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 6, 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 November 6, 2012, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter ended September 30, 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 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 6, 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: November 6, 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 November 6, 2012.

ISIS REPORTS FINANCIAL RESULTS AND HIGHLIGHTS FOR THIRD QUARTER 2012

- **Conference Call Webcast Tuesday, November 6, 11:30 a.m. ET at www.isispharm.com**

CARLSBAD, Calif., November 6, 2012 - Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) today reported a pro forma net operating loss (NOL) of $26.0 million and $36.0 million for the three and nine months ended September 30, 2012, respectively, compared to a pro forma NOL of $20.0 million and $44.9 million for the same periods in 2011. The Company ended the third quarter of 2012 with $343.6 million in cash.

"We have had a very successful year. With a number of exciting events on the horizon, the remainder of 2012 promises to be equally eventful. Of course, the most notable events this year are associated with KYNAMRO™. We are pleased with the positive recommendation from the FDA's advisory committee for KYNAMRO and look forward to the FDA's decision early next year. We believe KYNAMRO could have a profound impact on the lives of patients with homozygous FH, who are at extreme cardiovascular risk and are in need of new therapeutic options. We look forward to bringing this important new medicine to these patients," said B. Lynne Parshall, Chief Operating Officer and Chief Financial Officer at Isis.

"While KYNAMRO is the most notable of our successes, we have had many achievements across our pipeline. Most recently, we have completed key steps to move two of our severe and rare disease drugs toward commercial markets. We initiated the next clinical study in patients with spinal muscular atrophy for our drug, ISIS-SMN$_{Rx}$, which we partnered with Biogen Idec earlier this year. This study will be a relatively short study and will position us to initiate a registration-directed Phase 2/3 study next year. In addition, we and GSK amended the development plan for ISIS-TTR$_{Rx}$ to employ a more efficient route to the market. We plan to initiate the Phase 2/3 study evaluating ISIS-TTR$_{Rx}$ in patients with TTR amyloidosis later this year. Both of these drugs have the potential for substantial commercial markets within the next five years and could significantly change the lives of patients in need," continued Ms. Parshall. "We also benefit from our investments in our satellite companies, like Regulus, which recently completed an initial public offering, enabling it to be financially sustainable without the need for funding from us and increasing the value of our assets."

Potential Upcoming Key Milestones

- Report clinical data from multiple drugs in Isis' pipeline
- Initiate a Phase 2/3 study of ISIS-TTR$_{Rx}$ in patients with familial amyloid polyneuropathy
- Receive marketing approval of KYNAMRO in the United States and Europe
- Earn a $25 million milestone payment from Genzyme following FDA marketing approval for KYNAMRO

Financial Results

On a GAAP basis, Isis reported a loss from operations of $28.0 million and $42.8 million for the three and nine months ended September 30, 2012, respectively, compared to a loss from operations of $22.3 million and $52.5 million for the same periods in 2011.

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

Revenue

Revenue for the three and nine months ended September 30, 2012 was $11.6 million and $82.2 million, respectively, compared to $20.7 million and $66.7 million for the same periods 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. For example, Isis' revenue in the first nine months of 2012 was significantly higher than in 2011 primarily due to the $25 million milestone payment the Company earned from Genzyme for FDA acceptance of the KYNAMRO NDA. Also in the first nine months of 2012, Isis sold approximately $11 million of drug substance to Genzyme to support the planned commercial launch of KYNAMRO and began recognizing revenue from the $41 million in upfront payments the Company received from the partnerships it entered into with Biogen Idec this year. These increases were partially offset when the amortization of the upfront payments associated with the Genzyme collaboration ended in May 2012.

Operating Expenses

On a pro forma basis, operating expenses for the three and nine months ended September 30, 2012 were $37.6 million and $118.2 million, respectively, compared to $40.7 million and $111.6 million for the same periods in 2011. The moderately higher expenses in the first nine months of 2012 were primarily due to higher development costs associated with Isis' maturing pipeline of drugs offset by lower development expenses related to KYNAMRO because Genzyme is now sharing these expenses equally with Isis 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 and nine months ended September 30, 2012 were $39.6 million and $125.0 million, respectively, compared to $43.0 million and $119.2 million for the same periods in 2011.

Early Retirement of Debt

In August 2012, Isis issued $201.3 million of 2 ¾% Convertible Senior Notes due 2019 (2 ¾% Notes). In September 2012, Isis used a substantial portion of the net proceeds from the issuance of these notes to redeem the entire $162.5 million of the Company's 2 $^5/_8$% Convertible Subordinated Notes (2 $^5/_8$% Notes), at a redemption price plus accrued interest of $164.0 million. The carrying value of the 2 $^5/_8$% Notes on Isis' balance sheet included a discount based

on the estimated fair value of a similar debt instrument without the conversion feature. Isis was amortizing this discount over the expected life of the debt as additional non-cash interest expense. As a result of the early redemption of the 2 5/8% Notes, Isis recognized a $4.8 million loss in the third quarter of 2012. A significant portion of the loss, or $3.6 million, was non-cash and related to the unamortized debt discount and debt issuance costs while the remainder of the loss was related to a $1.2 million early redemption premium Isis paid to the holders of the 2 5/8% Notes.

Net Loss

Isis reported a net loss of $37.6 million and $62.8 million for the three and nine months ended September 30, 2012, respectively, compared to $26.9 million and $64.8 million for the same periods in 2011. Basic and diluted net loss per share for the three and nine months ended September 30, 2012 was $0.37 per share and $0.63 per share, compared to $0.27 per share and $0.65 per share for the same periods in 2011. Isis' net loss for the first nine months of 2012 decreased slightly compared to the same period in 2011 primarily due to a decrease in Isis' net operating loss offset, in part, by the $4.8 million loss on the Company's early retirement of its 2 5/8% Notes and additional non-cash interest expense the Company recorded for the long-term liability associated with its primary research and development facility.

Balance Sheet

As of September 30, 2012, Isis had cash, cash equivalents and short-term investments of $343.6 million compared to $343.7 million at December 31, 2011 and had working capital of $310.0 million at September 30, 2012 compared to $284.0 million at December 31, 2011. In the first nine months of 2012, Isis received $41 million in upfront payments from Biogen Idec, a $25 million milestone payment from Genzyme for FDA acceptance of the KYNAMRO NDA, and approximately $30 million in net proceeds from Isis' issuance of the 2 ¾% Notes after deducting offering fees and expenses and the redemption of the 2 5/8% Notes. Isis recorded the 2 ¾% Notes on its balance sheet at a discount based on the estimated fair value of a similar debt instrument without the conversion feature. Isis is amortizing this discount over the life of the debt as additional non-cash interest expense.

Investment in Regulus Therapeutics Inc.

In October 2012, Regulus Therapeutics, Inc., a company co-founded by Isis, completed an initial public offering of approximately 12.7 million shares of its common stock at $4.00 per share. Isis purchased $3.0 million of Regulus' common stock at the offering price and now owns approximately 7 million shares, or 17%, of Regulus' common stock on a fully diluted basis. Beginning in the fourth quarter, Isis will no longer use the equity method to account for its investment in Regulus because Isis now owns less than 20% of Regulus' common stock and no longer has significant influence over the operating and financial policies of Regulus. Instead, Isis will account for its investment in Regulus at fair value by adjusting the value to reflect fluctuations in Regulus' stock price each reporting period. In the fourth quarter, Isis will record a significant gain to reflect the change in its ownership percentage in Regulus.

Business Highlights

"With a pipeline of more than two dozen drugs in development, we have multiple opportunities for pipeline news. A number of our drugs will complete first-in-man studies this year, and we will share that data with you as it becomes available. We also plan to advance several drugs into later-stage clinical studies. These are drugs, like our TTR drug, that could have rapid routes to the market in orphan patient populations who have limited treatment options. In addition, as we have done every year for the past several years, we plan to add three to five new drugs to our pipeline. In short, we are on track to end the year with many significant accomplishments that demonstrate the therapeutic potential of our drugs and the productivity of our technology."

"We encourage the advancement of antisense drugs and support innovation in antisense technology, in part through our satellite company strategy, which allows us to work with a consortium of smaller companies in areas outside of our core focus. Often, the investments we make in our satellite company partners are not monetary, but rather, we provide our satellite company partners access to our intellectual property, expertise in antisense technology and manufacturing support in exchange for company equity, milestone payments and future royalties as programs advance toward the market. Regulus is a great example of the value of this strategy," commented Ms. Parshall. "We co-founded Regulus based on our know-how and clinical advances with antisense drugs and applied this knowledge to the field of microRNAs. Last month Regulus completed an initial public offering, which we supported, bringing our ownership in Regulus to approximately seven million shares of Regulus' common stock, which is currently valued at $35 million."

"In closing, 2012 has already been a very successful year, not just with our pipeline and with KYNAMRO, but also financially. A key goal for us this year was to refinance our existing debt on favorable terms. By taking advantage of the favorable market conditions and the considerable interest in Isis, we successfully completed a private placement of $201.3 million of 2 ¾% Convertible Senior Notes at an excellent interest rate and conversion price. More importantly, we used the proceeds from this placement to redeem the entire $162.5 million of our 2 5/8 % Convertible Subordinated Notes. The refinancing allowed us to take advantage of favorable market conditions to strengthen our balance sheet," continued Ms. Parshall.

Corporate and Drug Development Highlights

- KYNAMRO continues to advance in development and move closer to the market for patients with severe forms of familial hypercholesterolemia (FH; homozygous FH and severe heterozygous FH) through regulatory approval and with the FOCUS FH study.
  - The FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 9 to 6 that Genzyme had provided sufficient efficacy and safety data to support the marketing of KYNAMRO for the treatment of patients with homozygous FH.
  - Dr. Klaus Parhofer, a clinical investigator, presented an analysis of data from the KYNAMRO Phase 3 study in patients with severe heterozygous FH at the European Society of Cardiology. These data highlighted the potential of KYNAMRO to reduce the need for apheresis by lowering LDL-C values below the thresholds for apheresis eligibility in patients with severe heterozygous FH.
  - Isis received European GMP certification of its manufacturing facility for production of drug substance to support KYNAMRO commercial launch.

- Isis initiated a Phase 2 study on ISIS-FXI$_{Rx}$ in patients undergoing total knee replacement surgery and a Phase 1b/2a study on ISIS-SMN$_{Rx}$ in children with spinal muscular atrophy.
- Isis and GlaxoSmithKline amended the clinical development plan and financial terms relating to ISIS-TTR$_{Rx}$ to support an accelerated development plan for the drug. As a result of the revised agreement, Isis will receive a $2.5 million upfront payment and will receive $7.5 million upon initiation of the Phase 2/3 study for ISIS-TTR$_{Rx}$. Isis is also eligible to earn an additional $50 million in pre-licensing milestone payments to support the ISIS-TTR$_{Rx}$ Phase 2/3 study.
- Isis reported preliminary Phase 1 data on ISIS-STAT3$_{Rx}$ in patients with cancer and initiated a Phase 2 study evaluating ISIS-STAT3$_{Rx}$ in patients with advanced lymphoma.
- Isis and collaborators published a paper in Nature demonstrating that an antisense compound selectively and rapidly reduced target RNA in skeletal muscle and alleviated disease in animal models of muscular dystrophy type 1 (DM1).
- Isis and collaborators published two papers in the journal Cell demonstrating that single-stranded RNA-like antisense technology can activate the RNAi pathway and inhibit the expression of targeted genes.
- Isis benefits from its partners as they advance RNA-based technologies and products that incorporate Isis' technology resulting in financial benefits as these assets mature.

    - Isis earned $2.7 million from Alnylam as a result of Alnylam's licenses that included Isis' patents.
    - Regulus formed a strategic alliance with AstraZeneca for the discovery, development and commercialization of microRNA therapeutics.
    - Regulus formed a strategic alliance with Biogen Idec to identify microRNAs as biomarkers for multiple sclerosis.
    - Isis received a $1.25 million payment from Pfizer triggered by Pfizer's decision to advance EXC 001 into a Phase 2 study.

- Regulus Therapeutics completed an initial public offering and is now traded on The NASDAQ Global Market under the ticker RGLS. Isis purchased $3 million of Regulus' common stock at the offering price and remains a significant shareholder with approximately 17% ownership on a fully diluted basis.
- Isis completed a successful offering of $201.3 million of 2 ¾% Convertible Senior Notes. Isis used the proceeds of this offering to redeem the entire $162.5 million of 2 $^{5}/_{8}$% Convertible Subordinated Notes.

Conference Call

At 11:30 a.m. Eastern Time today, November 6, Isis will conduct a live webcast conference call to discuss this earnings release and business highlights. Interested parties may listen to the call by dialing 800-237-9752 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 25 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, in the United States and Europe following regulatory approval. 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. 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 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.

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,	Nine months ended,

	September 30,		September 30,	
	2012	2011	2012	2011
	(unaudited)		(unaudited)	
Revenue:				
Research and development revenue under collaborative agreements	$ 11,127	$ 20,189	$ 80,085	$ 64,508
Licensing and royalty revenue	474	524	2,091	2,175
Total revenue	11,601	20,713	82,176	66,683
Expenses:				
Research and development	36,551	39,924	115,700	110,178
General and administrative	3,096	3,105	9,281	8,989
Total operating expenses	39,647	43,029	124,981	119,167
Loss from operations	(28,046)	(22,316)	(42,805)	(52,484)
Other income (expense):				
Equity in net loss of Regulus Therapeutics Inc.	—	(386)	(1,139)	(2,275)
Investment income	408	575	1,485	1,896
Interest expense	(5,937)	(4,773)	(16,335)	(11,624)
Gain (loss) on investments, net	—	18	19	(267)
Loss on early retirement of debt	(4,770)	—	(4,770)	—
Loss before income tax benefit (expense)	(38,345)	(26,882)	(63,545)	(64,754)
Income tax benefit (expense)	706	—	704	(11)
Net loss	$ (37,639)	$ (26,882)	$ (62,841)	$ (64,765)
Basic and diluted net loss per share	$ (0.37)	$ (0.27)	$ (0.63)	$ (0.65)
Shares used in computing basic and diluted net loss per share	100,680	99,687	100,351	99,620

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

	Three months ended, September 30,		Nine months ended, September 30,	
	2012	2011	2012	2011
	(unaudited)		(unaudited)	
As reported operating expenses according to GAAP	$ 39,647	$ 43,029	$ 124,981	$ 119,167
Excluding compensation expense related to equity awards	(2,034)	(2,364)	(6,761)	(7,596)
Pro forma operating expenses	$ 37,613	$ 40,665	$ 118,220	$ 111,571
As reported loss from operations according to GAAP	$ (28,046)	$ (22,316)	$ (42,805)	$ (52,484)
Excluding compensation expense related to equity awards	(2,034)	(2,364)	(6,761)	(7,596)
Pro forma loss from operations	$ (26,012)	$ (19,952)	$ (36,044)	$ (44,888)

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)

	September 30, 2012	December 31, 2011
	(unaudited)	
Assets:		
Cash, cash equivalents and short-term investments	$ 343,573	$ 343,664
Other current assets	18,013	16,475
Property, plant and equipment, net	92,598	96,615
Other assets	31,497	28,140
Total assets	$ 485,681	$ 484,894

Liabilities and stockholders' equity:		
Other current liabilities	$ 28,174	$ 39,528
Current portion of deferred contract revenue	23,427	36,584
2 3/4% convertible senior notes	142,500	—
2 5/8% convertible subordinated notes	—	141,448
Long-term obligations, less current portion	78,779	74,002
Investment in Regulus Therapeutics Inc.	5,563	4,424
Long-term deferred contract revenue	36,961	17,474
Stockholders' equity	170,277	171,434
Total liabilities and stockholders' equity	$ 485,681	$ 484,894

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