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 5, 2011**

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 5, 2011, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter ended March 31, 2011. 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 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 5, 2011.

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 5, 2011

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 5, 2011.

ISIS REPORTS FINANCIAL RESULTS AND HIGHLIGHTS FOR FIRST QUARTER 2011

· **Conference Call Webcast Thursday, May 5, 4:30 p.m. ET at www.isispharm.com**

CARLSBAD, Calif., May 5, 2011 - Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced its financial results for the quarter ended March 31, 2011. The Company finished the first quarter of 2011 with a pro forma net operating loss (NOL) of $13.4 million compared to a pro forma NOL of $1.5 million in the first quarter of 2010. The Company finished the first quarter of 2011 with nearly $427 million in cash. Isis remains on track to meet its 2011 guidance of an NOL in the low $40 million range and a year-end cash balance of more than $350 million.

"The first quarter of 2011 has been very productive for Isis. Together with Genzyme, we reported the remaining data from our Phase 3 program that will support the first regulatory filings for mipomersen marketing approval in Europe for both homozygous FH and severe heterozygous FH, and in the United States for homozygous FH. Work is progressing well on these filings, bringing us closer to making mipomersen available to patients who are at great risk of dying from their cardiovascular disease," said B. Lynne Parshall, COO and CFO of Isis. "Marketing approval of mipomersen would be an important milestone for Isis and antisense technology, and would provide us with the opportunity to earn significant commercial revenue. Mipomersen would be the first systemic antisense drug to be commercialized, and we look forward to bringing mipomersen to patients in need."

Upcoming Key Milestones

· File for marketing approval for mipomersen in Europe early in the third quarter of 2011 for patients with homozygous FH and severe heterozygous FH
· File for marketing approval for mipomersen in the United States in the second half of 2011 for patients with homozygous FH

Financial Results

On a GAAP basis, Isis reported a NOL of $16.1 million for the three months ended March 31, 2011, compared to $4.9 million for the same period in 2010.

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 provided later in this release.

Revenue

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

Operating Expenses

On a pro forma basis, operating expenses for the three months ended March 31, 2011 were $34.5 million, compared to $31.5 million for the same period in 2010. The higher expenses in 2011 were primarily due to an increase in costs associated with Isis' maturing pipeline of drugs. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the costs of development increase. On a GAAP basis, Isis' operating expenses for the three months ended March 31, 2011 were $37.3 million, compared to $34.8 million for the same period in 2010.

Net Loss

Isis reported a net loss of $20.0 million for the three months ended March 31, 2011 compared to $9.7 million for the same period in 2010. Basic and diluted net loss per share for the three months ended March 31, 2011 was $0.20 per share, compared to $0.10 per share for the same period in 2010. The increase in Isis' net loss was primarily due to an $11.2 million increase in Isis' net operating loss described above.

Balance Sheet

As of March 31, 2011, Isis had cash, cash equivalents and short-term investments of $426.8 million compared to $472.4 million at December 31, 2010 and had working capital of $343.0 million at March 31, 2011 compared to $377.2 million at December 31, 2010. The decrease in cash and working capital primarily relates to cash used to fund Isis' operations.

Business Highlights

"The most significant event for Isis this year will be the submission of regulatory filings for mipomersen in both the United States and Europe. Together with Genzyme, we have completed four Phase 3 studies that will form a comprehensive package for our first regulatory filings for mipomersen. In all four studies, we observed consistent and robust efficacy with a safety profile that supports our initial market opportunities in patients who, despite being treated with maximally tolerated lipid-lowering therapies, are far from their recommended LDL-C goal. Mipomersen also lowers all other atherogenic lipids linked to cardiovascular disease and thus may provide substantial cardiovascular benefit to these patients, who are under-treated, often under-diagnosed, and at extreme

risk of cardiovascular death. In addition, we now have patients who have been successfully treated for as long as three years in our open-label studies. The overall safety profile, including the long-term exposure data, supports our development plan to treat patients who are at very high-risk of a cardiovascular-related death. In addition, together with Genzyme, we are making progress toward initiating a 12-month study to provide additional patient exposure to support a regulatory filing in the United States for severe heterozygous FH patients," continued Ms. Parshall.

"We anticipate having a steady flow of pipeline progress throughout the year, as we identify new drugs to move into our pipeline and advance a number of our drugs in clinical development. Already this year, we have reported data from our CRP drug, demonstrating, for the first time, that a selective CRP inhibitor could dramatically reduce the levels of CRP. We are ready to initiate Phase 2 studies on our CRP drug, in which we hope to demonstrate proof-of-concept and inform a broad development path in multiple diseases, each with a significant commercial opportunity. We have also made progress moving drugs into the clinic, including initiating a Phase 1 study on our anti-thrombotic drug that targets Factor XI and we are ready to begin a Phase 1 study on ISIS-TTR_{Rx}, the first drug advanced in our collaboration with GSK. We are continuing to work with GSK to identify the next drug to move forward, which should expand our severe and rare disease pipeline. Drugs for rare diseases typically have a very clear association between the target and the disease with the potential for a smaller, more rapid development program. Developing drugs to treat severe and rare diseases offers us the opportunity to quickly advance a drug through development to treat patients who have few or no therapeutic options while balancing programs in our pipeline to treat diseases for which larger, longer clinical studies are required. In summary, we have begun another eventful year, and we look forward to sharing more mipomersen and other news with you as the year progresses," concluded Ms. Parshall.

Corporate and Drug Development Highlights

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

Conference Call

At 4:30 p.m. Eastern Time today, May 5, 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 866-362-4832 and refer to passcode "ISIS 2011," 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 24 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 has designed and executed a patent strategy that has provided the Company with strong and extensive protection for Isis' drugs and technology. 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, 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, 2010, 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., its jointly owned subsidiary.

Isis Pharmaceuticals' Contacts:

Kristina Lemonidis
Director, Corporate Communications
760-603-2490

Amy Blackley, Ph.D.
Assistant Director, Corporate Communications
760-603-2772

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

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

Isis Pharmaceuticals, Inc.
Reconciliation of GAAP to Pro Forma Basis:
Condensed Consolidated Operating Expenses and Loss From Operations
(In Thousands)

	Three months ended, March 31,	
	2011	2010
	(unaudited)	
As reported operating expenses according to GAAP	$ 37,255	$ 34,806
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(2,732)	(3,356)
Pro forma operating expenses	$ 34,523	$ 31,450
As reported loss from operations according to GAAP	$ (16,108)	$ (4,880)
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(2,732)	(3,356)
Pro forma loss from operations	$ (13,376)	$ (1,524)

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 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 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, 2011 (unaudited)	December 31, 2010
Assets:		
Cash, cash equivalents and short-term investments	$ 426,822	$ 472,353
Other current assets	10,573	10,784
Property, plant and equipment, net	37,680	35,703
Other assets	30,867	31,637
Total assets	$ 505,942	$ 550,477
Liabilities and stockholders' equity:		
Other current liabilities	$ 21,007	$ 31,388
Current portion of deferred contract revenue	73,392	74,502
2 5/8% convertible subordinated notes	134,964	132,895
Long-term obligations, less current portion	15,085	15,867
Investment in Regulus Therapeutics Inc.	1,726	870
Long-term deferred contract revenue	32,065	50,413
Stockholders' equity	227,703	244,542
Total liabilities and stockholders' equity	$ 505,942	$ 550,477

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