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): **February 29, 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 February 29, 2012, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter and fiscal year ended December 31, 2011. In addition to disclosing results that are determined in accordance with Generally Accepted Accounting Principles (GAAP), the Company also discloses 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 February 29, 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: February 29, 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 February 29, 2012.

Exhibit 99.1

ISIS REPORTS FINANCIAL RESULTS AND HIGHLIGHTS FOR 2011

- **Conference Call Webcast Wednesday, February 29, 8:30 a.m. ET at www.isispharm.com**

CARLSBAD, Calif., February 29, 2012 - Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced its 2011 financial results and reviewed the highlights of the year. Isis finished 2011 with a pro forma net operating loss (NOL) of $61.3 million compared to a pro forma NOL of $36.2 million for 2010. The Company finished 2011 with nearly $344 million in cash. On a GAAP basis, Isis reported a loss from operations of $18.6 million and $71.1 million for the three and twelve months ended December 31, 2011, respectively, compared to $15.9 million and $48.4 million for the same periods in 2010.

"We ended 2011 in a strong financial position with nearly $344 million in cash. With the planned launch of KYNAMRO later this year and our anticipated share of commercial revenue likely beginning in 2013, we believe our financial strength is sustainable without the need to raise equity capital," said B. Lynne Parshall, J.D., Chief Operating Officer, Chief Financial Officer and Secretary of Isis.

"In 2012, we are predicting another year of consistent financial performance, while maintaining a level of activities that ensures the progress of many promising programs. We are projecting higher revenues this year, including $50 million of KYNAMRO milestone payments, half on U.S. NDA acceptance and half on U.S. NDA approval. We are planning a modest increase in expenses, primarily due to the expansion and maturation of our pipeline. As such, we are projecting 2012 financial guidance of a pro forma NOL in the low $40 million range. We expect to end 2012 with more than $300 million in cash, which reflects a lower cash burn than the last two years," continued Ms. Parshall. "We have an exciting year ahead. The successful execution of our business strategy allows us to generate significant revenue while managing cash burn year over year. In this way, we can invest in our pipeline while prudently managing our cash. Already this year, we formed a new strategic alliance with Biogen Idec potentially worth nearly $300 million of which we already received a $29 million initial payment. Genzyme plans to begin selling KYNAMRO in the second half of this year in important markets. We are also pleased to be investing with Genzyme to seek potential label expansion that could expand the commercial opportunities for this drug through the FOCUS FH study that was initiated late last year."

Upcoming Key Milestones

- File for marketing approval for KYNAMRO in the U.S. in the first quarter of 2012 for patients with homozygous Familial Hypercholesterolemia (FH).
- Initiate a Phase 1 study on ISIS-STAT3$_{Rx}$ in patients with cancer, a Phase 2 study on ISIS-APOCIII$_{Rx}$ in patients with high triglycerides and a clinical study on ISIS-TTR$_{Rx}$ in patients with Familial Amyloid Polyneuropathy.

Financial Results

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 and twelve months ended December 31, 2011 was $32.4 million and $99.1 million, respectively, compared to $26.4 million and $108.5 million for the same periods 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, revenue in 2011 included $17.7 million in revenue from GlaxoSmithKline (GSK), compared to $10.3 million in 2010, primarily due to the timing of milestone payments. This increase in revenue was offset by less revenue from Bristol-Myers Squibb and Alnylam Pharmaceuticals compared to 2010 because Isis was no longer amortizing the upfront fees.

Revenue in the fourth quarter of 2011 was higher than in the same period in 2010 because Isis sold $5.8 million of drug substance to Genzyme to support commercial launch of KYNAMRO and received a $5 million milestone payment from GSK for designating the second development candidate in the collaboration.

Operating Expenses

On a pro forma basis, operating expenses for the three and twelve months ended December 31, 2011 were $48.8 million and $160.3 million, respectively, compared to $39.6 million and $144.7 million for the same periods in 2010. Isis' operating expenses in 2011 reflected moderately higher development costs associated with Isis' maturing pipeline of drugs. In 2011, Isis satisfied its $125 million funding obligation for KYNAMRO. Beginning in 2012, Isis will share KYNAMRO development expenses equally with Genzyme until KYNAMRO is profitable, which will reduce the portion of Isis' development expenses related to KYNAMRO.

On a GAAP basis, Isis' operating expenses for the three and twelve months ended December 31, 2011 were $51.0 million and $170.2 million, respectively, compared to $42.3 million and $156.8 million for the same periods in 2010.

Net Loss

Isis reported a net loss of $20.0 million and $84.8 million for the three and twelve months ended December 31, 2011, respectively, compared to $14.0 million and $61.3 million for the same periods in 2010. Basic and diluted net loss per share for the three and twelve months ended December 31, 2011 was $0.20 per share and $0.85 per share, respectively, compared to $0.14 per share and $0.62 per share for the same periods in 2010. In 2011, Isis' net loss increased compared to the same period in 2010 primarily due to a $22.7 million increase in Isis' net operating loss.

Balance Sheet

As of December 31, 2011, Isis had cash, cash equivalents and short-term investments of $343.7 million compared to $472.4 million at December 31, 2010 and had working capital of $284.0 million at December 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.

Isis' leases on its former research and development facilities expired at the end of 2011. Rather than invest in costly renovations to these facilities, Isis chose to consolidate the majority of its operations in a new leased facility constructed by Biomed Realty Trust, Inc. (BMR). To make the Company's move in August 2011 as efficient as possible, Isis requested access to the new facility prior to the completion of construction, which required Isis to modify its lease to accept additional responsibility. As a result, accounting rules required Isis to record the cost of the facility as a fixed asset with a corresponding liability. Isis is depreciating the building over its economic life and Isis' rent payments, which began on January 1, 2012, will decrease the liability over the term of the lease.

2012 Goals

"We have numerous key events to look forward to in 2012, the most significant being the planned launch of KYNAMRO for our initial indication in patients with FH. We will also continue to enroll patients in our FOCUS FH study, which is designed to support a label expansion for KYNAMRO. In 2011, we reported significant achievements in our pipeline. We plan to continue this progress in 2012 as we advance the drugs in our pipeline. We are particularly excited about our severe and rare disease franchise. Many of the drugs in this franchise represent the opportunity for more rapid development paths and shortened times to the market, and we have strong partners committed to implementing development programs to achieve efficient routes to registration for these drugs," continued Ms. Parshall.

In 2012, Isis plans to achieve the following goals itself and with its partners:

- Together with Genzyme, advance KYNAMRO to the market for patients who cannot adequately control their cholesterol levels with current therapies.
    - File a new drug application for KYNAMRO marketing approval in the U.S. in the first quarter of 2012.
    - Receive marketing approval for KYNAMRO and launch in the second half of 2012.
    - Continue to enroll the FOCUS FH study to potentially expand the commercial opportunity for KYNAMRO.
- Report clinical data on seven drugs in its pipeline.
- Initiate Phase 2 or Phase 2/3 clinical studies on five drugs and initiate Phase 1 clinical studies on two drugs in its pipeline.
- Broaden its pipeline by adding three to five new drugs.
- Continue to successfully execute its business strategy to generate revenue and cash.

Business Highlights

"2011 was a year of significant clinical achievements for us. We completed Phase 1 clinical studies on numerous drugs in our pipeline and reported consistent, dose-dependent reductions of target in healthy volunteers for all of these drugs. We also showed associated disease-related changes to support early proof-of-concept validation in some cases. We plan to move most of these drugs into Phase 2 studies this year. We also advanced additional drugs into clinical studies that we plan to report data on this year and added six new drugs to our pipeline. We reported significant progress in our GSK collaboration. In less than two years, we received more than $50 million from GSK and added two new drugs to our severe and rare disease franchise. This year, we will advance one of these drugs, ISIS-TTR_{Rx}, into a clinical study in patients designed to achieve an efficient route to market. Most recently, we established an alliance with Biogen Idec to further develop ISIS-SMN_{Rx} to treat spinal muscular atrophy, which also represents an efficient path to market. This alliance provides Biogen Idec an option to license ISIS-SMN_{Rx} from us upon completion of the first successful Phase 2/3 trial. And finally, we continue to see strong interest in antisense from large pharmaceutical companies as further evidenced by Pfizer's recent acquisition of our satellite company partner, Excaliard. As you can see, 2011 was a very productive year, and we expect to continue this momentum through 2012. Our financial position remains strong and it enables us to invest in our business and our technology in ways that we believe will continue to generate value for our shareholders," concluded Ms. Parshall.

Drug Development Highlights

- KYNAMRO continues to advance in clinical development and move closer to the market for patients with severe forms of FH, at high cardiovascular risk, who cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies.
    - Genzyme submitted a marketing application for KYNAMRO in Europe for patients with homozygous FH and severe heterozygous FH, and plans to submit a marketing application for KYNAMRO in the U.S. for patients with homozygous FH in the first quarter of 2012. Genzyme

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is also preparing to file for marketing approval in markets beyond the U.S. and Europe.
    - Genzyme initiated the FOCUS FH study in FH patients that is designed to support potentially broadening the FH patient population beyond the first indication and support an alternative dosing regimen of three times a week dosing. Genzyme reached an agreement with the FDA on the design of the FOCUS FH study via a Special Protocol Assessment (SPA).
    - A clinical investigator presented data from an open-label extension study in patients treated with KYNAMRO for longer than one year, which demonstrated sustained reductions in all measured atherogenic lipids with a safety profile consistent with the Phase 3 studies.
    - Clinical investigators presented data from two studies of KYNAMRO at the 79th European Atherosclerosis Society Congress. The data highlight the potential of KYNAMRO in lowering Lp(a) and potentially reducing the necessity for lipid-apheresis.
- Isis received more than $23 million from partners in 2011 as its partners advanced drugs in development, including $10 million from GSK for advancing ISIS-TTR_{Rx} and selecting ISIS-AAT_{Rx} as a development candidate.
- Isis and its partners reported positive clinical data on eight drugs, and added six new drugs to its pipeline.
- Isis and its partners initiated Phase 1 clinical studies on eight drugs and initiated Phase 2 studies on three drugs.

Corporate Highlights

- Isis formed a new strategic alliance with Biogen Idec to develop and commercialize ISIS-SMN$_{Rx}$ to treat spinal muscular atrophy. 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 $4.4 million and is eligible to receive up to an additional $9.6 million in milestone payments from the sale of its equity ownership in Excaliard to Pfizer.
- Isis received Orphan Drug Designation and Fast Track Status in the U.S. for ISIS-SMN$_{Rx}$ for the treatment of spinal muscular atrophy.
- Isis and CHDI Foundation, Inc. renewed its collaboration to discover and develop an antisense drug for the treatment of Huntington's Disease.
- Isis and GSK expanded its collaboration by initiating a sixth program to discover and develop drugs to treat rare and infectious diseases for which Isis received a $3 million payment from GSK.
- Isis filed a patent infringement lawsuit against Santaris Pharma based upon Santaris' commercial activities selling antisense drugs and antisense drug discovery services to several pharmaceutical companies.

Conference Call

At 8:30 a.m. Eastern Time today, February 29, 2012, 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 800-599-9829 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 STATEMENT

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 (mipomersen), 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 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., 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, December 31,		Years ended, December 31,	
	2011	2010	2011	2010
	(unaudited)			
Revenue:				
Research and development revenue under collaborative agreements	$ 31,682	$ 25,437	$ 96,190	$ 102,921
Licensing and royalty revenue	721	983	2,896	5,552
Total revenue	32,403	26,420	99,086	108,473
Expenses:				
Research and development	47,219	39,333	157,397	145,160
General and administrative	3,800	2,944	12,789	11,669
Total operating expenses	51,019	42,277	170,186	156,829
Loss from operations	(18,616)	(15,857)	(71,100)	(48,356)
Other income (expense):				
Equity in net loss of Regulus Therapeutics Inc.	(1,279)	4,130	(3,554)	(2,228)
Investment income	518	780	2,414	3,370

Interest expense	(5,108)	(3,396)	(16,732)	(13,232)
Gain (loss) on investments, net	4,449	448	4,182	(713)
Loss before income tax expense	(20,036)	(13,895)	(84,790)	(61,159)
Income tax expense	—	(90)	(11)	(92)
Net loss	$ (20,036)	$ (13,985)	$ (84,801)	$ (61,251)
Basic and diluted net loss per share	$ (0.20)	$ (0.14)	$ (0.85)	$ (0.62)
Shares used in computing basic and diluted net loss per share	99,763	99,267	99,656	99,143

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

	Three months ended, December 31,		Years ended, December 31,	
	2011	2010	2011	2010
	(unaudited)		(unaudited)	
As reported operating expenses according to GAAP	$ 51,019	$ 42,277	$ 170,186	$ 156,829
Excluding compensation expense related to stock options	(2,249)	(2,712)	(9,845)	(12,159)
Pro forma operating expenses	$ 48,770	$ 39,565	$ 160,341	$ 144,670
As reported loss from operations according to GAAP	$ (18,616)	$ (15,857)	$ (71,100)	$ (48,356)
Excluding compensation expense related to stock options	(2,249)	(2,712)	(9,845)	(12,159)
Pro forma loss from operations	$ (16,367)	$ (13,145)	$ (61,255)	$ (36,197)

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)

	December 31, 2011	December 31, 2010
Assets:		
Cash, cash equivalents and short-term investments	$ 343,664	$ 472,353
Other current assets	16,475	10,784
Property, plant and equipment, net	96,615	35,703
Other assets	28,140	31,637
Total assets	$ 484,894	$ 550,477
Liabilities and stockholders' equity:		
Other current liabilities	$ 39,528	$ 31,388
Current portion of deferred contract revenue	36,584	74,502
2 5/8% convertible subordinated notes	141,448	132,895
Long-term obligations, less current portion	74,002	15,867
Investment in Regulus Therapeutics Inc.	4,424	870
Long-term deferred contract revenue	17,474	50,413
Stockholders' equity	171,434	244,542
Total liabilities and stockholders' equity	$ 484,894	$ 550,477

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