SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

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

Date of report (Date of earliest event reported): **May 6, 2010**

ISIS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Charter)

Delaware
(State or Other Jurisdiction of Incorporation)

000-19125	**33-0336973**
(Commission File No.)	(IRS Employer Identification No.)

1896 Rutherford Road
Carlsbad, CA 92008
(Address of Principal Executive Offices and Zip Code)

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

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

o Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

o Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

o Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

o Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Item 2.02. Results of Operations and Financial Condition.

On May 6, 2010, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter ended March 31, 2010. In addition to disclosing results that are determined in accordance with Generally Accepted Accounting Principles (GAAP), the Company also disclosed pro forma results of operations, which are adjusted from GAAP to exclude non-cash compensation related to stock options. The Company is presenting pro forma information excluding the effects of the non-cash compensation expense or benefit because the Company believes it is useful for investors in assessing the Company's operating results compared to the prior year. A copy of the release is furnished with this report as an exhibit pursuant to "Item 2.02. Results of Operations and Financial Condition" of Form 8-K in accordance with SEC Release Nos. 33-8216 and 34-47583.

The information in this Current Report on Form 8-K and the Exhibit attached hereto shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933 or the Exchange Act, regardless of any general incorporation language in such filing.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

99.1 Press Release dated May 6, 2010.

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

ISIS PHARMACEUTICALS, INC.

Dated: May 6, 2010

By: /s/ B. Lynne Parshall
B. LYNNE PARSHALL
Chief Operating Officer, Chief Financial Officer and Director

INDEX TO EXHIBITS

99.1	Press Release dated May 6, 2010.

ISIS REPORTS FINANCIAL RESULTS AND HIGHLIGHTS FOR FIRST QUARTER 2010

- **Conference Call Webcast Thursday, May 6, 8:30 a.m. ET at www.isispharm.com**

CARLSBAD, Calif., May 6, 2010 - Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced its financial results for the quarter ended March 31, 2010. The Company finished the first quarter of 2010 with a pro forma net operating loss (NOL) of $1.5 million compared to pro forma net operating income of $2.1 million in the first quarter of 2009. On a GAAP basis, Isis reported a net operating loss of $4.9 million for the three months ended March 31, 2010, compared to $642,000 for the same period in 2009. Isis' operating results in the first quarter of 2010 reflect a slight decrease in revenue and a slight increase in operating expenses compared to the same period last year. In the first quarter of 2010, Isis earned a $6 million milestone payment when Bristol-Myers Squibb (BMS) initiated Phase 1 studies on PCSK9, which was offset by the planned reduction in revenue related to the completion of amortization of the upfront fee that Isis received from Ortho-McNeil. The slight increase in Isis' operating expenses was due to an expected increase in research and development activities. As a result of adopting a new required accounting standard, Isis' 2010 NOL no longer includes Regulus' financial results. This accounting change has had a nominal effect on the Company's NOL, it has also meant that Isis no longer includes Regulus' cash in Isis' cash balance. The Company provides more details on the impact of this new standard on Isis' financial statements throughout the remainder of this release.

"The first quarter was a great start to 2010. We reported another positive Phase 3 study for mipomersen and continued our partnering successes with, most notably, our new preferred partnership with GSK. Over the last three years, we have significantly strengthened our balance sheet, bringing in over $650 million in cash. This financial strength provides us with the freedom to pursue new types of partnerships, such as our GSK partnership to develop antisense drugs for rare, ocular and infectious diseases. This alliance is exactly the type of deal we want to do. We retain control of the discovery and early development of our drugs while working together with a very high-quality partner to maximize the value of the drugs in late-stage development and commercialization. If all six programs are successful, we could receive nearly $1.5 billion from licensing fees and milestone payments with up to $155 million of that prior to licensing, including the $35 million upfront fee we recently received," said B. Lynne Parshall, COO and CFO of Isis. "Already this year, we have received more than $55 million from our partners, including the GSK upfront fee, a milestone payment from BMS related to the initiation of the PCSK9 Phase 1 clinical studies and the sublicensing fee from OncoGenex' licensing of OGX-011 to Teva. As a result, we are on track to exceed our guidance for the year. Since our current guidance does not include the effect of any significant new transactions, we plan to restate our guidance in the middle of the year."

Upcoming Key Milestones

- Report data from a Phase 3 study evaluating mipomersen in patients with severe high cholesterol (mid 2010)
- Report data from a Phase 3 study evaluating mipomersen in high-cholesterol patients at high risk for coronary heart disease (mid 2010)
- Report full data from the positive Phase 3 study evaluating mipomersen in heterozygous FH patients; top-line data reported in February 2010
- Complete and report data from the Phase 1 study of ISIS-CRP_{Rx} and begin a broad Phase 2 program
- Report Phase 1 data on ISIS-$GCGR_{Rx}$, full data from a Phase 2 study on ISIS113715 and data on multiple preclinical programs at the upcoming American Diabetes Association meeting
- OncoGenex and Teva to begin the broad Phase 3 program for OGX-011

Financial Results

Beginning in the first quarter of 2010, as a result of adopting a new required accounting standard, Isis is no longer including Regulus' revenue and operating expenses in its operating results and no longer including Regulus' cash in its balance sheet. Instead Isis is presenting its share of Regulus' operating results on a separate line in its statement of operations called "Equity in net loss of Regulus Therapeutics Inc." On its balance sheet, Isis is presenting its investment in Regulus on a separate line called "Investment in Regulus Therapeutics Inc." This new standard improves the operating expenses and NOL reported in Isis' financial statements while not significantly affecting the Company's net loss. The exclusion of Regulus' cash from total assets on the balance sheet results in a reduction in Isis' assets. A reconciliation presenting Isis' 2009 operating results on a comparable basis to 2010 appears later in this release.

All pro forma amounts referred to in this press release exclude non-cash stock compensation. Please refer to the reconciliation of pro forma and GAAP measures, which is explained later in this release.

Revenue

Revenue for the three months ended March 31, 2010 was $29.9 million, compared to $31.6 million for the same period in 2009. Isis' revenue fluctuates based on the nature and timing of payments under agreements with the Company's partners, including license fees, milestone-related payments and other payments. For example, Isis' revenue in the first quarter of 2010 included a $6 million milestone payment that Isis received from BMS for initiating Phase 1 studies on PCSK9. Although Isis recognized revenue from the BMS milestone payment in the first quarter of 2010, its revenue compared to the same period in 2009 decreased slightly, primarily because the amortization of the upfront fee from the Ortho-McNeil collaboration ended in the third quarter of 2009. Revenue also decreased by $638,000 because Isis is no longer including Regulus' revenue in its 2010 revenue. In the second quarter of 2010, Isis will begin amortizing the $35 million upfront payment it received from its recent alliance with GSK into revenue through March 2015.

Operating Expenses

On a pro forma basis, operating expenses for the three months ended March 31, 2010 were $31.5 million, compared to $29.5 million for the same period in 2009. The higher expenses in 2010 were primarily due to an increase in development activities related to the ongoing mipomersen development program and the research activities necessary to achieve Isis' goal of adding three to five new drugs to its pipeline offset by a $2.8 million decrease because Isis is no longer including Regulus' operating expenses in its 2010 operating expenses. On a GAAP basis, Isis' operating expenses from continuing operations for the three months ended March 31, 2010 were $34.8 million, compared to $32.2 million for the same period in 2009.

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

Net loss from continuing operations for the three months ended March 31, 2010 was $9.7 million, compared to $778,000 for the same period in 2009. The increase in Isis' net loss from continuing operations was primarily due to the following:

- $4.2 million increase in Isis' net operating loss;
- $1.2 million decrease in investment income due to a lower average cash balance and a lower average return on investments resulting from the current market conditions; and
- $880,000 in a non-cash loss related to the impairment of Isis' equity investment in Antisense Therapeutics Limited.

Net Income (Loss)

Isis reported a net loss of $9.7 million for the three months ended March 31, 2010, compared to net income of $186.2 million for the same period in 2009. Basic and diluted net loss per share for the three months ended March 31, 2010 was $0.10 per share, compared to basic and diluted net income per share of $1.91 for the same period in 2009. Net income and net income per share in 2009 primarily consisted of the $187.0 million gain, net of tax, which Isis recognized when it sold its subsidiary, Ibis Biosciences, to Abbott Molecular Inc. in the first quarter of 2009.

Balance Sheet

As of March 31, 2010, Isis had cash, cash equivalents and short-term investments of $519.1 million compared to $574.3 million at December 31, 2009 and had working capital of $438.3 million at March 31, 2010 compared to $484.7 million at December 31, 2009. The decrease in cash and working capital primarily relates to cash used in the first quarter of 2010 for Isis' operations, including a $7.7 million payment that Isis made for 2009 income taxes, along with a $30.7 million decrease because Isis is no longer including Regulus' cash in its cash balance. Isis' cash balance at March 31, 2010 does not include the $35 million upfront payment that the Company received in April 2010 from its recent preferred partnership with GSK. Including the money from GSK, so far in 2010, Isis has received more than $55 million from its corporate partnerships. Isis is confident that it will meet its 2010 guidance of more than $425 million of cash at the end of the year.

Business Highlights

"We and Genzyme continue to make excellent progress moving mipomersen toward the market. Together, we have already reported very positive data from two Phase 3 studies on mipomersen and will complete and report the remaining two Phase 3 studies in the middle of this year. Data from our first Phase 3 study in homozygous FH patients were recently published and featured in The Lancet, demonstrating that the academic and medical communities share our enthusiasm for mipomersen as a novel new therapeutic to treat patients with high cholesterol and high cardiovascular risk who cannot sufficiently reduce that risk with existing therapies. Together with Genzyme we are making progress preparing for our first NDA filings for mipomersen in the U.S. and Europe, and we remain on track to file both in the first half of 2011. Furthermore, we and Genzyme continue to make substantial headway in planning for the next regulatory filings outside of the U.S. and Europe. We look forward to sharing more mipomersen news with you this year," continued Ms. Parshall.

"We have a rich and diverse pipeline that is much more than mipomersen. Although we have an almost unlimited number of promising targets we could pursue, there are many factors that we consider when selecting targets and moving programs forward in development. For example, we select targets that take advantage of the properties of our antisense drugs and that are generally undruggable by other methods. This has allowed us to create a diverse pipeline of drugs that could provide significant therapeutic benefit to patients in need. The success of our drug discovery efforts is evident every quarter in the clinical advances of the drugs in our pipeline. Already this year, we have begun a clinical study on our SOD1 drug in patients with Lou Gehrig's disease. Our partner BMS initiated a Phase 1 study on our PCSK9 drug, an exciting cardiovascular target, which could offer a complimentary mechanism to mipomersen to reduce cholesterol. We have begun another productive year in which we expect to have more news as drugs in our pipeline advance. We will continue to invest in our technology and expand the therapeutic applications for antisense drugs, and we will expand our pipeline," concluded Ms. Parshall.

Drug Development Highlights

- Mipomersen is being developed by Isis and Genzyme for patients with high cardiovascular risk who cannot adequately control their cholesterol levels with current therapies and who need new treatment options. Isis and Genzyme reported positive data from two Phase 3 studies evaluating mipomersen in patients with familial hypercholesterolemia (FH).
  - The full data from a Phase 3 study evaluating mipomersen in patients with homozygous FH were featured and published in The Lancet.
  - In a Phase 3 study evaluating mipomersen in patients with heterozygous FH, Isis and Genzyme reported that the study met its primary endpoint with a 28% reduction in LDL-C after 26 weeks of treatment compared to an increase of 5% for placebo ($p<0.001$) and also met all of its secondary endpoints. Patients treated with mipomersen had an average LDL-C level of 104 mg/dL at the end of the study and 45% of the mipomersen-treated patients achieved LDL-C levels of less than 100 mg/dL.
- Isis and its partners initiated clinical studies on two drugs including Phase 1 studies on ISIS-SOD1$_{Rx}$ and BMS-PCSK9$_{Rx}$.

Corporate Highlights

- Isis formed a new strategic alliance worth up to nearly $1.5 billion with GSK to develop antisense drugs to treat rare and infectious diseases.
  - Isis is eligible to receive up to $155 million in pre-licensing payments for all six programs, including the $35 million upfront fee Isis recently received. Isis is also eligible to receive up to double-digit royalties on sales from any product that is successfully commercialized.
- Isis benefited financially as its partners advanced drugs in development.
  - Isis received $6 million in a milestone payment from BMS.
- Regulus formed a new alliance with GSK to develop and commercialize microRNA therapeutics targeting miR-122 for hepatitis C viral infection.

Conference Call

At 08:30 a.m. Eastern Time today, May 6, Isis will conduct a live webcast conference call to discuss this earnings release and related activities. Interested parties may listen to the call by dialing 866-783-2146 and refer to passcode "ISIS 2010," or access the webcast at www.isispharm.com. A webcast replay will be available for a limited time at the same address.

About Isis Pharmaceuticals, Inc.

Isis is exploiting its expertise in RNA to discover and develop novel drugs for its product pipeline and for its partners. The Company has successfully commercialized the world's first antisense drug and has 22 drugs in development. Isis' drug development programs are focused on treating cardiovascular,

metabolic, and severe neurodegenerative diseases and cancer. Isis' partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. Isis and Alnylam Pharmaceuticals are joint owners of Regulus Therapeutics Inc., a company focused on the discovery, development and commercialization of microRNA therapeutics. Isis also has made significant innovations beyond human therapeutics resulting in products that other companies, including Abbott, are commercializing. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of over 1,600 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

Forward Looking Statements

This press release includes forward-looking statements regarding Isis Pharmaceuticals' business, the financial position and outlook for Isis as well as Regulus its majority-owned subsidiary, and the therapeutic and commercial potential of the Company's technologies and products in development. Any statement describing Isis' 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. Isis' forward-looking statements also involve assumptions that, if

they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2009, which is on file with the SEC. Copies of this and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries, including Regulus Therapeutics Inc.

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ISIS PHARMACEUTICALS, INC.
SELECTED FINANCIAL INFORMATION
Condensed Consolidated Statements of Operations
(In Thousands, Except Per Share Data)

	Three months ended, March 31,	
	2010	2009(1)
	(unaudited)	
Revenue:		
Research and development revenue under collaborative agreements	$ 28,556	$ 29,685
Licensing and royalty revenue	1,370	1,891
Total revenue	29,926	31,576
Expenses:		
Research and development	31,987	28,541
General and administrative	2,819	3,677
Total operating expenses	34,806	32,218
Loss from operations	(4,880)	(642)
Other income (expense):		
Equity in net loss of Regulus Therapeutics Inc.	(1,486)	—
Investment income	955	2,134
Interest expense	(3,237)	(3,081)
Gain (loss) on investments, net	(1,010)	58
Loss from continuing operations, before income tax expense	(9,658)	(1,531)
Income tax expense	—	(160)
Net loss from continuing operations	(9,658)	(1,691)
Discontinued operations:		
Loss from discontinued operations	—	(29)
Gain on sale of Ibis Biosciences, Inc., net of tax	—	187,025
Net income (loss) from discontinued operations, net of tax	—	186,996
Net income (loss)	(9,658)	185,305
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	—	913
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (9,658)	$ 186,218
Basic and diluted net income (loss) per share:		
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.10)	$ (0.01)
Net income from discontinued operations	—	1.92
Basic and diluted net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.10)	$ 1.91

Shares used in computing basic and diluted net income (loss) per share	99,013	97,521

(1) During the preparation of the year end 2009 annual tax provision, Isis determined that certain tax items had been attributed to discontinued operations that are appropriately associated with continuing operations. As a result, Isis 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 operations for the three months ended March 31, 2009 reflects the revised tax provisions.

Isis Pharmaceuticals, Inc.
Reconciliation of Isis' 2009 Statement of Operations
Adjusted for Regulus Therapeutics Inc.
(In Thousands, Except Per Share Data)
(unaudited)

	Three months ended March 31, 2009 (as reported)	Adjustments for Regulus(1)	Three months ended March 31, 2009 (as adjusted)
Revenue:			
Research and development revenue under collaborative agreements	$ 29,685	$ (638)	$ 29,047
Licensing and royalty revenue	1,891	—	1,891
Total revenue	31,576	(638)	30,938
Expenses:			
Research and development	28,541	(1,844)	26,697
General and administrative	3,677	(659)	3,018
Total operating expenses	32,218	(2,503)	29,715
Income (loss) from operations	(642)	1,865	1,223
Other income (expense):			
Equity in net loss of Regulus Therapeutics Inc.	—	(2,789)	(2,789)
Investment income	2,134	(59)	2,075
Interest expense	(3,081)	40	(3,041)
Gain on investments	58	—	58
Income (loss) from continuing operations, before income tax expense	(1,531)	(943)	(2,474)
Income tax expense	(160)	—	(160)
Net income (loss) from continuing operations	(1,691)	(943)	(2,634)
Discontinued operations:			
Loss from discontinued operations	(29)	—	(29)
Gain on sale of Ibis Biosciences, Inc., net of tax	187,025	—	187,025
Net loss from discontinued operations, net of tax	186,996	—	186,996
Net income	185,305	(943)	184,362
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	913	(913)	—
Net income attributable to Isis Pharmaceuticals, Inc. common stockholders	$ 186,218	$ (1,856)	$ 184,362
Basic and diluted net income (loss) per share:			
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.01)		$ (0.03)
Net income from discontinued operations	1.92		1.92
Basic and diluted net income	$ 1.91		$ 1.89
Shares used in computing basic and diluted net income (loss) per share	97,521		97,521

(1) Assuming Isis would have adopted the new accounting standard retrospectively, these are the adjustments that would have been made to Isis' 2009 Statement of Operations.

Isis Pharmaceuticals, Inc.

Reconciliation of GAAP to Pro Forma Basis:
Condensed Consolidated Operating Expenses, Income (Loss) From Operations and Net Income (Loss)
(In Thousands)

	Three months ended, March 31, 2010	2009
	(unaudited)	
As reported operating expenses according to GAAP	$ 34,806	$ 32,218
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(3,356)	(2,703)
Pro forma operating expenses	$ 31,450	$ 29,515

As reported loss from operations according to GAAP	$ (4,880)	$ (642)
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(3,356)	(2,703)
Pro forma income (loss) from operations	$ (1,524)	$ 2,061

Reconciliation of GAAP to Pro Forma Basis

As illustrated in the Selected Financial Information in this press release, pro forma operating expenses, pro forma loss from operations and pro forma net income (loss) were adjusted from GAAP to exclude compensation expense related to stock options, which are non-cash. Isis has regularly reported non-GAAP measures for operating expenses and loss from operations as pro forma results. These measures are provided as supplementary information and are not a substitute for financial measures calculated in accordance with GAAP. Isis reports these pro forma results to better enable financial statement users to assess and compare its historical performance and project its future operating results and cash flows. Further, the presentation of Isis' pro forma results is consistent with how Isis' management internally evaluates the performance of its operations.

Isis Pharmaceuticals, Inc.
Condensed Consolidated Balance Sheets
(In Thousands)

	March 31, 2010 (unaudited)	December 31, 2009
Assets:		
Cash, cash equivalents and short-term investments	$ 519,119	$ 574,312
Other current assets	11,296	21,814
Property, plant and equipment, net	36,171	27,338
Other assets	33,137	33,720
Total assets	$ 599,723	$ 657,184
Liabilities and stockholders' equity:		
Other current liabilities	$ 21,205	$ 35,763
Current portion of deferred contract revenue	70,890	75,681
2 5/8% convertible subordinated notes	126,986	125,100
Long-term obligations, less current portion	14,621	11,478
Investment in Regulus Therapeutics Inc.	127	—
Long-term deferred contract revenue	81,457	107,097
Stockholders' equity	284,437	302,065
Total liabilities and stockholders' equity	$ 599,723	$ 657,184

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