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 6, 2014**

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:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ 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 6, 2014, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter ended March 31, 2014. 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 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 6, 2014.

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 6, 2014

By: /s/ B. Lynne Parshall
B. LYNNE PARSHALL
Chief Operating Officer,
and Director

INDEX TO EXHIBITS

99.1	Press Release dated May 6, 2014.

Exhibit 99.1

ISIS REPORTS FINANCIAL RESULTS AND HIGHLIGHTS FOR FIRST QUARTER 2014

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

CARLSBAD, Calif., May 6, 2014 - Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) today reported a pro forma net operating loss (NOL) of $22.6 million for the three months ended March 31, 2014 compared to pro forma operating income of $4.5 million for the same period in 2013. Isis' first quarter 2014 pro forma NOL was higher than the same period last year primarily due to variations in the timing of milestone payments from its partners and the planned increase in operating expenses associated with the Company's late-stage clinical programs. On a GAAP basis, Isis reported a loss from operations of $29.7 million for the three months ended March 31, 2014 compared to income from operations of $1.6 million for the same period in 2013. Isis maintained its strong cash position and ended the first quarter of 2014 with approximately $631 million in cash compared to $657 million at December 31, 2013.

"In the first quarter we have accomplished a number of significant milestones, setting the stage for a year of continuing growth. We reported positive clinical data on both ISIS-SMN_{Rx} and ISIS-$APOCIII_{Rx}$, and are on track to initiate Phase 3 programs for both of these drugs this year. These Phase 3 studies will add to our Phase 3 study already ongoing for ISIS-TTR_{Rx}, which we began dosing over a year ago and is progressing according to plan. We started our first clinical study on ISIS-$ANGPTL3_{Rx}$ and added new drugs to the pipeline, including ISIS-HTT_{Rx} to treat Huntington's Disease. The continued growth and maturation of our pipeline means that we will have numerous pipeline events throughout the year, including in the middle of the year, reporting Phase 2 data from ISIS-$GCGR_{Rx}$ and ISIS-FXI_{Rx}," said B. Lynne Parshall, chief operating officer at Isis.

"We started 2014 in a strong financial position and remain on track to meet our 2014 guidance. As our pipeline of partnered drugs mature, we have many opportunities to earn significant revenue from our partners. In the first quarter of 2014, we have earned more than $27 million from our partners. We are on track to meet our projection to end the year with more than $160 million in revenue, including more than $110 million in milestone payments as our partnered drugs achieve key development milestones. For example, we will earn $18 million from Biogen Idec when we initiate the Phase 3 study in infants with SMA. We plan to end 2014 with three drugs in Phase 3 development and nine drugs in Phase 2 development. This represents a significant maturation of our pipeline. Nevertheless we will continue to keep our spending increases consistent with our projections. As such, we are on track to end the year with a pro forma NOL in the low $50 million range and more than $575 million in cash," said Elizabeth L. Hougen, chief financial officer of Isis.

Upcoming Key Milestones

- Report Phase 2 clinical data on ISIS-FXI_{Rx} in patients undergoing total knee replacement
- Report Phase 2 clinical data on ISIS-$GCGR_{Rx}$ in patients with type 2 diabetes
- Initiate Phase 3 clinical studies on ISIS-SMN_{Rx} and ISIS-$APOCIII_{Rx}$
- Initiate Phase 1 clinical studies on ISIS-$AR_{Rx,}$ ISIS-PKK_{Rx} and ISIS-$DMPK_{Rx}$

Financial Results

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 months ended March 31, 2014 was $28.2 million compared to $43.4 million for the same period in 2013. Isis' revenue fluctuates based on the nature and timing of payments under agreements with Isis' partners, including license fees, milestone-related payments and other payments. For example, in the first quarter of 2014 Isis earned $7.7 million in sublicensing revenue from Alnylam related to its collaboration with Genzyme. In contrast, in the first quarter of 2013, Isis earned $32.5 million from milestone payments it received from Genzyme and GSK.

Operating Expenses

On a pro forma basis, Isis' operating expenses for the three months ended March 31, 2014 were $50.8 million compared to $38.9 million for the same period in 2013 due to higher development costs associated with Isis' maturing pipeline of drugs. On a GAAP basis, Isis' operating expenses for the three months ended March 31, 2014 were $57.8 million compared to $41.7 million for the same period in 2013. Isis' operating expenses on a GAAP basis included non-cash compensation expense related to equity awards, which increased significantly in 2014 compared to 2013 primarily due to the increase in Isis' stock price.

Net Loss

Isis reported a net loss of $31.3 million for the three months ended March 31, 2014 compared to $1.7 million for the same period in 2013. Basic and diluted net loss per share for the three months ended March 31, 2014 was $0.27 per share compared to $0.02 per share for the same period in 2013. Isis' net loss increased in the first quarter of 2014 primarily due to variations in the timing of revenue from milestone payments and an increase in operating expenses associated with the Company's maturing pipeline of drugs.

Balance Sheet

As of March 31, 2014, Isis had cash, cash equivalents and short-term investments of $631.3 million compared to $656.8 million at December 31, 2013 and had working capital of $621.2 million at March 31, 2014 compared to $637.7 million at December 31, 2013. Isis funded its operations in part by more than $30 million in cash received from its partners and from stock option exercises. Isis' working capital decreased slightly in the first quarter of 2014 primarily due to the decrease in cash.

Business Highlights

"Our innovative business strategy provides us with multiple opportunities to create and maintain value. We continue to successfully execute this strategy by establishing strategic partnerships that provide us with significant value not only when we begin a partnership, but also as our partnered drugs advance. Already this year, we have had numerous accomplishments with our partners that have led to the broadening and maturing of our pipeline. In less than a year, we have discovered and initiated development on a drug to treat Huntington's disease with our partners at Roche. Once we have completed the necessary studies to support clinical development, we will begin evaluating this drug in humans. Together with Biogen Idec, we have successfully advanced our drug, ISIS-SMN_{Rx}, for infants and children with spinal muscular atrophy, and plan to initiate the first Phase 3 study with this drug soon. We are preparing to initiate a Phase 1 study on our myotonic dystrophy drug, ISIS-$DMPK_{Rx}$ soon. We are also making significant progress with Biogen Idec in numerous other areas of our neurological disease alliance. Together with AstraZeneca, we plan to begin clinical development on the second anti-cancer drug in our alliance, ISIS-AR_{Rx}. Together with GSK, we have continued to advance the Phase 3 study for ISIS-TTR_{Rx}, moved our drug to treat hepatitis B virus into the clinic and added another new drug to our pipeline arising out of the collaboration. We are quite proud of this accomplishment. In our six target collaboration we have already delivered four development candidates to GSK, and we plan to deliver more. This level of success reflects the efficiency of antisense technology and the quality of the development candidates it can produce. These are just a few of our recent partnering successes," concluded Ms. Parshall.

Corporate and Drug Development Highlights

- Isis reported positive Phase 2 data on ISIS-APOCIII$_{Rx}$ in patients with high to extremely high triglyceride levels and as a single agent as well as in combination with fibrates.
  - Isis presented final Phase 2 data on ISIS-APOCIII$_{Rx}$ in combination with fibrates in patients with high triglycerides. In this study, patients achieved statistically significant reductions in triglycerides, apoC-III protein and statistically significant increases in HDL-C on top of improvements achieved with each patient's existing therapeutic regimen of triglyceride lowering drugs. These data were presented at the American College of Cardiology meeting.
  - Isis presented final Phase 2 data on ISIS-APOCIII$_{Rx}$ in patients with type 2 diabetes and high triglycerides. In this study, patients with diabetes experienced statistically significant improvements in glucose control with trends toward enhanced insulin sensitivity. These data were presented at the Arteriosclerosis, Thrombosis and Vascular Biology meeting.
  - Isis presented final Phase 2 data on ISIS-APOCIII$_{Rx}$ in patients with familial chylomicronemia. In this study, patients with extremely high triglycerides experienced substantial reductions of triglycerides that correlated with substantial reductions in triglyceride-rich chylomicrons. These data were presented at the National Lipid Association meeting.
  - Isis received European Orphan Drug Designation for ISIS-APOCIII$_{Rx}$ for the treatment of patients with familial chylomicronemia syndrome.
- Isis reported positive clinical results for ISIS-SMN$_{Rx}$ in children and infants with SMA. These data were presented at the American Academy of Neurology meeting.
  - Isis presented results from both of the ongoing multiple-dose Phase 2 studies of ISIS-SMN$_{Rx}$ in infants and children with SMA, which were consistent with earlier reported data. In the ongoing studies, Isis reported increases in muscle function scores in infants and children treated with multiple-doses of ISIS-SMN$_{Rx}$.
  - Isis reported results from an assay that measures SMN protein levels in the cerebral spinal fluid. Isis observed dose-dependent increases in SMN protein levels which were more than two-fold greater than baseline levels at the highest dose in children treated with ISIS-SMN$_{Rx}$ from both the single- and multiple-dose studies.
- Isis' collaborators presented preclinical data on an antisense drug targeting hepatitis B virus (HBV) demonstrating that antisense targeting of HBV produced dose-dependent reductions in HBV. Isis initiated a Phase 1 clinical trial on ISIS-HBV$_{Rx}$, an antisense drug to treat patients with HBV.
- Isis initiated a Phase 1 study of ISIS-ANGPTL3$_{Rx}$, an antisense drug to treat patients with hyperlipidemia.
- Isis added a new drug, ISIS-HTT$_{Rx}$, to its pipeline. ISIS-HTT$_{Rx}$ is part of Isis' alliance with Roche and is in development to treat patients with Huntington's Disease.
- Isis received a positive opinion on European Orphan Drug Designation in the EU for ISIS-TTR$_{Rx}$ to treat patients with TTR amyloidosis.
- In 2014 to date, Isis received more than $31 million in payments from its partners, including $11.9 million from Biogen Idec related to the development of ISIS-SMN$_{Rx}$, $7.7 million from Alnylam related to Alnylam's alliance with Genzyme and $9 million from GSK related to the development of ISIS-TTR$_{Rx}$ and ISIS-HBV$_{Rx}$.
- Isis added Joseph Loscalzo, M.D., Ph.D. to its Board of Directors.

Conference Call

At 11:30 a.m. Eastern Time today, May 6, 2014, 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 877-443-5662 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 32 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO®, in the United States and other countries for the treatment of patients with homozygous FH. 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. 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, 2013, 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.

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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,	
	2014	2013
Revenue:	(unaudited)	
Research and development revenue under collaborative agreements	$ 19,550	$ 41,671
Licensing and royalty revenue	8,611	1,689
Total revenue	28,161	43,360
Expenses:		
Research, development and patent expenses	53,448	38,312
General and administrative	4,380	3,423
Total operating expenses	57,828	41,735
Income (loss) from operations	(29,667)	1,625
Other income (expense):		
Investment income	657	376
Interest expense	(4,943)	(4,795)
Gain on investments, net	397	1,058
Loss before income tax benefit	$ (33,556)	$ (1,736)
Income tax benefit	2,276	64
Net loss	$ (31,280)	$ (1,672)
Basic and diluted net loss per share	$ (0.27)	$ (0.02)
Shares used in computing basic and diluted net loss per share	117,128	101,875

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

	Three months ended, March 31,	
	2014	2013
	(unaudited)	
As reported operating expenses according to GAAP	$ 57,828	$ 41,735
Excluding compensation expense related to equity awards	(7,069)	(2,869)
Pro forma operating expenses	$ 50,759	$ 38,866
As reported income (loss) from operations according to GAAP	$ (29,667)	$ 1,625
Excluding compensation expense related to equity awards	(7,069)	(2,869)
Pro forma income (loss) from operations	$ (22,598)	$ 4,494
As reported net loss according to GAAP	$ (31,280)	$ (1,672)
Excluding compensation expense related to equity awards	(7,069)	(2,869)
Pro forma net income (loss)	$ (24,211)	$ 1,197

Reconciliation of GAAP to Pro Forma Basis

As illustrated in the Selected Financial Information in this press release, pro forma operating expenses, pro forma income (loss) from operations, and proforma net income (loss) 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 results 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, 2014 (unaudited)	December 31, 2013
Assets:		
Cash, cash equivalents and short-term investments	$ 631,293	$ 656,761
Investment in Regulus Therapeutics Inc.	63,586	52,096
Other current assets	27,174	26,653
Property, plant and equipment, net	86,641	86,198
Other assets	25,922	25,448
Total assets	$ 834,616	$ 847,156
Liabilities and stockholders' equity:		
Other current liabilities	$ 46,408	$ 49,677
Current portion of deferred contract revenue	54,428	48,135
2 3/4% convertible senior notes	152,005	150,334
Long-term obligations, less current portion	76,918	77,830
Long-term deferred contract revenue	130,755	142,790
Stockholders' equity	374,102	378,390
Total liabilities and stockholders' equity	$ 834,616	$ 847,156

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