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 8, 2012**

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.)

2855 Gazelle Court
Carlsbad, CA 92010
(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 8, 2012, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter ended March 31, 2012. 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 8, 2012.

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 7, 2012

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 8, 2012.

ISIS REPORTS FINANCIAL RESULTS AND HIGHLIGHTS FOR FIRST QUARTER 2012

- **Conference Call Webcast Tuesday, May 8, 4:30 p.m. ET at www.isispharm.com**

CARLSBAD, Calif., May 8, 2012 - Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today reported a pro forma net operating loss (NOL) of $16.2 million for the first quarter of 2012 compared to a pro forma NOL of $13.4 million for the same period in 2011. The Company ended the first quarter of 2012 with nearly $334 million in cash.

"Already in 2012, we have had multiple important accomplishments. Our partners at Genzyme submitted the KYNAMRO™ new drug application (NDA) to the FDA. With this submission, we are one step closer to commercializing KYNAMRO for patients who are at great risk of dying from their cardiovascular disease. In addition, the European regulatory review is proceeding as planned, and Genzyme is actively preparing to launch KYNAMRO. The commercialization of KYNAMRO will be an important milestone for Isis. Not only does it represent the commercialization of the first systemic antisense drug, but it also represents the opportunity to significantly change our financial position by adding commercial revenue," said B. Lynne Parshall, COO and CFO of Isis. "The value of Isis, however, is much greater than the commercial potential of KYNAMRO. The drugs in the pipeline are maturing. There are many that could be part of the next wave of product launches after KYNAMRO. Even shorter term, there are numerous drugs that should complete Phase 2 studies in the next two years, making them potentially very attractive licensing candidates. With KYNAMRO as the foundation, our broad and deep pipeline should provide many opportunities for continued revenue growth in the future."

Upcoming Key Milestones

- Present an analysis of Lp(a) data from the KYNAMRO Phase 3 program at the European Atherosclerosis Society.
- Earn a $25 million milestone from Genzyme following FDA acceptance for the NDA submission of KYNAMRO for patients with homozygous FH.
- Initiate a clinical study of ISIS-TTR$_{Rx}$ in patients with Familial Amyloid Polyneuropathy.

Financial Results

On a GAAP basis, Isis reported a loss from operations of $18.5 million for the three months ended March 31, 2012, compared to $16.1 million for the same period in 2011.

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, 2012 was $23.2 million, compared to $21.1 million for the same period in 2011. 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 earned new revenue in the first quarter of 2012 from the $29 million upfront fee it received from its new partner, Biogen Idec, which the Company is amortizing over four years.

Operating Expenses

On a pro forma basis, operating expenses for the three months ended March 31, 2012 were $39.4 million, compared to $34.5 million for the same period in 2011. Isis' operating expenses in the first three months of 2012 reflected higher development costs associated with Isis' maturing pipeline of drugs offset by lower development expenses related to KYNAMRO because Isis is sharing these expenses equally with Genzyme until KYNAMRO is profitable. Genzyme is paying all of the marketing and selling expenses until KYNAMRO is profitable.

On a GAAP basis, Isis' operating expenses for the three months ended March 31, 2012 were $41.7 million, compared to $37.3 million for the same period in 2011.

Net Loss

Isis reported a net loss of $24.0 million for the three months ended March 31, 2012, compared to $20.0 million for the same period in 2011. Basic and diluted net loss per share for the three months ended March 31, 2012 was $0.24 per share, compared to $0.20 per share for the same period in 2011. In 2012, Isis' net loss increased compared to the same period in 2011 primarily due to an increase in Isis' net operating loss and additional non-cash interest expense the Company recorded for the long-term liability associated with its new facility.

Balance Sheet

As of March 31, 2012, Isis had cash, cash equivalents and short-term investments of $333.9 million compared to $343.7 million at December 31, 2011 and had working capital of $285.9 million at March 31, 2012 compared to $284.0 million at December 31, 2011. The decrease in cash in the first quarter of 2012 primarily relates to cash used to fund Isis' operations offset by the $29 million upfront fee Isis received from Biogen Idec.

Business Highlights

"In 2012, we are looking forward to a watershed event for Isis: the commercial launch of KYNAMRO. KYNAMRO is an important drug for many reasons. It should be the first systemic antisense drug on the market and it will be Isis' first important commercial asset. Most importantly, it is a drug that has the potential to help seriously ill patients with severe FH in desperate need of a lifesaving therapy," continued Ms. Parshall. "We recently reported data from our long-term extension study in patients who have been treated with KYNAMRO for two years and longer. In these patients, we continue to see sustained and robust reductions of LDL-cholesterol and other key atherogenic lipids with a safety profile that supports our plan to treat patients who are at very high risk of a cardiovascular-related death. While our initial registration dossiers are filed in the United States and Europe, we and Genzyme continue to invest to expand the commercial potential of KYNAMRO. We initiated a study called FOCUS FH late last year designed to support the addition of severe heterozygous FH to the label for KYNAMRO."

"While KYNAMRO is our flagship drug, our pipeline goes well beyond KYNAMRO. With drugs in numerous therapeutic areas, we have many opportunities for both short- and long-term revenue growth. We have several drugs that may provide substantial commercial opportunities with product launches that could occur within the next five years. These include our TTR amyloidosis and Spinal Muscular Atrophy drugs from our severe and rare disease franchise, which, due to the significant unmet medical need and orphan patient populations, could warrant an accelerated path to market. We expect that, if successful, they could be available for patients within the next five years. In addition, we are implementing a staged development path for our triglyceride-lowering drug, ISIS-APOCIII$_{Rx}$, that could bring this important new medicine to the market sooner for patients with extremely high and poorly controlled triglycerides who, as a result, are at severe risk of disease," continued Ms. Parshall.

"In addition to the potential near-term product opportunities in our pipeline, we have several drugs that could represent significant licensing opportunities in the next year or two. With robust Phase 2 data packages, we may be able to command lucrative licensing terms for these drugs. Among these near-term licensing opportunities is our anticoagulant drug targeting Factor XI and our CRP drug from our cardiovascular franchise. Both of these drugs have the potential to treat numerous diseases with significant market potential. In addition, we have several drugs from our metabolic franchise that could complete Phase 2 studies in the next two years and could also provide significant licensing opportunities. These drugs represent novel approaches to the treatment of type 2 diabetes, and are designed to provide long-term control in patients who cannot control their glucose levels with existing therapies. With type 2 diabetes being the most rapidly growing epidemic worldwide, we believe bringing forward novel medicines to add to the treatment paradigm for these patients is a wise investment," continued Ms. Parshall.

"In summary, we have begun another productive year in which we expect to report data on many of the drugs in our pipeline, initiate larger, longer studies for our Factor XI and TTR drugs, and continue to move promising new drugs into our pipeline. We look forward to KYNAMRO commercialization and bringing this important new medicine to patients in great need," concluded Ms. Parshall.

Corporate and Drug Development Highlights

- Genzyme submitted a new drug application for KYNAMRO in the United States for homozygous FH patients.
- Dr. Raul Santos presented data from the long-term extension study of KYNAMRO at the International Symposium on Atherosclerosis. The data highlight the long-term safety and efficacy of KYNAMRO in patients who have been treated with KYNAMRO.
- Isis initiated a Phase 2 study on ISIS-APOCIII$_{Rx}$ in patients with elevated triglycerides and a Phase 1 study on ISIS-STAT3$_{Rx}$ in patients with cancer.
- Isis reported data from a Phase 1 study of ISIS-TTR$_{Rx}$ showing that ISIS-TTR$_{Rx}$ produced statistically significant reductions in TTR protein.
- Isis formed a new strategic alliance with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ to treat Spinal Muscular Atrophy (SMA). Isis received a $29 million upfront payment and is eligible to receive up to an additional $270 million in a license fee and milestone payments, and double-digit royalties on sales of ISIS-SMN$_{Rx}$.
- Isis received Orphan Drug Designation for ISIS-SMN$_{Rx}$ in Europe for the treatment of SMA.
- OncoGenex reported preliminary positive Phase 1 data at the American Society of Clinical Oncology showing that treatment with OGX-427 produced a trend toward increased tumor cell death in patients with bladder cancer and preliminary Phase 2 data showing that treatment with OGX-427 decreased prostate specific antigen in patients with metastatic prostate cancer.
- Xenon Pharmaceuticals selected a drug targeting the hepcidin-hemojuvelin pathway as a development candidate to treat anemia of inflammation, a common form of anemia.

Conference Call

At 4:30 p.m. Eastern Time today, May 8, 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 866-831-6162 and refer to passcode "ISIS 2012," 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 leadership position in antisense technology to discover and develop novel drugs for its product pipeline and for its partners. Isis' broad pipeline consists of 26 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, and cancer. Isis' partner, Genzyme, plans to commercialize Isis' lead product, KYNAMRO, following regulatory approval, which is expected in 2012. Isis' patents provide strong and extensive protection for its 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' financial position and outlook, Isis' business, and the therapeutic and commercial potential of Isis' technologies and products in development, including the business of Regulus, Isis' jointly owned subsidiary. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs, including the planned commercialization of KYNAMRO, 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, 2011, 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.

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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,	
	2012	2011
	(unaudited)	
Revenue:		
Research and development revenue under collaborative agreements	$ 21,818	$ 20,014
Licensing and royalty revenue	1,417	1,133
Total revenue	23,235	21,147
Expenses:		
Research and development	38,714	34,245
General and administrative	2,976	3,010
Total operating expenses	41,690	37,255
Loss from operations	(18,455)	(16,108)
Other income (expense):		
Equity in net loss of Regulus Therapeutics Inc.	(976)	(856)
Investment income	600	705
Interest expense	(5,179)	(3,415)
Gain (loss) on investments, net	17	(318)
Loss before income tax expense	$ (23,993)	$ (19,992)
Income tax expense	(2)	(2)
Net loss	$ (23,995)	$ (19,994)
Basic and diluted net loss	$ (0.24)	$ (0.20)
Shares used in computing basic and diluted net loss per share	100,157	99,569

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,	
	2012	2011
	(unaudited)	
As reported operating expenses according to GAAP	$ 41,690	$ 37,255
Excluding compensation expense related to equity awards	(2,267)	(2,732)
Pro forma operating expenses	$ 39,423	$ 34,523

As reported loss from operations according to GAAP	$ (18,455)	$ (16,108)
Excluding compensation expense related to equity awards	(2,267)	(2,732)
Pro forma loss from operations	$ (16,188)	$ (13,376)

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 equity awards, 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, 2012	December 31, 2011
	(unaudited)	
Assets:		
Cash, cash equivalents and short-term investments	$ 333,944	$ 343,664
Other current assets	13,669	16,475
Property, plant and equipment, net	95,132	96,615
Other assets	28,062	28,140
Total assets	$ 470,807	$ 484,894
Liabilities and stockholders' equity:		
Other current liabilities	$ 27,387	$ 39,528
Current portion of deferred contract revenue	34,320	36,584
2 5/8% convertible subordinated notes	143,717	141,448
Long-term obligations, less current portion	73,642	74,002
Investment in Regulus Therapeutics Inc.	5,400	4,424
Long-term deferred contract revenue	35,469	17,474
Stockholders' equity	150,872	171,434
Total liabilities and stockholders' equity	$ 470,807	$ 484,894

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