of Novartis AG.

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

	September 30, 2010 (Unaudited)	December 31, 2009
ASSETS		
Current assets:		
Cash and cash equivalents	$ 100,122	$ 105,255
Short-term investments	397,782	469,057
Contracts receivable	1,341	10,899
Inventories	1,996	2,768
Other current assets	6,309	8,147
Total current assets	507,550	596,126
Property, plant and equipment, net	35,549	27,338

Licenses, net	12,893	14,542
Patents, net	16,208	15,909
Deposits and other assets	3,658	3,269
Total assets	$ 575,858	$ 657,184
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 3,392	$ 4,696
Accrued compensation	4,833	7,135
Income taxes payable	—	7,323
Accrued liabilities	10,285	12,339
Current portion of long-term obligations	5,138	4,270
Current portion of deferred contract revenue	77,268	75,681
Total current liabilities	100,916	111,444
2 5/8% convertible subordinated notes	130,882	125,100
Long-term obligations, less current portion	4,304	11,478
Long-term financing obligation	10,147	—
Investment in Regulus Therapeutics Inc.	5,000	—
Long-term deferred contract revenue	70,900	107,097
Total liabilities	322,149	355,119
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 99,225,177 and 98,850,934 shares issued and outstanding at September 30, 2010 and December 31, 2009, respectively	99	99
Additional paid-in capital	995,149	985,620
Accumulated other comprehensive income	1,162	2,153
Accumulated deficit	(742,701)	(696,150)
Total Isis Pharmaceuticals, Inc. stockholders' equity	253,709	291,722
Noncontrolling interest in Regulus Therapeutics Inc.	—	10,343
Total stockholders' equity	253,709	302,065
Total liabilities and stockholders' equity	$ 575,858	$ 657,184

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,	
	2010	2009 (1)	2010	2009 (1)
Revenue:				
Research and development revenue under collaborative agreements	$ 27,785	$ 25,962	$ 77,484	$ 86,415
Licensing and royalty revenue	839	809	4,569	2,924
Total revenue	28,624	26,771	82,053	89,339
Expenses:				
Research and development	34,716	33,832	105,827	94,519
General and administrative	2,855	3,335	8,724	10,685
Total operating expenses	37,571	37,167	114,551	105,204
Loss from operations	(8,947)	(10,396)	(32,498)	(15,865)
Other income (expense):				
Equity in net loss of Regulus Therapeutics Inc.	(930)	—	(6,358)	—
Investment income	776	1,430	2,590	5,241
Interest expense	(3,338)	(3,185)	(9,835)	(9,421)
Gain (loss) on investments, net	(15)	123	(1,162)	2,794
Loss from continuing operations, before income tax expense	(12,454)	(12,028)	(47,263)	(17,251)
Income tax expense	—	(724)	(2)	(873)
Net loss from continuing operations	(12,454)	(12,752)	(47,265)	(18,124)
Discontinued operations:				
Loss from discontinued operations	—	—	—	(29)
Gain on sale of Ibis Biosciences, Inc., net of tax	—	34	—	187,153

Net income from discontinued operations, net of tax	—	34	—	187,124
Net income (loss)	(12,454)	(12,718)	(47,265)	169,000
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	—	1,136	—	2,906
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (12,454)	$ (11,582)	$ (47,265)	$ 171,906
Basic and diluted net income (loss) per share:				
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.13)	$ (0.12)	$ (0.48)	$ (0.16)
Net income from discontinued operations	—	—	—	1.91
Basic and diluted net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.13)	$ (0.12)	$ (0.48)	$ 1.75
Shares used in computing basic and diluted net income (loss) per share	99,196	98,320	99,101	97,988

(1) During the preparation of the year end 2009 annual tax provision, we determined that certain tax items had been attributed to discontinued operations that are appropriately associated with continuing operations. As a result, we revised the tax provisions reflected in each of the first three quarters during 2009 to reflect the correction of this allocation. The historical condensed consolidated statements of operations for the three and nine months ended September 30, 2009 reflect the revised tax provisions.

See accompanying notes.

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

	Nine Months Ended September 30,	
	2010	2009(1)
Net cash used in operating activities	$ (38,090)	$ (77,079)
Investing activities:		
Purchases of short-term investments	(429,631)	(626,703)
Proceeds from the sale of short-term investments	483,476	440,705
Purchases of property, plant and equipment	(12,740)	(11,662)
Proceeds from land sold to BioMed	10,147	—
Reduction of cash due to deconsolidation of Regulus Therapeutics Inc. upon adoption of a new accounting standard	(16,228)	—
Acquisition of licenses and other assets	(3,430)	(1,915)
Purchases of strategic investments	(658)	(349)
Proceeds from sale of strategic investments	—	2,848
Net cash provided by (used in) investing activities	30,936	(197,076)
Financing activities:		
Net proceeds from issuance of equity	2,036	9,795
Excess tax benefits on share-based compensation	—	170
Proceeds from equipment financing arrangement	3,083	6,394
Principal payments on debt obligations	(3,098)	(1,896)
Proceeds from sale of Ibis Biosciences, Inc. to Abbott Molecular Inc.	—	175,000
Proceeds from Alnylam's capital contribution to Regulus Therapeutics Inc.	—	10,000
Net cash provided by financing activities	2,021	199,463
Net decrease in cash and cash equivalents	(5,133)	(74,692)
Cash and cash equivalents at beginning of period	105,255	223,985
Cash and cash equivalents at end of period	$ 100,122	$ 149,293
Supplemental disclosures of cash flow information:		
Interest paid	$ 4,694	$ 4,666
Income taxes paid	$ 7,700	$ 10,205
Supplemental disclosures of non-cash investing activities:		
Amounts accrued for capital and patent expenditures	$ 927	$ 1,240

(1) During the preparation of the year end 2009 annual tax provision, we determined that certain tax items had been attributed to discontinued operations that are appropriately associated with continuing operations. As a result, we revised the tax provisions reflected in each of the first three quarters during 2009 to reflect the correction of this allocation. The historical condensed consolidated statement of cash flows for the nine months ended September 30, 2009 reflects the revised tax provisions.

See accompanying notes.

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ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
September 30, 2010
(Unaudited)

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three and nine month periods ended September 30, 2010 and 2009 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2009. 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. 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, 2009 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 our equity investment in Regulus Therapeutics Inc., an entity we identified as a variable interest entity. Beginning in the first quarter of 2010, as a result of adopting a new accounting standard for identifying which enterprise has the power to direct activities of a variable interest entity, we concluded that we are no longer the primary beneficiary of Regulus. As such we have presented our share of Regulus' operating results on a separate line in our condensed consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc." On our condensed consolidated balance sheet, we have presented our investment in Regulus on a separate line in the non-current liabilities section called "Investment in Regulus Therapeutics Inc." Prior to the adoption of the new accounting standard, we were the primary beneficiary of Regulus and as such we consolidated Regulus' financial results on a line-by-line basis. We have not reclassified amounts in the prior period financial statements to conform to the current period presentation. As a result of completing the sale of Ibis Biosciences, Inc. to Abbott Molecular Inc., or AMI, in January 2009, we presented Ibis' financial position and results of operations separately as discontinued operations in our condensed consolidated financial statements. All significant intercompany balances and transactions have been eliminated in consolidation.

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 our condensed consolidated balance sheet.

Research and development revenue under collaborative agreements

We often enter into collaborations under which we receive non-refundable upfront payments 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, the amounts are not refundable and we have no future performance obligations related to the achievement of the milestone.

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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 five million shares of our common stock at $30 per share. The price Genzyme paid for our common stock represented a significant premium over the fair value of our stock. Using a Black-Scholes option valuation model, we determined that the value of the premium was $100 million, which represented 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 current research and development plan.

Licensing and royalty revenue

We often enter into agreements to license our proprietary patent rights on an exclusive or non-exclusive basis in exchange for license fees and/or royalties. We generally recognize as revenue immediately those licensing fees and royalties for which we have no significant future performance obligations and are reasonably assured of collecting the resulting receivable.

Short-term investments

We consider all liquid investments with maturities of 90 days or less when purchased to be cash equivalents. Our short-term investments have initial maturities of greater than 90 days from date of purchase. We classify our short-term investments as "available-for-sale" and carry them at fair market value based upon prices for identical or similar items on the last day of the fiscal period. We record unrealized gains and losses as a separate component of stockholders' equity and include net realized gains and losses in gain (loss) on investments in the condensed consolidated statement of operations. We use the specific identification method to determine the cost of securities sold.

We have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20 percent in each of the respective companies except Regulus, our jointly owned subsidiary, which we began accounting for using the equity method in the first quarter of 2010. Prior to 2010, we consolidated Regulus' financial results on a line-by-line basis. In determining if and when a decrease in market value below our cost in our equity positions is temporary or other-than-temporary, we examine historical trends in the stock price, the financial condition of the company, near term prospects of the company and our current need for cash. We record unrealized gains and losses related to temporary declines in the publicly-held companies as a separate component of stockholders' equity and account for securities in the privately-held companies, except for Regulus, under the cost method of accounting because we own less than 20 percent and do not have significant influence in their operations. When we determine that a decline in value in either a public or private investment is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs. During the first nine months of 2010, we recognized a $1.2 million loss on investments primarily consisting of an $880,000 non-cash loss related to the other-than-temporary impairment of our equity investment in Antisense Therapeutics Limited and $349,000 of valuation allowances we recorded related to the investments we made in Excaliard Pharmaceuticals, Inc. and Achaogen, Inc. Because realization of our Excaliard and Achaogen investments is uncertain we recorded a full valuation allowance. During the first nine months of 2009, we recognized a $2.8 million gain on investments primarily consisting of a $2.5 million gain when we sold all of the common stock of OncoGenex Pharmaceuticals Inc. that we owned. We determined that there were no other-than-temporary declines in value of our investments during the first nine months of 2009.

Inventory valuation

We capitalize the costs of raw materials that we purchase for use in producing our drugs because until we use these raw materials they have alternative future uses. We include in inventory raw material costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We can use each of our raw materials in multiple products and, as a result, each raw material has future economic value independent of the development status of any single drug. For example, if one of our drugs failed, we could use the raw materials allocated for that drug to manufacture our other drugs. We expense these costs when we deliver the drugs to our partners, or as we provide these drugs for our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf life of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. We did not record any inventory write-offs during the first nine months of 2010 and 2009. Total inventory, which consisted of raw materials, was $2.0 million and $2.8 million as of September 30, 2010 and December 31, 2009.

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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. 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 2010 and 2009, we recorded a non-cash charge of $1.0 million and $497,000, respectively, which we included in research and development expenses, related to the write-down of our patent costs to their estimated net realizable values.

Long-lived assets

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

Equity method of accounting

On January 1, 2010, we adopted an accounting standard, which replaced 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 impacts the variable interest entity's economic performance and (1) the obligation to absorb losses of the variable interest entity or (2) the right to receive benefits from the variable interest entity. As a result of adopting this new accounting standard, we were required to change the way we account for our variable interest in Regulus. Since we and Alnylam Pharmaceuticals, Inc. share the ability to impact Regulus' economic performance, we are no longer the primary beneficiary of Regulus. We adopted the new standard on a prospective basis; therefore, beginning in the first quarter of 2010, we deconsolidated Regulus from our condensed consolidated financial statements and began to account for

our ownership interest in Regulus using the equity method of accounting. This means that we no longer include Regulus' revenue and operating expenses in our operating results. Instead we include our share of Regulus' operating results on a separate line in our condensed consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc." On our condensed consolidated balance sheet, we present our investment in Regulus on a separate line in the non-current liabilities section called "Investment in Regulus Therapeutics Inc." We have not reclassified amounts in the prior period financial statements to conform to the current period presentation. For additional information, see Note 3, *Investment in Regulus Therapeutics Inc.*

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. As we incurred a loss from continuing operations for the three and nine months ended September 30, 2010 and 2009, we did not include the following diluted common equivalent shares in the computation of diluted net loss from continuing operations per share because the effect would have been anti-dilutive:

- 2 5/8% convertible subordinated notes;
- GlaxoSmithKline convertible promissory notes;
- Dilutive stock options; and
- Warrants issued to Symphony GenIsis Holdings LLC

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, 2010, we had collaborative arrangements with eight entities that we consider to be variable interest entities. We are not the primary beneficiary for any of these entities. 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. As a result of adopting the new accounting standard related to our investment in Regulus in the first quarter of 2010, we deconsolidated Regulus because we are no longer the primary beneficiary of Regulus. See Note 3, *Investment in Regulus Therapeutics Inc.*, for additional details.

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Comprehensive income (loss)

We report, in addition to net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders, comprehensive income (loss) and its components as follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2010	2009	2010	2009
Comprehensive income (loss):				
Unrealized holding gains (losses)	$ 221	$ 1,351	$ (66)	$ 4,341
Reclassification adjustment for realized losses included in net income (loss)	—	—	(925)	(1,648)
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	(12,454)	(11,582)	(47,265)	171,906
Comprehensive income (loss)	$ (12,233)	$ (10,231)	$ (48,256)	$ 174,599

Convertible debt

We account for our 2 5/8% convertible notes by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate when we recognize interest expense in subsequent periods. As a result, we assigned a value to the debt component of our 2 5/8% 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 September 30, 2010, the principal and accrued interest payable on our 2 5/8% convertible notes was $162.5 million and $545,000, respectively, and the fair value using quoted market prices was $152.7 million. At December 31, 2009, the principal and accrued interest payable on the notes was $162.5 million and $1.6 million, respectively, and the fair value using quoted market prices was $165.8 million.

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, 2010 and 2009, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Nine Months Ended September 30,	
	2010	2009
Risk-free interest rate	2.8%	1.9%
Dividend yield	0.0%	0.0%
Volatility	55.7%	56.9%
Expected Life	5.2 years	4.9 years

Board of Director Stock Options:

	Nine Months Ended September 30,	
	2010	2009
Risk-free interest rate	2.7%	3.4%
Dividend yield	0.0%	0.0%
Volatility	57.7%	61.5%
Expected Life	7.8 years	7.7 years

ESPP:

	Nine Months Ended September 30,	
	2010	2009
Risk-free interest rate	0.2%	0.3%
Dividend yield	0.0%	0.0%
Volatility	47.8%	56.5%
Expected Life	6 months	6 months

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Stock-based compensation expense (in thousands, except per share data) was allocated as follows:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2010	2009	2010	2009
Research and development	$ 2,476	$ 2,893	$ 7,912	$ 8,031
General and administrative	484	653	1,535	1,783
Non-cash compensation expense related to stock options included in continuing operations	2,960	3,546	9,447	9,814
Non-cash compensation expense related to stock options included in equity in net loss of Regulus Therapeutics Inc.	128	—	429	—
Non-cash compensation benefit related to stock options included in discontinued operations	—	—	—	(1,558)
Total	$ 3,088	$ 3,546	$ 9,876	$ 8,256
Basic and diluted stock-based compensation expense, per share:				
Net loss per share included in continuing operations	$ (0.03)	$ (0.04)	$ (0.10)	$ (0.10)
Net loss per share related to stock options included in equity in net loss of Regulus Therapeutics Inc.	—	—	—	—
Net income per share included in discontinued operations	—	—	—	0.02
Total	$ (0.03)	$ (0.04)	$ (0.10)	$ (0.08)

As part of our Regulus joint venture, both we and Alnylam issued our own company's stock options to members of Regulus' Board of Directors, Scientific Advisory Board and employees of Regulus. In January 2009 as part of Regulus' conversion to a C-Corporation 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.

As of September 30, 2010, total unrecognized compensation cost related to non-vested stock-based compensation plans was $11.5 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 1.3 years.

Impact of recently issued accounting standards

In October 2009, the FASB issued a new accounting standard for revenue arrangements with multiple deliverables. This new standard requires companies to separate multiple-deliverable arrangements and at inception allocate arrangement consideration using a selling price hierarchy. The new standard also requires additional disclosures about multiple-deliverable arrangements. This guidance is effective prospectively for revenue arrangements entered into or materially modified in fiscal years beginning on or after June 15, 2010 and is effective for our fiscal year 2011. We do not expect this new standard to have a material impact on our financial statements.

In March 2010, the FASB issued a new accounting standard that establishes a revenue recognition method for milestone payments in research and development agreements. Under the new standard, entities can make an accounting policy election to recognize a payment that is contingent upon the achievement of a substantive milestone in its entirety in the period in which the milestone is achieved. We have historically applied a revenue recognition

method for milestone payments that is consistent with this new standard. Therefore when we adopt this new standard in 2011, the only change required is to provide additional disclosures about the substantive nature of the milestone payments we are entitled to under our research and development agreements.

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3. Investment in Regulus Therapeutics Inc.

In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development, and commercialization of microRNA-based therapeutics. Regulus combines the strengths and assets of our and Alnylam's technologies, know-how, and intellectual property relating to microRNA-based therapeutics.

We and Alnylam each granted Regulus exclusive licenses to our respective intellectual property for microRNA therapeutic applications, as well as certain early fundamental patents in the microRNA field. Alnylam made an initial investment of $10 million in Regulus to balance venture ownership. As of September 30, 2010, we owned 51 percent of Regulus and Alnylam owned the remaining 49 percent. In October 2010, Regulus received a $10 million equity investment from sanofi-aventis in connection with the collaboration the two companies entered into in June 2010. 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 a limited liability company to a C-Corporation. In March 2009, Regulus raised $20 million in a Series A preferred equity financing, in which we and Alnylam were the sole and equal investors.

Regulus Collaborations

sanofi-aventis

In June 2010, Regulus entered into a global, strategic alliance with sanofi-aventis to discover, develop, and commercialize microRNA therapeutics. The alliance includes $750 million of potential milestone payments in addition to a $25 million upfront fee, a $10 million equity investment in Regulus that sanofi-aventis made in October 2010 and annual research support for three years with the option to extend two additional years. In addition, Regulus is eligible to receive royalties on microRNA therapeutic products commercialized by sanofi-aventis. Sanofi-aventis also received an option for a broader technology alliance that provides Regulus certain rights to participate in development and commercialization of resulting products. If exercised, this three-year option is worth up to an additional $50 million to Regulus. We and Alnylam are each eligible to receive 7.5% of the upfront payment and all potential milestone payments, in addition to royalties on product sales. As a result, in July 2010 we received a payment of $1.9 million from Regulus.

GlaxoSmithKline

In April 2008, Regulus entered into a strategic alliance with GlaxoSmithKline, or GSK, to discover, develop and commercialize novel microRNA-targeted therapeutics to treat inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. The alliance utilizes Regulus' expertise and intellectual property position in the discovery and development of microRNA-targeted therapeutics and provides GSK with an option to license drug candidates directed at four different microRNA targets with relevance in inflammatory disease. Regulus will be responsible for the discovery and development of the microRNA antagonists through completion of clinical proof of concept, unless GSK chooses to exercise its option earlier. After exercise of the option, GSK will have an exclusive license to drugs Regulus develops under each program for the relevant microRNA target for further development and commercialization on a worldwide basis. Regulus will have the right to further develop and commercialize any microRNA therapeutics which GSK chooses not to develop or commercialize.

In 2008, Regulus received $20 million in upfront payments from GSK, including a $15 million option fee and a $5 million note. The note plus interest will convert into Regulus 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 if Regulus does not repay the note in cash by April 2011, we, Alnylam and Regulus may elect to repay the note plus interest with shares of each company's common stock or cash. Regulus is eligible to receive from GSK up to $144.5 million in development, regulatory and sales milestone payments for each of the four microRNA-targeted drugs discovered and developed as part of the alliance. In May 2009, Regulus received a $500,000 discovery milestone payment from its collaboration with GSK for demonstrating a pharmacological effect in immune cells by specific microRNA inhibition. In addition, Regulus would receive from GSK tiered royalties up to double digits on worldwide sales of drugs resulting from the alliance.

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In February 2010, Regulus announced the establishment of a new worldwide strategic alliance with GSK to develop and commercialize microRNA therapeutics targeting microRNA 122, or miR-122, for the treatment of hepatitis C virus, or HCV, infection. The new HCV alliance expands the ongoing GSK-Regulus immuno-inflammatory disease alliance formed in 2008. Under the terms of this HCV collaboration, Regulus received $8 million from GSK, including a $3 million license fee and a second $5 million note (guaranteed by Isis and Alnylam) that will convert into Regulus stock in the future if Regulus achieves a minimum level of financing with institutional investors. In addition, Regulus is eligible to receive several near-term significant payments associated with the advancement of an HCV drug, plus additional milestone payments with the potential to earn more than $150 million in miR-122-related combined payments and double-digit royalties consistent with the existing immuno-inflammatory diseases alliance terms established in April 2008. Because GSK has selected Regulus' miR-122 for the new collaboration, the number of immuno-inflammatory programs GSK has an option to license under the 2008 immuno-inflammatory alliance has been reduced from four to three.

As part of the HCV collaboration, Regulus granted GSK a limited license to develop and commercialize the miR-122 antagonist SPC 3649, if GSK acquires rights to this compound. Regulus will receive development and regulatory milestones as well as royalties if GSK develops and commercializes SPC 3649.

Equity method of accounting

On January 1, 2010, as a result of adopting the new accounting standard for identifying which enterprise has the power to direct activities of a variable interest entity, we prospectively changed the way we account for our variable interest in Regulus. Since we and Alnylam share the ability to impact Regulus' economic performance, we are no longer the primary beneficiary of Regulus. Beginning in the first quarter of 2010, we deconsolidated Regulus from our condensed consolidated financial statements and began to account for our ownership interest in Regulus using the equity method of accounting. Below is a table summarizing the accounting impact to our balance sheet as of January 1, 2010 as a result of adopting the equity method of accounting (in thousands):

	As Originally Reported	As Adjusted	Effect of Change
Total Assets	$ 657,184	$ 626,006	$ (31,178)
Total Liabilities	$ (355,121)	$ (335,524)	$ 19,597
Total Stockholders' Equity	$ (302,063)	$ (290,482)	$ 11,581

Under the equity method of accounting, we are required to suspend losses if our share of Regulus' net loss exceeds the amount of funding we were required to provide. Since we and Alnylam are guarantors of both of the convertible notes that Regulus issued to GSK, we continued to recognize losses in excess of our net investment in Regulus up to the $5 million we guaranteed. If we had been applying the equity method from inception, we would have suspended recognizing our share of Regulus' losses in 2008 because it would have exceeded the amount we guaranteed under the first GSK convertible note. When we made the $10 million investment in March 2009 we would have recognized all of the suspended losses.

4. Discontinued Operations

In January 2009, AMI completed its acquisition of Ibis for a total purchase price of $215 million. 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. 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 $15.4 million of income tax expense. The components of discontinued operations for the nine months ended September 30, 2009 are as follows (in thousands):

Revenue	$ —
Total operating expenses	35
Loss from operations	(35)
Loss attributed to noncontrolling interest in Ibis Biosciences, Inc.	6
Loss from discontinued operations	(29)
Gain on sale of Ibis Biosciences, Inc., net of tax	187,153
Net income from discontinued operations, net of tax	$ 187,124

We do not have any remaining assets and liabilities from discontinued operations in our accompanying condensed consolidated balance sheets at September 30, 2010 and December 31, 2009. We have not separately classified cash flows from discontinued operations in our condensed consolidated statement of cash flows.

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5. Investments

As of September 30, 2010, 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, 2010:

One year or less	83%
After one year but within five years	17%
Total	100%

At September 30, 2010, 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 Santaris Pharma A/S, Achaogen, Atlantic Pharmaceuticals Limited, Altair Therapeutics Inc. and Excaliard, which are privately-held and ATL and iCo Therapeutics Inc., which are publicly-traded. We account for securities in the privately-held companies under the cost method of accounting. During the first nine months of 2010, we recognized a $1.2 million loss on investments primarily consisting of an $880,000 non-cash loss related to the other-than-temporary impairment of our equity investment in ATL and $349,000 of valuation allowances we recorded related to the investments we made in Excaliard and Achaogen. Because realization of our Excaliard and Achaogen investments is uncertain we recorded a full valuation allowance.

Beginning in the first quarter of 2010, we deconsolidated Regulus from our condensed consolidated financial statements and began to account for our ownership interest in Regulus using the equity method of accounting. As a result, our short-term investments balance at September 30, 2010 did not include Regulus' short-term investments, compared to $14.5 million at December 31, 2009. The following is a summary of our investments (in thousands):

September 30, 2010	Amortized Cost	Unrealized Gains	Unrealized Losses	Other-Than-Temporary Impairment Loss	Estimated Fair Value
Short-term investments:					

Corporate debt securities	$ 138,096	$ 292	$ (22)	$ —	$ 138,366
Debt securities issued by U.S. government agencies	134,235	116	(3)	—	134,348
Debt securities issued by the U.S. Treasury	49,773	44	—	—	49,817
Debt securities issued by states of the United States and political subdivisions of the states	6,786	7	—	—	6,793
Total securities with a maturity of one year or less	328,890	459	(25)	—	329,324
Corporate debt securities	63,162	311	(32)	—	63,441
Debt securities issued by U.S. government agencies	5,010	7	—	—	5,017
Total securities with a maturity of more than one year	68,172	318	(32)	—	68,458
Subtotal	$ 397,062	$ 777	$ (57)	$ —	$ 397,782
Equity securities:					
Current portion (included in Other current assets)	$ 1,538	$ 1,247	$ —	$ (880)	$ 1,905
Long-term portion (included in Deposits and other assets)	625	—	—	—	625
Subtotal	$ 2,163	$ 1,247	$ —	$ (880)	$ 2,530
	$ 399,225	$ 2,024	$ (57)	$ (880)	$ 400,312

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December 31, 2009	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value
Short-term investments:				
Corporate debt securities	$ 102,598	$ 174	$ (34)	$ 102,738
Debt securities issued by U.S. government agencies	151,008	178	(17)	151,169
Debt securities issued by the U.S. Treasury	32,027	42	(10)	32,059
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	285,908	394	(61)	286,241
Corporate debt securities	41,388	262	(103)	41,547
Debt securities issued by U.S. government agencies	110,313	65	(218)	110,160
Debt securities issued by U.S. Treasury	31,136	2	(29)	31,109
Total securities with a maturity of more than one year	182,837	329	(350)	182,816
Subtotal	$ 468,745	$ 723	$ (411)	$ 469,057
Equity securities:				
Current portion (included in Other current assets)	$ 1,229	$ 2,645	$ —	$ 3,874
Long-term portion (included in Deposits and other assets)	625	—	—	625
Subtotal	$ 1,854	$ 2,645	$ —	$ 4,499
	$ 470,599	$ 3,368	$ (411)	$ 473,556

Investments we consider to be temporarily impaired at September 30, 2010 are as follows (in thousands):

		Less than 12 months of temporary impairment	
	Number of Investments	Estimated Fair Value	Unrealized Losses
Corporate debt securities	20	$ 46,218	$ (54)
Debt securities issued by U.S. government agencies	2	8,104	(3)
Total temporarily impaired securities	22	$ 54,322	$ (57)

We believe that the decline in value of these securities is temporary and primarily related to the change in market interest rates since purchase. We believe it is more likely than not that we will be able to hold these securities to maturity. Therefore we anticipate full recovery of their amortized cost basis at maturity.

6. Fair Value Measurements

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets, which includes our money market funds and treasury securities classified as available-for-sale securities and equity securities in publicly-held biotechnology companies; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring an entity to develop its own assumptions. To estimate the fair value of securities classified as Level 2, we utilize the services of various fixed income pricing providers that use an industry standard valuation model, which is based on a market approach. The significant inputs for the valuation model include reported trades, broker/dealer quotes, benchmark securities and bids.

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Below is a table of the 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, 2010 (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)	$ 99,730	$ 80,925	$ 18,805	$ —
Corporate debt securities (2)	201,807	—	201,807	—
Debt securities issued by U.S. government agencies (2)	139,365	—	139,365	—
Debt securities issued by the U.S. Treasury (2)	49,817	49,817	—	—
Debt securities issued by states of the United States and political subdivisions of the states (2)	6,793	—	6,793	—
Equity securities (3)	1,906	1,906	—	—
Total	$ 499,418	$ 132,648	$ 366,770	$ —

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

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

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

7. Long-Term Obligations

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 $18.4 million and $1.0 million, respectively, in principal to finance the purchase of equipment until the end of the draw down period, which ended in July 2010. 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 draw down under the loan agreement has a term of three years, with principal and interest payable monthly. We calculate interest on amounts we borrow under the loan agreement based upon the three year interest rate swap at the time we make each draw down plus 4 percent. We are using the equipment purchased under the loan agreement as collateral. In June 2010, we drew down an additional $3.1 million in principal under the loan agreement. As of September 30, 2010, we have drawn down $15.1 million in principal under this loan agreement at a weighted average interest rate of 6.47 percent. The carrying balance under this loan agreement at September 30, 2010 and December 31, 2009 was $9.1 million and $10.0 million, respectively.

8. Lease Agreements

We currently occupy approximately 138,500 square feet of laboratory and office space, including a 28,704 square foot facility, which houses our manufacturing suites for our drug development business built to meet Good Manufacturing Practices. We are located in four buildings in Carlsbad, California. We lease all of these buildings under lease agreements. The leases on the three buildings we primarily use for laboratory and office space for our drug development business expire at the end of 2011.

On March 30, 2010 we entered a new lease agreement with an affiliate of BioMed Realty, L.P. Under the lease, BioMed will construct a new 176,000 square foot research facility in Carlsbad, California. Upon completion of construction, we will lease the new facility and consolidate the majority of our operations in the new facility. The lease has an initial term of 20 years with an option to extend the lease for up to four five-year periods.

Our rent under the new lease is based on a percentage of the total construction costs spent by BioMed to acquire the land and build the new facility. We will begin paying rent on January 1, 2012. Once the new facility is complete, we will be responsible for the costs associated with owning and maintaining the facility. Since our rent is based on a percentage of total construction costs spent by BioMed to acquire the land and build the new facility, and the facility is not yet built, it is difficult for us to calculate our future payment obligations under the lease. However, as of September 30, 2010, we estimate that the maximum potential future payments we may be required to make over the 20 year term of the lease are $172 million.

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Under the lease we have an option to purchase the facility at the end of the fifth, sixth, seventh, eighth, ninth, fifteenth and twentieth year of the lease. The purchase price for the purchase options ending on the fifth through ninth year will be set based on the total construction costs spent by BioMed to acquire the land and build the new facility less rent payments made through the purchase date. The purchase price for the purchase options ending on the fifteenth and twentieth year will be based on fair market value at those times.

In conjunction with the new lease agreement with BioMed, we purchased a parcel of land for $10.1 million and subsequently sold it to BioMed, who will construct the new facility on it. Since we have the option to purchase the facility, including the land, we have continuing involvement in the land which requires us to account for the purchase and sale of the land as a financing transaction. As such, our fixed assets at September 30, 2010 included the land. Additionally, we have recorded a corresponding amount in our non-current liabilities as a long-term financing obligation. Since land is not a depreciable asset, the value of the land and financing obligation we recorded will not change until we exercise our purchase option or the lease is terminated.

We also lease from BioMed an approximately 28,700 square foot facility that houses our manufacturing suites for our drug development business. On March 30, 2010 we amended the lease to extend the term through December 31, 2031, subject to four five-year options to extend the lease, and to obtain an option to purchase the manufacturing facility on similar terms as the purchase options described above.

9. Income Taxes

At December 31, 2009, our balance sheet included an income taxes payable of $7.3 million. As of September 30, 2010 our balance sheet included an income tax receivable of $517,000. This change relates to $7.7 million of income tax payments made to various taxing authorities during the first quarter of 2010 for our 2009 estimated tax liability. The income tax receivable primarily represents the amount that will be refunded to us in the fourth quarter of 2010.

10. Collaborative Arrangements and Licensing Agreements

The information discussed below represents significant partnerships we entered into during 2010 and material changes to partnerships entered into prior to 2010. 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, 2009.

Traditional Pharmaceutical Alliances and Licensing

Bristol-Myers Squibb

In July 2010, we and Bristol-Myers Squibb extended our collaboration and license agreement by two years to develop a follow-on drug that targets PCSK9. Bristol-Myers Squibb recently discontinued a Phase 1 study of BMS-PCSK9$_{Rx}$ and will focus efforts on developing a follow-on drug. When we initially entered into the collaboration and license agreement with Bristol-Myers Squibb in 2007, we received a $15 million upfront fee, which we finished amortizing into revenue when our period of performance in the original agreement ended in April 2010.

GlaxoSmithKline

In March 2010, we entered into a new strategic alliance with GSK that will apply our antisense drug discovery platform to seek out and develop new therapeutics against targets for rare and serious disease, including infectious diseases and some conditions causing blindness.

Under the terms of the agreement, which covers up to six programs, we received an upfront $35 million payment from GSK, which we began amortizing into revenue in the second quarter of 2010 over the five year period of our performance based on the research plan included in the agreement. For the three and nine months ended September 30, 2010, we recognized revenue of $6.8 million and $8.5 million, respectively, including a $5M milestone payment from GSK for the identification of ISIS-GSK1$_{Rx}$ as a development candidate, and our balance sheet included deferred revenue of $31.5 million relating to the $35 million upfront payment. We are also eligible to receive on average up to $20 million in milestone payments per program up to Phase 2 proof-of-concept. GSK has the option to license drugs from these programs at Phase 2 proof-of-concept, and will be responsible for all further development and commercialization. We will be eligible to receive license fees and milestone payments, totaling up to nearly $1.5 billion, in the event all six programs are successfully developed for one or more indications and commercialized through to pre-agreed sales targets. In addition, we will receive up to double-digit royalties on sales from any product that GSK successfully commercializes.

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11. Segment Information and Concentration of Business Risk

Segment information

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 alliances with GSK and sanofi-aventis.

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

	Isis Drug Discovery and Development	Regulus
Three Months Ended September 30, 2010		
Revenue:		
Research and development	$ 27,785	$ 2,309
Licensing and royalty	839	—
Total segment revenue	$ 28,624	$ 2,309
Loss from operations	$ (8,947)	$ (2,434)

	Drug Discovery and Development	Regulus	Consolidated 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)

	Isis Drug Discovery and Development	Regulus
Nine Months Ended September 30, 2010		

Revenue:		
Research and development	$ 77,484	$ 3,804
Licensing and royalty	4,569	—
Total segment revenue	$ 82,053	$ 3,804
Loss from operations	$ (32,498)	$ (13,377)
Total assets as of September 30, 2010	$ 575,858	$ 53,951

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	Drug Discovery and Development	Regulus	Consolidated Total
Nine Months Ended September 30, 2009			
Revenue:			
Research and development	$ 84,027	$ 2,388	$ 86,415
Licensing and royalty	2,924	—	2,924
Total segment revenue	$ 86,951	$ 2,388	$ 89,339
Loss from operations	$ (9,989)	$ (5,876)	$ (15,865)
Total assets as of December 31, 2009	$ 634,820	$ 22,364	$ 657,184

As a result of adopting the new accounting standard related to our investment in Regulus, we deconsolidated Regulus from our condensed consolidated financial statements and began to account for ownership interest in Regulus using the equity method of accounting. Therefore in the first quarter of 2010 we began presenting our net share of Regulus' operating results on a separate line in our statement of operations called "Equity in net loss of Regulus Therapeutics Inc."

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,	
	2010	2009	2010	2009
Partner A	59%	62%	61%	56%
Partner B	24%	0%	10%	0%
Partner C	2%	8%	14%	7%
Partner D	0%	18%	0%	21%

Contract receivables from four significant partners comprised approximately 45%, 20%, 15% and 11% of contract receivables at September 30, 2010. Contract receivables from one significant partner comprised approximately 92% of contract receivables at December 31, 2009.

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 jointly 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 drugs. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning our programs are described in additional detail in our Annual Report on Form 10-K for the year ended December 31, 2009, which is on file with the U.S. Securities and Exchange Commission, and those identified within this Item entitled "Risk Factors" beginning on page 29 of this Report.

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Overview

We are the leading company in antisense technology, exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. Antisense technology is a direct route from genomics to drugs. With our highly efficient and prolific drug discovery platform we can expand our drug pipeline and our partners' pipelines with antisense drugs that address significant unmet medical needs. Our business strategy is to do what we do best—to discover unique antisense drugs and develop these drugs to key 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 late-stage development, commercialization and marketing expertise, such as Bristol-Myers

Squibb, Genzyme, GSK and Eli Lilly and Company. Additionally, we have 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, a company we established and jointly own 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 Ibis, a subsidiary of ours that we sold in early 2009 to AMI. 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 1,500 issued patents worldwide. With our ongoing research and development, our patent portfolio continues to grow. The patents not only protect our key assets—our technology and our drugs—they also form the basis for lucrative licensing and partnering arrangements. To date, we have generated more than $395 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. Our clinical experience with mipomersen demonstrates that antisense drugs work in man. We and Genzyme have completed four positive Phase 3 studies planned to support the initial regulatory filings for marketing approval of mipomersen in both the U.S. and Europe in the first half of 2011. Across all four studies, treatment with mipomersen produced promising results in patients who have persistently high LDL-C levels despite being treated on maximally tolerated lipid-lowering therapy. These data are consistent with our observations of mipomersen in earlier clinical studies and support the profile of the drug as a novel treatment to reduce LDL-C in patients with high cholesterol, and at high cardiovascular risk and who cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies.

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

Since 2007, our partnerships, including our strategic alliance with GSK, have generated an aggregate of more than $825 million in payments from licensing fees, equity purchase payments and milestone payments. In addition, for our partnered drugs we have the potential to earn more than $3.2 billion in future milestone payments. We also will share in the future commercial success of our inventions and drugs resulting from these partnerships through earn out, profit sharing, and/or royalty arrangements. Our strong financial position is a result of the persistent execution of our business strategy and our inventive and focused research and development capabilities.

Business 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. With our proprietary drug discovery platform we can 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 22 drugs in development. Our partners are developing, with our support, 11 of these 22 drugs, which substantially reduces our development costs.

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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.

Beginning in the first quarter of 2010, as a result of adopting a new accounting standard, we no longer included Regulus' revenue and operating expenses in our operating results and no longer included Regulus' cash in our cash balance. See Note 2, *Significant Accounting Policies*, and Note 3, *Investment in Regulus Therapeutics Inc.*, in the Notes to the condensed consolidated financial statements for a more detailed explanation of this change.

Recent Events

Drug Development and Corporate Highlights

- Mipomersen is being developed by us and Genzyme for patients at high cardiovascular risk who cannot adequately control their cholesterol levels with current therapies. Mipomersen has been shown to substantially lower LDL-C as well as lowering other atherogenic lipids linked to cardiovascular disease, including apoB, Lp(a), triglycerides and VLDL. We and Genzyme completed the four Phase 3 studies that are planned to be included in the initial U.S. and E.U. filings for marketing approval for mipomersen. These filings, expected in the first half of 2011, will seek approval for the treatment of patients with homozygous FH, and may also include patients with severe heterozygous FH. Genzyme is also planning for filings in markets beyond the U.S. and E.U.
- We reported data on mipomersen from two Phase 3 studies that met all primary, secondary and tertiary endpoints.
  - In the first Phase 3 study evaluating mipomersen in patients with severe hypercholesterolemia, we and Genzyme reported that the study met its primary endpoint with a 36 percent reduction in LDL-C compared with a 13 percent increase in placebo.
  - In the second Phase 3 study evaluating mipomersen in patients with high-cholesterol at high risk for developing coronary heart disease, we and Genzyme reported that the study met its primary endpoint with a 37 percent reduction in LDL-C compared with a 5 percent decrease in placebo.
  - In both studies, frequently observed adverse events were injection site reaction and flu-like symptoms. Elevations in liver transaminases were observed that were generally similar in character with those seen in other studies.
- We added to our pipeline ISIS-GSK1$_{Rx}$, the first drug selected as part of our collaboration with GSK to treat severe and rare diseases.

- Our partners continued to advance the drugs in our pipeline with the initiation of two Phase 3 studies for OGX-011, a Phase 2 study for OGX-427 in patients with cancer.
- We benefit financially as the drugs in our pipeline advance in development earning $13 million in milestone payments this year, including a $5 million milestone payment from GSK for the identification of ISIS-GSK1$_{Rx}$ as a development candidate.
- Our partner, Excaliard, reported positive Phase 2 data demonstrating that treatment with EXC 001 reduced scarring in patients following elective surgery.
- Sanofi-aventis invested $10 million in Regulus acquiring less than 10% ownership of the preferred outstanding shares. The remaining preferred outstanding shares are owned by Alnylam Pharmaceuticals and us.

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;

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- 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 when we are the primary beneficiary for entities that we identify as variable interest entities;
- Determination of the fair value of convertible debt without the conversion feature; 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, 2009.

Consolidation of variable interest entities

On January 1, 2010, we adopted an accounting standard, which replaced 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 impacts the variable interest entity’s economic performance and (1) the obligation to absorb losses of the variable interest entity or (2) the right to receive benefits from the variable interest entity. As a result of adopting this new accounting standard, we were required to change the way we account for our variable interest in Regulus. Since we and Alnylam Pharmaceuticals, Inc. share the ability to impact Regulus’ economic performance, we are no longer the primary beneficiary of Regulus. We adopted the new standard on a prospective basis, therefore beginning in the first quarter of 2010, we deconsolidated Regulus from our condensed consolidated financial statements and began to account for our ownership interest in Regulus using the equity method of accounting. This means that we no longer include Regulus’ revenue and operating expenses in our operating results. Instead we include our share of Regulus’ operating results on a separate line in our condensed consolidated statement of operations called “Equity in net loss of Regulus Therapeutics Inc.” On our condensed consolidated balance sheet, we present our investment in Regulus on a separate line in the non-current liabilities section called “Investment in Regulus Therapeutics Inc.” We have not reclassified amounts in the prior period financial statements to conform to the current period presentation. For additional information, see Note 3, *Investment in Regulus Therapeutics Inc.*

Results of Operations

As a result of adopting the new accounting standard related to our investment in Regulus, we have presented our net share of Regulus’ operating results on a separate line in our statements of operations called “Equity in net loss of Regulus Therapeutics Inc.” for the three and nine months ended September 30, 2010, compared to the line-by-line consolidation for the same periods in 2009. We have not reclassified amounts in the prior period financial statements to conform to the current period presentation. We discuss Regulus’ operating results in a separate section below.

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 2009 in our financial statements separately as discontinued operations.

Revenue

Total revenue for the three and nine months ended September 30, 2010 was $28.6 million and $82.1 million, respectively, compared to $26.8 million and $89.3 million for the same periods in 2009. 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. We recognized new revenue in the first nine months of 2010 in the form of an upfront fee from our new partnership with GSK, which is amortized through the first quarter of 2015, milestone payments from GSK, BMS and Achaogen and sublicensing income from Regulus' collaboration with sanofi-aventis. Although we recognized this new revenue, our revenue for 2010 decreased compared to 2009 because the amortization of the upfront fee from our Ortho-McNeil-Janssen Pharmaceuticals, Inc., or OMJP, collaboration ended in the third quarter of 2009. Additionally, revenue for the first nine months of 2010 decreased by $2.4 million because we are no longer including Regulus' revenue in our 2010 revenue.

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

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, 2010 was $27.8 million and $77.5 million, respectively, compared to $26.0 million and $86.4 million for the same periods in 2009. Although we recognized $13 million of revenue for the milestone payments we received and the $3.5 million of amortization of revenue related to the upfront payment we received from GSK in the first nine months of 2010, our revenue compared to the first nine months of 2009 decreased, primarily because revenue from our collaborations with OMJP ended in the third quarter of 2009. Research and development revenue also decreased by $2.4 million because we are no longer including Regulus' revenue in our 2010 revenue.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties for the three and nine months ended September 30, 2010 was $839,000 and $4.6 million, respectively, compared to $809,000 and $2.9 million for the same periods in 2009. The increase primarily relates to the $1.9 million sublicensing revenue we earned from Regulus in the second quarter of 2010 when Regulus entered into a strategic alliance with sanofi-aventis.

Operating Expenses

Operating expenses for the three and nine months ended September 30, 2010 were $37.6 million and $114.6 million, respectively, compared to $37.2 million and $105.2 million for the same periods in 2009. The higher expenses in 2010 were primarily due to an increase in costs associated with advancing mipomersen toward its initial regulatory filings for marketing approval planned for the first half of next year and offset in part by an $8.3 million decrease because we are no longer including Regulus' operating expenses in our 2010 operating expenses. We expect to increase operating expenses in the fourth quarter of 2010 as we initiate a broad Phase 2 program on one of the drugs in our pipeline.

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 from our operating expenses. We believe non-cash compensation expense is not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding it.

Research and Development Expenses

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

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2010	2009	2010	2009
Research and development expenses	$ 32,240	$ 30,939	$ 97,915	$ 86,488
Non-cash compensation expense related to stock options	2,476	2,893	7,912	8,031
Total research and development expenses	$ 34,716	$ 33,832	$ 105,827	$ 94,519

For the three and nine months ended September 30, 2010, we incurred total research and development expenses of $32.2 million and $97.9 million, respectively, compared to $30.9 million and $86.5 million for the same periods in 2009. The higher expenses in 2010 were primarily due to an increase in costs associated with advancing mipomersen toward its initial regulatory filings for marketing approval planned for the first half of next year offset in part by a $6.5 million decrease because we are no longer including Regulus' research and development expenses in our 2010 operating expenses. All amounts discussed exclude non-cash compensation expense related to stock options.

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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.

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,	
	2010	2009	2010	2009
Antisense drug discovery	$ 8,481	$ 6,987	$ 24,520	$ 18,386
Non-cash compensation expense related to stock options	722	771	2,304	2,281
Total antisense drug discovery	$ 9,203	$ 7,758	$ 26,824	$ 20,667

Antisense drug discovery costs for the three and nine months ended September 30, 2010 were $8.5 million and $24.5 million, respectively, compared to $7.0 million and $18.4 million for the same periods in 2009, all amounts exclude non-cash compensation expense related to stock options. The higher expenses in 2010 were primarily due to our planned investment to expand our pipeline by adding three to five new drugs this year and additional spending to implement an improved chemistry platform for our drugs, called Generation 2.5, that should increase the potency, expand the available routes of administration and enhance the commercial potential of our drugs. These activities resulted in an increase in personnel, laboratory supplies and research services provided by third parties in 2010.

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,	
	2010	2009	2010	2009
Mipomersen	$ 4,992	$ 7,605	$ 20,851	$ 17,894
Other antisense development projects	6,249	3,487	17,412	11,766
Development overhead costs	1,511	1,174	4,269	3,621
Non-cash compensation expense related to stock options	779	893	2,461	2,661
Total antisense drug development	$ 13,531	$ 13,159	$ 44,993	$ 35,942

Antisense drug development expenditures were $12.8 million and $42.5 million for the three and nine months ended September 30, 2010, compared to $12.3 million and $33.3 million for the same periods in 2009, all amounts exclude non-cash compensation expense related to stock options. We attribute the increase to the broad Phase 3 program for mipomersen and an increase in other antisense development projects due to the expansion of our drug pipeline.

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We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Our Phase 1 and Phase 2 programs are clinical research programs that fuel our Phase 3 pipeline. When our products are in Phase 1 or Phase 2 clinical trials, they are in a dynamic state where we continually adjust the development strategy for each product. Although we may characterize a product as "in Phase 1" or "in Phase 2," it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product's particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous products in preclinical and early stage clinical research, the fluctuations in expenses from product to product, in large part, offset one another. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related cost. Our partners are developing, with our support, 11 of our 22 drug candidates, which substantially reduces our development costs. As part of our collaboration with Genzyme, we are over time transitioning the development responsibility to Genzyme and Genzyme will be responsible for the commercialization of mipomersen. We are contributing up to the first $125 million in funding for the development costs of mipomersen. 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,	
	2010	2009	2010	2009
Manufacturing and operations	$ 4,661	$ 3,467	$ 13,432	$ 10,078

Non-cash compensation expense related to stock options	353	353	1,156	1,052
Total manufacturing and operations	$ 5,014	$ 3,820	$ 14,588	$ 11,130

Manufacturing and operations expenses for the three and nine months ended September 30, 2010 were $4.7 million and $13.4 million, respectively, compared to $3.5 million and $10.1 million for the same periods in 2009, all amounts exclude non-cash compensation expense related to stock options. The increase in expenses was primarily a result of an increase in personnel costs and services provided by third parties to support our expanded clinical development programs including our broad Phase 3 program for mipomersen and depreciation expense related to the upgrades made to our manufacturing facility to prepare to manufacture mipomersen for launch.

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.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2010	2009	2010	2009
Personnel costs	$ 1,959	$ 1,910	$ 5,905	$ 5,807
Occupancy	1,769	2,242	4,782	5,568
Depreciation and amortization	1,872	1,350	4,616	4,981
Insurance	224	224	705	681
Other	522	625	1,422	2,048
Non-cash compensation expense related to stock options	622	761	1,992	2,276
Total R&D support costs	$ 6,968	$ 7,112	$ 19,422	$ 21,361

R&D support costs for the three and nine months ended September 30, 2010 were $6.3 million and $17.4 million, respectively, compared to $6.4 million and $19.1 million for the same periods in 2009, all amounts exclude non-cash compensation expense related to stock options. The decrease in expenses in 2010 compared to 2009 primarily relates to lease modification fees that were paid in September 2009 and a decrease in patent amortization costs. Other R&D support costs also decreased because we are no longer including Regulus' R&D support costs in our 2010 operating 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, and finance. Additionally, we include in general and administrative expenses such costs as rent, repair and maintenance of buildings and equipment, depreciation, utilities, information technology and procurement costs that we need to support the corporate functions listed above.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2010	2009	2010	2009
General and administrative expenses	$ 2,372	$ 2,681	$ 7,189	$ 8,902
Non-cash compensation expense related to stock options	483	654	1,535	1,783
Total general and administrative expenses	$ 2,855	$ 3,335	$ 8,724	$ 10,685

General and administrative expenses for the three and nine months ended September 30, 2010 were $2.4 million and $7.2 million, respectively, compared to $2.7 million and $8.9 million for the same periods in 2009. The decrease primarily relates to Regulus' general and administrative expenses of $1.8 million for the nine months ended September 30, 2009 which we are no longer including in our 2010 operating expenses. All amounts discussed exclude non-cash compensation expense related to stock options.

Equity in Net Loss of Regulus Therapeutics Inc.

Beginning in the first quarter of 2010, as a result of adopting a new accounting standard, we no longer include Regulus' revenue and operating expenses in our operating results. Instead we are presenting our share of Regulus' operating results on a separate line in our condensed consolidated statement of operations called "Equity in net loss of Regulus Therapeutics Inc." Prior to the adoption of the new accounting standard, we consolidated Regulus' financial results on a line-by-line basis. See Note 2, *Significant Accounting Policies*, and Note 3, *Investment in Regulus Therapeutics Inc.*, in the Notes to the condensed consolidated financial statements for a more detailed explanation of this change.

Our equity in net loss of Regulus for the three and nine months ended September 30, 2010 was $930,000 and $6.4 million, respectively. We had the option to adopt the new accounting standard on a retrospective or prospective basis. We chose to adopt it prospectively therefore we did not adjust our prior period results. If we had retrospectively adopted the new standard, the equity in net loss of Regulus for the three and nine months ended September 30, 2009 would have been $1.1 million and $4.7 million, respectively, which would have represented our share of Regulus' loss in the three and nine months ended September 30, 2009 plus $1.7 million in

losses for the first nine months of 2009 which would have been previously suspended. The increase in our equity in net loss of Regulus primarily represents the increase in Regulus' operating expenses in 2010. We discuss expenses related to Regulus in a separate section below. Under the equity method of accounting, we are required to suspend recognizing losses if our share of Regulus' net loss exceeds the amount of funding we are required to provide to Regulus. In the third quarter of 2010, because our share of Regulus' net loss exceeded the $5 million guarantee we provided on the convertible notes Regulus issued to GSK, we suspended recording our portion of Regulus' loss. As of September 30, 2010, we have $261,000 of suspended losses, which we have not recognized.

Investment Income

Investment income for the three and nine months ended September 30, 2010 totaled $776,000 and $2.6 million, respectively, compared to $1.4 million and $5.2 million for the same periods in 2009. The decrease in investment income was primarily due to a lower average return on our investments resulting from the current market conditions and a lower average cash balance.

Interest Expense

Interest expense for the three and nine months ended September 30, 2010 was $3.3 million and $9.8 million and was slightly higher compared to $3.2 million and $9.4 million for the same periods in 2009.

Gain (Loss) on Investments, Net

Loss on investments for the three and nine months ended September 30, 2010 was $15,000 and $1.2 million, respectively, compared to a gain on investment of $123,000 and $2.8 million for the same periods in 2009. The net loss on investments for the first nine months of 2010 consists of an $880,000 non-cash loss related to the other-than-temporary impairment of our equity investment in ATL and $349,000 of valuation allowances we recorded related to the investments we made in Excaliard and Achaogen. Because realization of our Excaliard and Achaogen investments is uncertain we recorded a full valuation allowance. The gain on investments for the first nine months of 2009 primarily represents a $2.5 million gain when we sold all of the common stock of OncoGenex that we owned.

Income Tax Expense

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 in early 2009. We recorded income tax expense of $873,000 for the first nine months of 2009 as part of our financial results from continuing operations.

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

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2010	2009	2010	2009
Net loss from continuing operations, including income tax benefit (expense) and equity in net loss of Regulus Therapeutics Inc.	$ (12,454)	$ (12,752)	$ (47,265)	$ (18,124)
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	—	1,136	—	2,906
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (12,454)	$ (11,616)	$ (47,265)	$ (15,218)

Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders for the three and nine months ended September 30, 2010 was $12.5 million and $47.3 million, respectively, compared to $11.6 million and $15.2 million for the same periods in 2009. The increase in our net loss from continuing operations for the first nine months of 2010 compared to 2009 was primarily due to the following:

- $22.5 million increase in net operating loss, excluding Regulus, as described above;
- $3.4 million increase in our share of Regulus' net loss;
- $2.7 million decrease in investment income; and
- $4.0 million decrease in gain (loss) on investments.

Net Income from Discontinued Operations

Since we sold Ibis to AMI in the first quarter of 2009 and Ibis met the criteria for a component of an entity, we reflected Ibis as a discontinued operation on our financial statements. Accordingly, we have presented the operating results of Ibis in our condensed consolidated statements of operations as discontinued operations. Net income from discontinued operations, net of tax, for the three and nine months ended September 30, 2009 was $34,000 and $187.1 million, respectively, and primarily consisted of the $202.5 million gain less $15.3 million of income taxes.

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 and nine months ended September 30, 2010 was $12.5 million and $47.3 million, respectively, compared to a net loss of $11.6 million for the three months ended September 30, 2009 and net income of $171.9 million for the nine months ended September 30, 2009. Basic and diluted net loss per share for the three and nine months ended September 30, 2010 was $0.13 per share and $0.48 per share, respectively, compared to basic and diluted net loss of $0.12 per share for the three months ended September 30, 2009 and diluted net income per share of $1.75 for the nine months ended September 30, 2009. Net income and net income per share for the first nine months of 2009 primarily consisted of the $187.2 million gain, net of tax, which we recognized when we sold Ibis to AMI in the first quarter of 2009.

Regulus Therapeutics Segment

Regulus' revenue for the three and nine months ended September 30, 2010 was $2.3 million and $3.8 million, respectively, compared to $625,000 and $2.4 million for the same periods in 2009. The increase primarily relates to the amortization of the $25 million upfront payment Regulus received from sanofi-aventis in July 2010 and the $3 million upfront license fee Regulus received from GSK in February 2010 for its HCV alliance targeting miR-122. Regulus is amortizing the $25 million and $3 million upfront payments it received from sanofi-aventis and GSK ratably into revenue through June 2015 and April 2014, respectively, which represents the end of its performance obligations based on the research and development plans included in the agreements.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2010	2009	2010	2009
Research and development expenses	$ 3,803	$ 2,109	$ 14,099	$ 6,521
General and administrative expenses	812	621	2,653	1,757
Non-cash compensation expense/(benefit) related to stock options	128	207	429	(14)
Total Regulus' operating expenses	$ 4,743	$ 2,937	$ 17,181	$ 8,264

Operating expenses for Regulus were $4.6 million and $16.8 million for the three and nine months ended September 30, 2010, compared to $2.7 million and $8.3 million for the same periods in 2009, all amounts exclude non-cash compensation expense related to stock options. The increase primarily relates to the $3.8 million of sublicense fees paid to us and Alnylam from Regulus' strategic alliance with sanofi-aventis, Regulus' continued efforts to build its team to support its internal microRNA programs and the efforts associated with its GSK collaboration. With the strategic alliances with GSK and sanofi-aventis, we anticipate that Regulus' expenses will increase going forward as Regulus advances its research and development activities.

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, 2010, we have earned approximately $900.8 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, 2010, we have raised net proceeds of approximately $818.1 million from the sale of our equity securities and we have borrowed approximately $565.3 million under long-term debt arrangements to finance a portion of our operations.

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As of September 30, 2010, we had cash, cash equivalents and short-term investments of $497.9 million and stockholders' equity of $253.7 million. In comparison, we had cash, cash equivalents and short-term investments of $574.3 million and stockholders' equity of $302.1 million at December 31, 2009. At September 30, 2010, we had consolidated working capital of $406.6 million, compared to $484.7 million at December 31, 2009. The decrease in cash and working capital primarily relates to cash used in the first nine months of 2010 for our operations, including a $7.7 million payment that we made for 2009 income taxes. Our cash and working capital also decreased because we are no longer including Regulus' cash, which was $30.7 million at December 31, 2009, in our cash balance.

As of September 30, 2010, our debt and other obligations totaled $140.3 million, compared to $140.8 million at December 31, 2009. The decrease primarily relates to the $5.3 million convertible promissory note and the $949,000 equipment financing arrangement on the books of Regulus as of December 31, 2009 which we are no longer consolidating in our 2010 balance sheet. Also contributing to the decrease was $3.1 million of principal payments we made in the first nine months of 2010 on our equipment financing arrangement, offset by $3.1 million of additional draw downs on our equipment financing arrangement and an increase in the carrying value of our $2^5/_8$ percent convertible notes related to $5.8 million of non-cash amortization of the debt discount we recorded in the first nine months of 2010. 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, 2010. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in the paragraphs following the table:

	Payments Due by Period (in millions)				
Contractual Obligations (selected balances described below)	Total	Less than 1 year	1-3 years	3-5 years	After 5 years
$2^5/_8$ percent Convertible Subordinated Notes (principal and interest payable)	$ 177.4	$ 4.3	$ 8.5	$ 164.6	$ —
Equipment Financing Arrangements (principal and interest payable)	$ 9.7	$ 5.6	$ 4.1	$ —	$ —
Other Obligations (principal and interest payable)	$ 1.6	$ 0.1	$ 0.1	$ 0.1	$ 1.3
Operating Leases	$ 30.8	$ 3.3	$ 3.0	$ 2.3	$ 22.2
Total	$ 219.5	$ 13.3	$ 15.7	$ 167.0	$ 23.5

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

In January 2007, we completed a $162.5 million convertible debt offering, which raised proceeds of approximately $157.1 million, net of $5.4 million in issuance costs. We included the issuance costs in our balance sheet and are amortizing these costs to interest expense over the life of the debt. The $162.5 million convertible subordinated notes mature in 2027 and bear interest at 2 5/8 percent, which is payable semi-annually. The 2 5/8 percent notes are convertible, at the option of the note holders, into approximately 11.1 million shares of our common stock at a conversion price of $14.63 per share. We will be able to redeem these notes at a redemption price equal to 100.75 percent of the principal amount between February 15, 2012 and February 14, 2013; 100.375 percent of the principal amount between February 15, 2013 and February 14, 2014; and 100 percent of the principal amount thereafter. Holders of the 2 5/8 percent notes may also require us to repurchase the 2 5/8 percent notes on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100 percent of the principal amount of the 2 5/8 percent notes being repurchased plus unpaid interest.

In October 2008, we entered into a loan agreement related to an equipment financing and in September 2009, we amended the loan agreement to increase the aggregate maximum amount of principal we can draw under the agreement. Under the loan agreement, we and Regulus could borrow up to $18.4 million and $1.0 million, respectively, in principal to finance the purchase of equipment until the end of the draw down period, which ended in July 2010. 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 draw down under the loan agreement has a term of three years, with principal and interest payable monthly. We calculate interest on amounts we borrow under the loan agreement based upon the three year interest rate swap at the time we make each draw down plus 4 percent. We are using the equipment purchased under the loan agreement as collateral. In June 2010, we drew down an additional $3.1 million in principal under the loan agreement. As of September 30, 2010, we have drawn down $15.1 million in principal under this loan agreement at a weighted average interest rate of 6.47 percent. The carrying balance under this loan agreement at September 30, 2010 and December 31, 2009 was $9.1 million and $10.0 million, respectively.

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We currently occupy approximately 138,500 square feet of laboratory and office space, including a 28,704 square foot facility, which houses our manufacturing suites for our drug development business built to meet Good Manufacturing Practices. We are located in four buildings in Carlsbad, California. We lease all of these buildings under lease agreements. The leases on the three buildings we primarily use for laboratory and office space for our drug development business expire at the end of 2011.

On March 30, 2010 we entered a new lease agreement with an affiliate of BioMed Realty, L.P. Under the lease, BioMed will construct a new 176,000 square foot research facility in Carlsbad, California. Upon completion of construction, we will lease the new facility and consolidate the majority of our operations in the new facility. The lease has an initial term of 20 years with an option to extend the lease for up to four five-year periods.

Our rent under the new lease is based on a percentage of the total construction costs spent by BioMed to acquire the land and build the new facility. We will begin paying rent on January 1, 2012. Once the new facility is complete, we will be responsible for the costs associated with owning and maintaining the facility. Since our rent is based on a percentage of total construction costs spent by BioMed to acquire the land and build the new facility, and the facility is not yet built, it is difficult for us to calculate our future payment obligations under the lease. However, as of September 30, 2010, we estimate that the maximum potential future payments we may be required to make over the 20 year term of the lease are $172 million.

We also lease from BioMed an approximately 28,700 square foot facility that houses our manufacturing suites for our drug development business. On March 30, 2010 we amended the lease to extend the term through December 31, 2031, subject to four five-year options to extend the lease, and to obtain an option to purchase the manufacturing facility on similar terms as the purchase options described above.

In addition to contractual obligations, we had outstanding purchase orders as of September 30, 2010 for the purchase of services, capital equipment and materials as part of our normal course of business.

We plan to continue to enter into collaborations with partners to provide for additional revenue to us and we may be required to incur additional cash expenditures related to our obligations under any of the new agreements we may enter into. We currently intend to use our cash 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, 2009.

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 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.

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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 NSCLC 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 a new drug application 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 consistently profitable.

Our success will depend upon the medical community, patients and third-party payors accepting our products as medically useful, cost-effective and safe. 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 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;

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- 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.

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.

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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 its board approves. 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 these third parties conduct each of our clinical trials 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.

Risks Associated with our Businesses as a Whole

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

Because 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, 2010, we had an accumulated deficit of approximately $742.7 million and stockholders' equity of approximately $253.7 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from research grants and the sale or licensing of our patents as well as interest income. We 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.

Our corporate partners are developing and/or funding, many of the drugs in our development pipeline, including ATL, Atlantic Pharmaceuticals, Bristol-Myers Squibb, iCo, Eli Lilly and Company, OncoGenex, and Teva. In addition, we have 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, Eli Lilly and Company discontinued its investment in Affinitak.

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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.

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 and Bristol-Myers Squibb, 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 or Bristol-Myers Squibb, could determine that it is in its financial interest to:

- pursue alternative technologies or develop alternative products that may be competitive with the 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-C 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 preclinical studies for carcinogenicity to be included in the hoFH filing, which is now anticipated to take place in the first half of 2011. 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, or 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, 2010, we had cash, cash equivalents and short-term investments equal to $497.9 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.

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding September 30, 2010, the market price of our common stock ranged from $7.59 to $14.59 per share. On November 1, 2010, the closing price of our common stock on The Nasdaq Global Select Market was $9.01. 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 percent of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15 percent or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. We 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 $2^5/_8$ percent convertible subordinated notes, including the approximately 11.1 million shares issuable upon conversion of the notes. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

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, or PCAOB, or The Nasdaq Global Select Market. Any such action could adversely affect our financial results and the market price of our common stock.

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

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

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to changes in interest rates primarily from our long-term debt arrangements and, secondarily, investments in certain short-term investments. We invest our excess cash in highly liquid short-term investments that 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.

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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, 2010. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to September 30, 2010.

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 remains in its early stage. As such, we have no basis on which to predict or record a loss related to this claim as of September 30, 2010. 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. (REMOVED AND RESERVED)

Not applicable

ITEM 5. OTHER INFORMATION

Not applicable

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ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	First Amendment to Collaboration Research and License Agreement dated July 27, 2010 between Bristol Myers Squibb Company and the Registrant. *Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.*
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	The following financial statements from the Isis Pharmaceuticals, Inc. Quarterly Report on Form 10-Q for the quarter ended September 30, 2010, formatted in Extensive Business Reporting Language (XBRL): (i) condensed consolidated balance sheets, (ii) condensed consolidated statements of operations, (iii) condensed consolidated statements of cash flows, and (iv) notes to condensed consolidated financial statements (tagged as blocks of text).

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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 4, 2010
/s/ B. Lynne Parshall B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	November 4, 2010

Exhibit 10.1

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R §§ 200.80(b)4, AND 240.24b-2

Execution Copy

FIRST AMENDMENT

TO COLLABORATION RESEARCH AND LICENSE AGREEMENT

THIS FIRST AMENDMENT TO COLLABORATION AND LICENSE AGREEMENT (the "Amendment") is made and entered into effective as of July 27, 2010 (the "First Amendment Effective Date") by and between **Bristol-Myers Squibb Company**, a Delaware corporation ("BMS") and **Isis Pharmaceuticals, Inc.**, a Delaware Corporation ("Isis").

WHEREAS, BMS and Isis entered into a Collaboration and License Agreement effective May 8, 2007 (the "Collaboration Agreement") relating to the discovery, development and commercialization of ASOs targeting PCSK9;

WHEREAS, the initial 3-year Research Term for the conduct of the Research Program under the Collaboration Agreement ended May 8, 2010; and

WHEREAS, the Parties now desire to amend the Collaboration Agreement to extend the Research Term for the continuation of the Research Program in accordance with and subject to the Collaboration Agreement as amended by this Amendment.

NOW, THEREFORE in consideration of the foregoing and the mutual covenants herein contained, the Parties do hereby agree as follows.

1. Definitions. The terms in this Amendment with initial letters capitalized shall have the meaning set forth in this Amendment and if not defined in this Amendment shall have the meaning set forth in the Collaboration Agreement. Unless stated otherwise, reference to a Section refers to that Section in the Collaboration Agreement.

2. Extension of the Research Program. The initial Research Term under the Collaboration ended May 8, 2010. The Parties now desire to extend the Research Term (and the Research Term is hereby extended) to continue from May 8, 2010 for an additional period ending June 30, 2012 (such period being the "Extended Research Term"). BMS shall have the option to extend the Research Term for [***] additional [***] after such 2-year period in accordance with the provisions of Sections 3.2.1 and 3.2.2 as applied to such BMS option to extend the Research Term. The Research Program to be carried out during the Extended Research Term is referred to herein as the "Extended Research Program").

3. Research Plan for Extended Research Program. The Research Plan for the Extended Research Program is attached hereto as Attachment A.

4. FTE Funding and Research Program Cost Payments by BMS for Conduct of Extended Research Program. BMS shall fund the number of Isis FTEs as set forth in Attachment A hereto for the conduct of the Extended Research Program. Such FTE funding payments shall be made in accordance with Section 3.5.2 of the Collaboration Agreement, except that the first such payment which is for the 3rd Calendar Quarter of 2010 (for [***] Isis FTEs) shall be made within 30 days following the Amendment Effective Date. The budget for the Research Program Costs for the Extended Research Program are set forth in Attachment A hereto. The FTE Rate during the Extended Research Term shall be $[***] per FTE per year (i.e., without further adjustment).

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5. Success Compound. It is the objective of the Extended Research Program to identify one or more Success Compounds. "Success Compound" means a Compound identified during the Extended Research Program either (i) meeting both the Success Criteria and the [***] Criteria as reasonably determined by BMS or (ii) for which [***] has been initiated by BMS using [***] in accordance with [***] of the Collaboration Agreement. "Success Criteria" has the meaning set forth in Attachment A hereto. BMS shall act in good faith in its reasonable determination as to whether a Compound meets the Success Criteria.

6. [***]. "[***] Criteria" means a Compound which is or would be expected to be [***]) by a [***] during the Extended Research Term and which would be expected to have [***]). In order to meet the [***] Criteria a Compound must:

(1) [***]), and

(2) demonstrate in pre-clinical studies [***]. For clarity, a Compound having a [***], will satisfy the condition set forth in the foregoing clause (2).

If Isis disputes BMS' determination that a Compound has not met the [***] Criteria, Isis will provide BMS written notice thereof, and, notwithstanding Section 13.4 of the Agreement, the Parties will promptly refer the dispute to a mutually agreed [***] expert for resolution, and the determination by such expert will be binding on the Parties.

7. Additional Milestone Payments for First Success Compound. The following milestone payments would be payable by BMS for the first Success Compound to achieve the milestone:

$[***] [***]);

$[***] [***];

$[***] [***].

The milestone payments set forth above shall be payable by BMS within 60 days following the achievement of such milestone event (subject to Section 8 below).

For clarity, in addition to the milestones set forth above, Compounds (including without limitation any Success Compound(s)) resulting from the Extended Research Program will be subject to the milestone and royalty obligations (under Article 5 of the Collaboration Agreement), and other terms and conditions, as set forth in the Collaboration Agreement.

8. Termination.

8.1 BMS Right to Terminate Agreement at Time First Compound First Demonstrated to be Success Compound. At the time that the first Compound is demonstrated to achieve the Success Milestone, BMS shall have the right to elect to pay the Success Milestone payment (as set forth in Section 7 above) with the Collaboration Agreement continuing in effect in accordance with its terms as amended by this Amendment, or alternatively, BMS may elect at its discretion to terminate the Collaboration Agreement in its entirety by providing Isis with written notice of such termination within [***] days following such first achievement of the Success Milestone. Such termination of the Agreement shall be effective upon such written notice and Sections 9.5, 9.6.1 and 10.1 shall apply following such termination, *provided however*, that BMS shall have no obligation to pay the Success Milestone payment following such termination of the Agreement by BMS.

8.2 Reduction or Termination of Research Program Upon Payment of Success Milestone Payment. BMS shall have the right to reduce the scope of or terminate the Research Program, and accordingly reduce or terminate the further funding of Isis FTEs by BMS under Section 4 above, effective upon the [***]th day following written notice being given by BMS to Isis, which written notice by BMS may be given at any time following the first Compound becoming a Success Compound. In addition, Section 3.5 of the Collaboration Agreement shall apply to each Research Year during the Extended Research Term, with the "Research Year" during the Extended Research Term being the 12 month period beginning on July 1, and each such Research Year being deemed to be a "1 year extension of the Research Term" for purposes of Section 3.5. In addition, without limiting Section 3.5, the Parties may mutually agree in writing to reduce or change the scope of or terminate the Research Program (and accordingly reduce or terminate the further funding of Isis FTEs by BMS under Section 4 above).

8.3 For clarity, upon termination of the Collaboration Agreement pursuant to Article 9 of the Collaboration Agreement, BMS shall only be obligated to fund Isis FTEs under Section 4 above for the period prior to such termination (and shall have no obligation to fund Isis FTEs for the period thereafter).

9. No Other Amendment; Continuation of the Collaboration Agreement. This Amendment does not and shall not amend or modify the covenants, terms, conditions, rights and obligations of the Parties under the Collaboration Agreement except as specifically set forth herein. The Collaboration Agreement shall continue in full force and effect in accordance with its terms as amended by this Amendment.

10. Counterparts. This Amendment may be executed simultaneously in two or more counterparts, any one of which need not contain the signature of more than one party, but all such counterparts taken together shall constitute one and the same instrument, and may be executed and delivered through the use of email of pdf copies of the executed Amendment.

* * * signature page follows * * *

IN WITNESS WHEREOF, the Parties hereto intending to be legally bound have caused this Amendment to be executed by their duly authorized representatives.

BRISTOL-MYERS SQUIBB COMPANY

By: /s/ Arthur H. Bertelsen

Name: Arthur H. Bertelsen

Title: VP Research Collaborations

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall

Name: B. Lynne Parshall

Title: Chief Operating Officer and CFO

Attachment A

Research Plan for Extended Research Program

[***]

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 4, 2010

/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 4, 2010

/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, 2010, 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 4, 2010

/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.