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 28, 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:

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 28, 2014, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter and fiscal year ended December 31, 2013. 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 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 28, 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: February 28, 2014

By: /s/ B. Lynne Parshall

B. LYNNE PARSHALL
Chief Operating Officer,
and Director

INDEX TO EXHIBITS

99.1	Press Release dated February 28, 2014.

ISIS REPORTS FINANCIAL RESULTS AND HIGHLIGHTS FOR 2013

- **Outperforms 2013 Projections for Pro Forma Net Operating Loss and Year-end Cash**
- **Conference Call Webcast Friday, February 28, 11:30 a.m. ET at www.isispharm.com**

CARLSBAD, Calif., February 28, 2014 - Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced its 2013 financial results and reviewed the highlights of the year. Isis ended the year in a strong financial position and outperformed both its pro forma net operating loss (NOL) guidance and its cash guidance for the year. For the year ended December 31, 2013, Isis had an NOL of $40.2 million compared to $60.4 million for 2012. Isis' strong financial performance in 2013 is the result of the Company's successful execution of its business strategy. Isis added a substantial amount of cash to its balance sheet in 2013, ending the year with $657 million. The increase in the Company's cash position was primarily due to the significant amount of cash received from its partners as well as the net proceeds from the equity offering it completed in 2013. On a GAAP basis, Isis reported a loss from operations of $19.9 million and $51.7 million for the three and twelve months ended December 31, 2013, respectively, compared to $26.1 million and $68.9 million for the same periods in 2012.

"2013 was a year of significant growth for Isis with successes in every aspect of our business. KYNAMRO® is the first systemic antisense drug for chronic use to be sold commercially. This was an important event for patients with homozygous FH, for Isis and for antisense technology. Our pipeline of novel antisense drugs also matured substantially. We reported positive data on a number of drugs, including ISIS-APOCIII$_{Rx}$ and ISIS-SMN$_{Rx}$, both of which are scheduled to begin Phase 3 development this year," said B. Lynne Parshall, chief operating officer of Isis. "Our successes, however, go beyond our pipeline. We added new partnerships and expanded existing partnerships, which we believe will provide us with extensive resources and expertise to advance our severe and rare disease and cancer programs. All of these activities have substantially contributed to our financial performance in 2013 and to the increase in value of our technology and drugs in development. We have continued this momentum into 2014 and look forward to another year of progress in all aspects of our business."

"Our financial performance in 2013 resulted from the successful execution of our business model. We received $225 million in payments from our partners, including $130 million from our new partnerships with Roche and Biogen Idec and $75 million in milestone payments as our drugs advanced in development. As such, we ended the year in a very strong financial position with more than $650 million in cash, significantly higher than our projection of more than $625 million. In addition, although many drugs in our pipeline advanced into late-stage development, we kept our spending in line with projections and ended the year with a pro forma NOL of $40 million," said Elizabeth L. Hougen, chief financial officer of Isis.

"As we carry this momentum into 2014, we have many opportunities to earn significant revenue from our partnerships as our drugs continue to advance. Although we are planning to end 2014 with three drugs in Phase 3 development and ten drugs in Phase 2 development, we are projecting to end 2014 with a pro forma NOL in the low $50 million range. We are also projecting to end the year with more than $575 million in cash. Already this year, we have earned more than $16 million from our partners as our and our partners' drugs in development continue to mature. In addition, although we are optimistic about the commercial potential of KYNAMRO and believe that KYNAMRO sales will increase this year, we continue to be conservative in our projections and will not include KYNAMRO profit share revenue at this point in the year," concluded Ms. Hougen.

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 and twelve months ended December 31, 2013 was $42.2 million and $147.3 million, respectively, compared to $19.9 million and $102.0 million for the same periods in 2012. Isis' revenue fluctuates based on the nature and timing of payments under agreements with its partners, including license fees, milestone-related payments and other payments. In 2013, Isis earned $83 million in revenue from milestone and licensing payments including:

- $26.5 million from GlaxoSmithKline because Isis advanced ISIS-TTR$_{Rx}$, ISIS-GSK3$_{Rx}$ and ISIS-GSK4$_{Rx}$ in development;
- $25 million from Genzyme when the FDA approved the KYNAMRO NDA;
- $10 million when AstraZeneca added a second development candidate, ISIS-AR$_{Rx}$, to its collaboration;
- $17 million from Biogen Idec because Isis advanced the Phase 2 study of ISIS-SMN$_{Rx}$ in infants and for selecting and advancing ISIS-DMPK$_{Rx}$ in development; and
- $3.5 million when Xenon licensed XEN701.

Isis' revenue in 2013 also included $64 million primarily from the amortization of upfront fees and manufacturing services performed for its partners.

Operating Expenses

As projected, Isis' pro forma operating expenses of $59.0 million and $187.5 million for the three and twelve months ended December 31, 2013, respectively, were higher compared to $44.2 million and $162.4 million for the same periods in 2012. The increase in operating expenses was primarily due to higher costs associated with the maturation and expansion of Isis' pipeline.

On a GAAP basis, Isis' operating expenses for the three and twelve months ended December 31, 2013 were $62.1 million and $199.0 million, respectively, compared to $46.0 million and $171.0 million for the same periods in 2012.

Income Tax Benefit

Isis recognized a tax benefit of $5.9 million for the year ended December 31, 2013 compared to a tax benefit of $9.1 million in 2012. Isis' tax benefit is the result of unrealized gains on its equity investments in its satellite companies, including Regulus, a company it co-founded with Alnylam Pharmaceuticals. Isis' tax benefit declined in 2013 compared to 2012 primarily because the unrealized gains in 2013 were not as large as in 2012.

Net Loss

Isis reported a net loss of $24.3 million and $60.6 million for the three and twelve months ended December 31, 2013, respectively, compared to $2.6 million and $65.5 million for the same periods in 2012. Basic and diluted net loss per share for the three and twelve months ended December 31, 2013 was $0.21 per share and $0.55 per share, respectively, compared to $0.03 per share and $0.65 per share for the same periods in 2012. Isis' net loss for the year ended December 31, 2013 decreased compared to 2012 due to a decrease in the Company's net operating loss resulting primarily from the significant increase in revenue that Isis earned from its partners in 2013. The decrease in the Company's net operating loss was partially offset by the following items that occurred in 2012 and did not reoccur in 2013:

- $18.4 million gain the Company realized in 2012 because of the increase in Regulus' valuation resulting from its initial public offering;
- $4.8 million loss, $3.6 million of which was non-cash, the Company recorded in 2012 on the early retirement of its 2 5/8% convertible subordinated notes.

Balance Sheet

As of December 31, 2013, Isis had cash, cash equivalents and short-term investments of $656.8 million compared to $374.4 million at December 31, 2012 and working capital of $637.7 million at December 31, 2013 compared to $349.1 million at December 31, 2012. During 2013, Isis received $225 million in cash from its partners as a result of Isis' successful execution of its business strategy. In addition, Isis received approximately $236 million in cash from the issuance of its common stock. Isis' working capital increased significantly in 2013 primarily due to the cash Isis received in 2013 and from an increase in the carrying value of Isis' investment in Regulus.

2014 Goals

"We expect 2014 to be another year of continued maturation for our pipeline of novel, first-in-class drugs. We plan to begin Phase 3 development for ISIS-APOCIII$_{Rx}$ and ISIS-SMN$_{Rx}$. In addition, we plan to report clinical data from numerous drugs in development in every area of our pipeline, including our severe and rare, and metabolic disease programs. We plan to continue to grow the pipeline by adding new drugs into development. And finally, we expect to explore partnering opportunities that are the best fit for Isis and our programs. Revenue from our existing partnerships allows us to continue to invest in our technology and our pipeline," said Ms. Parshall.

In 2014, Isis plans to achieve the following goals itself and with its partners:

- Together with Genzyme, Isis will continue to support KYNAMRO development, marketing and commercialization activities.
  - Advance FOCUS FH with data planned in 2015.
  - Pursue marketing approval for KYNAMRO in other countries.
  - Support commercial launch activities in the United States and in other countries for patients with HoFH.
- Mature its pipeline.
  - Report clinical data from the Phase 2 studies on ISIS-SMN$_{Rx}$ at the upcoming American Academy of Neurology meeting.
  - Report data from up to seven drugs in late-stage development, including Phase 2 data on ISIS-FXI$_{Rx}$ and ISIS-GCGR$_{Rx}$.
  - Initiate up to five Phase 3 studies, including Phase 3 studies on ISIS-APOCIII$_{Rx}$ and ISIS-SMN$_{Rx}$.
  - Initiate Phase 2 studies on up to three drugs.
- Broaden its pipeline by adding up to five new drugs in both partnered and unpartnered programs.
- Continue to successfully execute its business strategy to generate revenue and cash.

Business Highlights

"The approval of KYNAMRO validated antisense technology and demonstrated that the drug discovery technology platform we developed can produce drugs that are safe and can treat devastating diseases. The rest of the pipeline continues to mature and this progress ensures that we will have many readouts of important clinical data to look forward to this year," concluded Ms. Parshall. "We also continued to successfully execute our partnering strategy, bringing in $225 million in cash from our partners. We established a broad strategic relationship with Biogen Idec in neurological disorders that we expect will bolster ours and Biogen Idec's pipelines, we added Roche as a preferred partner for our Huntington's disease program and we continued to progress our partnered programs with AstraZeneca and GlaxoSmithKline. All of these activities enabled us to end the year with a substantially improved financial position, which sets us up for a productive 2014."

Drug Development Highlights

- Isis and Genzyme were successful in bringing KYNAMRO to the market in the United States, Mexico, South Korea and Argentina for patients with homozygous FH. These patients are at high cardiovascular risk and may not be able to reduce their LDL-C sufficiently with currently available lipid-lowering therapies.
  - Isis received a $25 million milestone payment from Genzyme related to the marketing approval of KYNAMRO by the FDA.
  - Genzyme notes trends toward increases in qualified physicians, prescriptions and patients on drug, with optimism that these trends will continue in 2014. Genzyme is supporting the commercial success of KYNAMRO by:

- Qualifying hundreds of treating physicians under the KYNAMRO REMS program to prescribe KYNAMRO,
- Completing a Phase 1 KYNAMRO study in Japan to support ongoing discussions with Japan regulatory authorities regarding the next steps in development,
- Expanding KYNAMRO commercial markets by obtaining marketing approval for KYNAMRO in the United States, Mexico, Argentina and South Korea and pursuing regulatory approvals in other countries. Genzyme has stated that it has the infrastructure in place to successfully bring KYNAMRO to patients in these new markets.

- Isis reported five sets of positive Phase 2 data demonstrating that ISIS-APOCIII$_{Rx}$ can effectively lower triglyceride levels in patients with high to extremely high triglyceride levels and can work as effectively as a single agent or in combination with fibrates. In addition, Isis reported that treated patients with type 2 diabetes experienced improvements in glucose control with trends toward enhanced insulin sensitivity.
  - Isis published data in the journal Circulation Research demonstrating that antisense inhibition of ApoC-III produced significant reductions of ApoC-III and triglycerides in humans and other animal species.
  - Isis received European Orphan Drug Designation for ISIS-APOCIII$_{Rx}$ for the treatment of patients with familial chylomicronemia syndrome.
- Isis reported positive clinical data in children and infants with SMA demonstrating that ISIS-SMN$_{Rx}$ is well tolerated with increases in muscle function scores observed in the type 2/3 children.
  - Isis presented interim results from both multiple-dose Phase 2 studies in infants and children with SMA demonstrating that ISIS-SMN$_{Rx}$ continues to be well tolerated at all doses. In the infant study, all four infants from the 6 mg cohort have been in the study for over six months and all have received three doses of ISIS-SMN$_{Rx}$, and one infant has received a fourth dose of ISIS-SMN$_{Rx}$. In the childhood onset study, Isis reported dose- and time-dependent increases in muscle function scores in children treated with multiple-doses of ISIS-SMN$_{Rx}$. In children treated with 9 mg of ISIS-SMN$_{Rx}$, Isis reported an average increase in muscle function score of 3.7 points.
  - Isis reported results from an assay that measures SMN protein levels in the cerebral spinal fluid. The Company observed dose-dependent increases in SMN protein levels in children treated with ISIS-SMN$_{Rx}$ from both the single- and multiple-dose studies.
  - Dr. Kathy Swoboda presented follow up data from a single-dose open-label Phase 1 study of ISIS-SMN$_{Rx}$ in children with SMA at the International Congress of the World Muscle Society. In this study, data suggest that children from the two highest doses continued to show increases in muscle function scores up to 14 months after a single injection of ISIS-SMN$_{Rx}$.

- Dr. Claudia Chiriboga reported Phase 1 data on ISIS-SMN$_{Rx}$ at the American Academy of Neurology. In this open-label study conducted in a small population, ISIS-SMN$_{Rx}$ was well tolerated in children with SMA and increases in muscle function scores were observed in a number of these children.
- Isis received a positive opinion on European Orphan Drug Designation in the EU for ISIS-TTR$_{Rx}$ for the treatment of patients with TTR amyloidosis.
- Isis and its partners reported positive data from six drugs, including multiple results from Phase 2 studies of ISIS-SMN$_{Rx}$ and ISIS-APOCIII$_{Rx}$, and Isis added five drugs to its pipeline.
- Isis and its partners initiated clinical studies on ten drugs.

Corporate Highlights

- Isis formed a broad strategic alliance with Biogen Idec to discover and develop antisense drugs to treat neurological disorders, which combines Biogen Idec's expertise in neurology with Isis' leadership in antisense technology.
  - Isis received a $100 million upfront payment from Biogen Idec.
  - Isis is eligible to receive substantial milestone payments, license fees and royalty payments for all treatments developed through this collaboration.
- Isis formed a new alliance with Roche to discover and develop antisense drugs to treat Huntington's disease.
  - Isis received a $30 million upfront payment and is eligible to receive up to $362 million in a license fee and milestone payments.
  - In addition, Isis is eligible to receive up to $136.5 million in milestone payments for each additional drug successfully developed plus up to $50 million in commercial milestones if a drug using Roche's proprietary brain shuttle technology is successfully commercialized.
- Isis is also eligible to receive tiered royalties on sales of drugs arising from the alliance.
- Isis received $6 million from AstraZeneca related to the continuation of the research collaboration between it and AstraZeneca to discover and develop novel antisense drugs to treat cancer.
- In 2014 to date, Isis has earned more than $16 million in payments from its partners as the Company's and its partners' drugs in development continue to mature.
- Isis successfully completed a public offering of common stock raising $173.3 million in net proceeds. Isis is using the proceeds from this offering to support the Phase 3 development of ISIS-APOCIII$_{Rx}$, retain other drugs longer in development and advance the rest of its pipeline.
- Isis added Mr. Breaux Castleman and Joseph Loscalzo, M.D., Ph.D. to its Board of Directors.
- Isis' founder, CEO and chairman of the board of directors, Stanley T. Crooke, Ph.D., M.D., was awarded the 2013 Director of the Year Award for Companies in Transition by the Corporate Directors Forum and the 2013 Distinguished Scientist Award by the San Diego section of the American Chemical Society.

Conference Call

At 11:30 a.m. Eastern Time today, February 28, 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 866-652-5200, 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 31 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, including the commercial potential 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, 2012, 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.

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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,	
	2013	2012	2013	2012
	(unaudited)			
Revenue:				
Research and development revenue under collaborative agreements	$ 41,275	$ 17,890	$ 144,194	$ 96,415
Licensing and royalty revenue	973	1,983	3,091	5,634
Total revenue	$ 42,248	19,873	147,285	102,049
Expenses:				
Research, development and patent expenses	57,430	42,758	184,033	158,458
General and administrative	4,676	3,234	14,918	12,515
Total operating expenses	62,106	45,992	198,951	170,973
Loss from operations	(19,858)	(26,119)	(51,666)	(68,924)
Other income (expense):				
Equity in net loss of Regulus Therapeutics Inc.	—	(267)	—	(1,406)
Investment income	686	359	2,085	1,844
Interest expense	(4,885)	(4,817)	(19,355)	(21,152)
Gain on investments, net	305	1,446	2,378	1,465
Gain on investment in Regulus Therapeutics, Inc.	—	18,356	—	18,356
Loss on early retirement of debt	—	—	—	(4,770)
Loss before income tax benefit (expense)	(23,752)	(11,042)	(66,558)	(74,587)
Income tax benefit (expense)	(524)	8,405	5,914	9,109
Net loss	$ (24,276)	$ (2,637)	$ (60,644)	$ (65,478)
Basic and diluted net loss per share	$ (0.21)	$ (0.03)	$ (0.55)	$ (0.65)
Shares used in computing basic and diluted net loss per share	116,122	101,246	110,502	100,576

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,	
	2013	2012	2013	2012

	(unaudited)		(unaudited)	
As reported operating expenses according to GAAP	$ 62,106	$ 45,992	$ 198,951	$ 170,973
Excluding compensation expense related to equity awards	(3,101)	(1,811)	(11,418)	(8,571)
Pro forma operating expenses	$ 59,005	$ 44,181	$ 187,533	$ 162,402
As reported loss from operations according to GAAP	$ (19,858)	$ (26,119)	$ (51,666)	$ (68,924)
Excluding compensation expense related to equity awards	(3,101)	(1,811)	(11,418)	(8,571)
Pro forma loss from operations	$ (16,757)	$ (24,308)	$ (40,248)	$ (60,353)

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 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)

	December 31, 2013	December 31, 2012
Assets:		
Cash, cash equivalents and short-term investments	$ 656,761	$ 374,446
Investment in Regulus Therapeutics Inc.	52,096	33,622
Other current assets	26,653	15,370
Property, plant and equipment, net	86,198	91,084
Other assets	25,448	31,164
Total assets	$ 847,156	$ 545,686
Liabilities and stockholders' equity:		
Other current liabilities	$ 49,677	$ 38,397
Current portion of deferred contract revenue	48,135	35,925
2 3/4% convertible senior notes	150,334	143,990
Long-term obligations, less current portion	77,830	77,952
Long-term deferred contract revenue	142,790	66,656
Stockholders' equity	378,390	182,766
Total liabilities and stockholders' equity	$ 847,156	$ 545,686

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