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): **November 4, 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 November 4, 2010, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter ended September 30, 2010. In addition to disclosing results that are determined in accordance with Generally Accepted Accounting Principles (GAAP), the Company also discloses pro forma or non-GAAP 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 November 4, 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: November 4, 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 November 4, 2010.

ISIS REPORTS FINANCIAL RESULTS AND HIGHLIGHTS FOR THIRD QUARTER 2010

· **Conference Call Webcast Thursday November 4, 4:30 p.m. ET at www.isispharm.com**

CARLSBAD, Calif., November 4, 2010 - Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced its financial results for the quarter ended September 30, 2010. The Company finished the third quarter of 2010 with a pro forma net operating loss (NOL) of $6.0 million and $23.1 million for the three and nine months ended September 30, 2010, respectively, compared to a pro forma net operating loss of $6.9 million and $6.1 million for the same periods in 2009. On a GAAP basis, Isis reported a loss from operations of $8.9 million and $32.5 million for the three and nine months ended September 30, 2010, respectively, compared to $10.4 million and $15.9 million for the same periods in 2009.

"In 2010, our most notable accomplishment is the completion of two more positive Phase 3 studies of mipomersen. The successful completion of the Phase 3 program for mipomersen to support our initial market brings us closer to the commercialization of a first-in-class drug for patients who are in desperate need of new therapies. Genzyme is on track to file for marketing approval of mipomersen in both the U.S. and Europe in the first half of next year. We believe that the initial market for mipomersen represents a significant financial opportunity, and we are excited to bring this new medicine to an underserved patient population," said B. Lynne Parshall, COO and CFO of Isis.

"We continue to maintain a strong financial position in large part due to our partnership successes that have continued to generate new revenue for us. For example, our 2010 revenue includes the amortization of upfront fees from our new collaboration with GSK and new sublicensing revenue from Regulus' alliance with sanofi-aventis. In addition, we have earned $13 million in milestone payments from our partners. We earned many of these milestone payments in the middle of this year. When we look at the remainder of 2010, we do not anticipate receiving any significant milestone payments; therefore we expect that our revenue in the fourth quarter will be less than in earlier quarters. Additionally in the fourth quarter, we have a number of internal drugs that are advancing in clinical development. We will begin two Phase 2 programs for our CRP and eIF-4E drugs and two Phase 1 programs for our FXI and APOCIII drugs. We will also expand our development pipeline. These activities will result in an increase in our expenses in the fourth quarter. Even with these changes, we are on track to meet or improve upon the revised guidance of a pro forma net operating loss in the mid to high $40 million range and year-end cash of more than $450 million that we announced in August."

Upcoming Key Milestones

- Genzyme expects to file for marketing approval for mipomersen in the U.S. and E.U. in the first half of 2011
- Report full data from the positive Phase 3 studies evaluating mipomersen in high-cholesterol patients at high risk for coronary heart disease and in patients with severe hypercholesterolemia
- Initiate the broad Phase 2 program of ISIS-EIF4E$_{Rx}$ in patients with cancer
- Complete and report data from the Phase 1 study of ISIS-CRP$_{Rx}$ and initiate the Phase 2 program
- Excaliard to complete and report data from the remaining Phase 2 studies of EXC 001

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 and debt on its balance sheet. 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 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. 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. Isis recognized new revenue in the first nine months of 2010 in the form of an upfront fee from the Company's new partnership with GlaxoSmithKline (GSK), which is amortized through the first quarter of 2015, milestone payments from GSK, Bristol-Myer Squibb and Achaogen and sublicensing income from Regulus' collaboration with sanofi-aventis. Although Isis recognized this new revenue, its revenue for 2010 decreased compared to 2009 because the amortization of the upfront fee from the Company's Ortho-McNeil collaboration ended in the third quarter of 2009. Additionally, revenue for the first nine months of 2010 decreased by $2.4 million because Isis is no longer including Regulus' revenue in its 2010 revenue.

Operating Expenses

On a pro forma basis, operating expenses for the three and nine months ended September 30, 2010 were $34.6 million and $105.1 million, respectively, compared to $33.6 million and $95.4 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 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 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.

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

Net loss from continuing operations 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 Isis' net loss from continuing operations for the nine months was primarily due to the following:

- $22.5 million increase in net operating loss, excluding Regulus, as described above;

- $3.4 million increase in Isis' share of Regulus' net loss;
- $2.7 million decrease in investment income due to a lower average return on investments resulting from the current market conditions and a lower average cash balance; and
- $880,000 non-cash loss that Isis recognized in 2010 related to the impairment of its equity investment in Antisense Therapeutics Limited compared to a $2.5 million gain in 2009 from the sale of OncoGenex common stock that Isis owned.

Net Income (Loss)

Isis reported a net loss of $12.5 million and $47.3 million for the three and nine months ended September 30, 2010, 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 per share of $0.12 for the three months ended September 30, 2009 and 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 Isis recognized when it sold its subsidiary, Ibis Biosciences, to Abbott Molecular Inc. in the first quarter of 2009.

Balance Sheet

As of September 30, 2010, Isis had cash, cash equivalents and short-term investments of $497.9 million compared to $574.3 million at December 31, 2009 and had working capital of $406.6 million at September 30, 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 nine months of 2010 for Isis' operations, including a $7.7 million payment that Isis made for 2009 income taxes. Isis' cash and working capital also decreased because Isis is no longer including Regulus' cash, which was $30.7 million at December 31, 2009, in Isis' cash balance.

Business Highlights

"The performance of mipomersen continues to be consistent across the entire Phase 3 program with four positive Phase 3 studies in which all primary, secondary and tertiary endpoints were met with statistical significance," continued Ms. Parshall. "The robust efficacy we have observed for mipomersen, combined with a safety profile that is emerging as we gain more patient exposure experience, support our initial market opportunity for mipomersen in patients who, despite being treated with maximally tolerated lipid-lowering therapies, are far from their recommended LDL-C goal and as a result are at high risk for a cardiovascular event or death.

"Our other partners continue to advance the drugs in our pipeline with the initiation of multiple Phase 2 and Phase 3 studies. For example, Teva and OncoGenex initiated a broad Phase 3 program in cancer for OGX-011. Our partner, Excaliard, presented positive clinical data on EXC 001 from the first of three Phase 2 studies showing the value of antisense drugs delivered locally for the treatment of fibrosis and opening up new market opportunities. Most recently, sanofi-aventis made a $10 million investment in Regulus, providing external establishment of the significant value of our Regulus ownership. Overall the progress we and our partners have made this year provide a snapshot of the potential of our technology and our pipeline as well as the significant upside for Isis as our partners continue to advance the drugs in our pipeline. Already this year, we have earned more than $65 million from our partnerships," concluded Ms. Parshall.

Drug Development and Corporate Highlights

- Mipomersen is being developed by Isis 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. Isis 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.
- Isis 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, Isis 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, Isis 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 reactions and flu-like symptoms. Elevations in liver transaminases were observed that were generally similar in character with those seen in other studies.
- Isis added to its pipeline ISIS-GSK1$_{Rx}$, the first drug selected as part of its collaboration with GSK to treat severe and rare diseases.
- Isis' partners continued to advance the drugs in Isis' pipeline with the initiation of two Phase 3 studies for OGX-011, and a Phase 2 study for OGX-427 in patients with cancer.
- Isis benefits financially as the drugs in its 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.
- Isis' 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 Isis.

Conference Call

At 4:30 p.m. Eastern Time today, November 4, 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 866-804-6924 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 more than 1,500 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 jointly 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 and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these 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.

Isis Pharmaceuticals' Contacts:

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

	Three months ended, September 30,		Nine months ended, September 30,	
	2010	2009(1)	2010	2009(1)
	(unaudited)		(unaudited)	
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,	$ (0.13)	$ (0.12)	$ (0.48)	$ 1.75

Inc. common stockholders				
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, 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 statements of operations for the three and nine months ended September 30, 2009 reflect 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)

	Nine months ended September 30, 2009 (as reported)	Adjustments for Regulus(1)	Nine months ended September 30, 2009 (as adjusted)
Revenue:			
Research and development revenue under collaborative agreements	$ 86,415	$ (2,388)	$ 84,027
Licensing and royalty revenue	2,924	—	2,924
Total revenue	89,339	(2,388)	86,951
Expenses:			
Research and development	94,519	(6,282)	88,237
General and administrative	10,685	(1,982)	8,703
Total operating expenses	105,204	(8,264)	96,940
Loss from operations	(15,865)	5,876	(9,989)
Other income (expense):			
Equity in net loss of Regulus Therapeutics Inc.	—	(4,666)	(4,666)
Investment income	5,241	(141)	5,100
Interest expense	(9,421)	122	(9,299)
Gain on investments	2,794	(3)	2,791
Loss from continuing operations, before income tax expense	(17,251)	1,188	(16,063)
Income tax expense	(873)	—	(873)
Net loss from continuing operations	(18,124)	1,188	(16,936)
Discontinued operations:			
Loss from discontinued operations	(29)	—	(29)
Gain on sale of Ibis Biosciences, Inc., net of tax	187,153	—	187,153
Net income from discontinued operations, net of tax	187,124	—	187,124
Net income	169,000	1,188	170,188
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	2,906	(2,906)	—
Net income attributable to Isis Pharmaceuticals, Inc. common stockholders	$ 171,906	$ (1,718)	$ 170,188
Basic and diluted net income (loss) per share:			
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.16)		$ (0.17)
Net income from discontinued operations	1.91		1.91
Basic and diluted net income	$ 1.75		$ 1.74
Shares used in computing basic and diluted net income (loss) per share	97,988		97,988

(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 and Income (Loss) From Operations
(In Thousands)

	Three months ended, September 30,		Nine months ended, September 30,	
	2010	2009	2010	2009
	(unaudited)		(unaudited)	
As reported operating expenses according to GAAP	$ 37,571	$ 37,167	$ 114,551	$ 105,204
Excluding compensation expense related to stock options	(2,960)	(3,546)	(9,448)	(9,814)

Pro forma operating expenses	$ 34,611	$ 33,621	$ 105,103	$ 95,390
As reported loss from operations according to GAAP	$ (8,947)	$ (10,396)	$ (32,498)	$ (15,865)
Excluding compensation expense related to stock options	(2,960)	(3,546)	(9,448)	(9,814)
Pro forma loss from operations	$ (5,987)	$ (6,850)	$ (23,050)	$ (6,051)

Reconciliation of GAAP to Pro Forma Basis

As illustrated in the Selected Financial Information in this press release, pro forma operating expenses and pro forma income (loss) from operations 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 income (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)

	September 30, 2010 (unaudited)	December 31, 2009
Assets:		
Cash, cash equivalents and short-term investments	$ 497,904	$ 574,312
Other current assets	9,646	21,814
Property, plant and equipment, net	35,549	27,338
Other assets	32,759	33,720
Total assets	$ 575,858	$ 657,184
Liabilities and stockholders' equity:		
Other current liabilities	$ 23,648	$ 35,763
Current portion of deferred contract revenue	77,268	75,681
2 5/8% convertible subordinated notes	130,882	125,100
Long-term obligations, less current portion	14,451	11,478
Investment in Regulus Therapeutics Inc.	5,000	—
Long-term deferred contract revenue	70,900	107,097
Stockholders' equity	253,709	302,065
Total liabilities and stockholders' equity	$ 575,858	$ 657,184

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