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 12, 2008**

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.)

1896 Rutherford Road
Carlsbad, CA 92008
(Address of Principal Executive Offices and Zip Code)

Registrant's telephone number, including area code: **(760) 931-9200**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

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

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

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

o Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Item 2.02. Results of Operations and Financial Condition.

On May 12, 2008, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter ended March 31, 2008. In addition to disclosing results that are determined in accordance with Generally Accepted Accounting Principles (GAAP), the Company also discloses pro forma or non-GAAP results of operations, which are adjusted from GAAP to exclude non-cash compensation related to stock options. The Company is presenting pro forma information excluding non-cash compensation expense or benefit because the Company believes it is useful for investors in assessing the Company's operating results compared to the prior year. A copy of the release is furnished with this report as an exhibit pursuant to "Item 2.02. Results of Operations and Financial Condition" of Form 8-K in accordance with SEC Release Nos. 33-8216 and 34-47583.

The information in this Current Report on Form 8-K and the Exhibit attached hereto shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933 or the Exchange Act, regardless of any general incorporation language in such filing.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

99.1 Press Release dated May 12, 2008.

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 12, 2008

By: /s/ **B. LYNNE PARSHALL**
B. LYNNE PARSHALL
Executive Vice President,
Chief Financial Officer and Director

INDEX TO EXHIBITS

99.1	Press Release dated May 12, 2008.

ISIS REPORTS FINANCIAL RESULTS AND HIGHLIGHTS FOR FIRST QUARTER OF 2008

- **Conference Call Webcast Monday, May 12, 08:30 a.m. EDT at www.isispharm.com**

CARLSBAD, Calif., May 12, 2008 - Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced its financial results for the quarter ended March 31, 2008. The Company finished the quarter with a pro forma net operating loss (NOL) of $5.1 million, excluding compensation expense related to stock options, compared to a pro forma NOL of $18.5 million in the first quarter of 2007. This 73% reduction in NOL was driven primarily by significantly increased revenue from Isis' successful partnering activities. On a GAAP basis, Isis recorded a 2008 loss from operations for the quarter of $8.8 million, compared to $20.9 million in the first quarter of 2007, a 58% decrease. Isis remains on track to meet its 2008 guidance for a NOL, excluding non-cash compensation expense, of less than $15 million.

"Isis ends the first quarter of 2008 in the strongest financial position in our history, and we are on track to meet our NOL and cash guidance for the year. As a result of recent transactions, both Ibis and Regulus are fully funded and are tangible examples of the value being created through our satellite company strategy," said B. Lynne Parshall, Chief Operating Officer and Chief Financial Officer of Isis. "In addition to the significant cash position with which we ended 2007, we have received $192 million in cash so far in 2008 to end the quarter with nearly $340 million."

Results of Operations

The 58% decrease in the Company's loss from operations for the first quarter of 2008 compared to the first quarter of 2007 was primarily a result of a significant increase in revenue in 2008 from Isis' corporate partnerships, offset in part, by higher expenses associated with the expansion of the companies' key programs and an increase in non-cash stock compensation expense reflecting the increase in Isis' stock price from the first quarter of 2007 to the first quarter of 2008. The reasons for the decrease in the Company's pro forma loss from operations were the same as those for the decrease in the Company's loss from operations according to GAAP other than the effect of non-cash compensation expense related to stock options. The reconciliation of pro forma and GAAP measures is explained later in this release.

Revenue

Total revenue for the first quarter of 2008 was $21.4 million compared to $2.5 million for the first quarter of 2007. Revenue was significantly higher in the first quarter of 2008 due to the addition of revenue from new collaborations. As part of Isis' new strategic relationship with Genzyme Corporation, Genzyme purchased $150 million of Isis stock at $30 per share. Isis is amortizing the premium on the stock, $100 million calculated using a Black-Scholes option valuation model, over the four-year period of the collaboration beginning in the first quarter of 2008. Also contributing to the increase in Isis' revenue was an increase in Ibis' revenue, which is discussed further in the Ibis Biosciences section below.

Expenses

On a pro forma basis, operating expenses for the quarter ended March 31, 2008 were $26.4 million compared to $21.0 million for the same period in 2007. Isis has expanded its clinical development programs as its drugs advance in development, resulting in an increase in operating expenses of $1.5 million in the first quarter of 2008 compared to the first quarter of 2007. Additionally, Ibis' operating expenses have increased by $2.2 million to support the growth of its commercial business and the cost of activities to achieve milestones as part of Abbott's investment and purchase option. Also contributing to the increase in operating expenses was $1.5 million of expenses associated with Isis' joint venture, Regulus, which are expected to increase over the year as Regulus increases its staffing and operations. On a GAAP basis, Isis' operating expenses for the quarter ended March 31, 2008 were $30.2 million compared to $23.4 million for the same period in 2007, including non-cash

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compensation expense related to stock options of $3.8 million and $2.4 million for the quarters ended March 31, 2008 and 2007, respectively.

Ibis Biosciences, Inc.

Ibis' revenue for the quarter ended March 31, 2008 was $3.0 million compared to $1.6 million for the same period in 2007. As a result of the increased number of T5000 Biosensor System placements during fiscal year 2007, Ibis' commercial revenue of $1.2 million for the first quarter of 2008 was approximately double its commercial revenue of $631,000 in the first quarter of 2007. Commercial revenue consisted of revenue from sales of Ibis T5000 Biosensor Systems and assay kits, as well as revenue from Ibis' assay services business. Ibis' revenue from government contracts was $1.8 million for the first quarter of 2008, representing an increase of 89% over $945,000 in the first quarter of 2007, driven primarily by recently awarded contracts that support commercial as well as government applications of the T5000.

Excluding non-cash compensation expense related to stock options, operating expenses for Ibis were $6.4 million for the quarter ended March 31, 2008, compared to $4.3 million for the same period in 2007. The increase in operating expenses primarily reflects an increase in costs to support the growth of Ibis' commercial business and the cost to achieve milestones as part of the Abbott transaction. Ibis generated a loss from operations, excluding non-cash compensation expense related to stock options, of $3.4 million for the quarter ended March 31, 2008, compared to $2.7 million for the same period in 2007. Ibis' non-cash compensation expense related to stock options was $476,000 and $409,000 for the quarters ended March 31, 2008 and 2007, respectively.

Regulus Therapeutics LLC

In April 2008, Regulus entered into a strategic alliance with GlaxoSmith Kline (GSK) to discover, develop and market novel microRNA-targeted therapeutics. Regulus received $20 million in upfront payments from GSK, including a $15 million option fee and a $5 million note that will convert into Regulus common stock in the future under certain specified circumstances. The $15 million option fee will be amortized into revenue over Regulus' six-year period of performance. The $5 million note will be shown as a liability on Isis' Consolidated Balance Sheet.

Net Loss Applicable to Common Stock

Isis' net loss for the quarter ended March 31, 2008 was $4.3 million or $0.05 per share compared to $13.0 million or $0.16 per share for the first quarter of 2007. Isis' net loss for the first quarter of 2008 was lower than the first quarter of 2007 primarily due to the decrease in the Company's loss from operations and lower interest expense, offset by an increase in investment income and the $6.8 million loss attributed to the noncontrolling interest in Symphony GenIsis, Inc. that Isis recorded in the first quarter of 2007. Isis did not record this benefit in the first quarter of 2008 because it purchased all of the equity of Symphony GenIsis in the third quarter of 2007, saving $75 million in the predetermined purchase price.

Balance Sheet

As of March 31, 2008, Isis had cash, cash equivalents and short-term investments of $338.4 million compared to $193.7 million at December 31, 2007. As of March 31, 2008, Isis had consolidated working capital of $272.6 million compared to $145.1 million at December 31, 2007. The cash Isis received in the first quarter of 2008 from Genzyme ($150 million) and Abbott ($20 million) primarily led to the increase in Isis' consolidated working capital offset by $25 million of deferred revenue from Genzyme that is included in current liabilities. In connection with the Genzyme transaction, Isis recorded the $100 million premium on the $150 million equity investment as a liability and is amortizing it into revenue over the four-year period of the collaboration beginning in the first quarter of 2008. Isis recorded the remaining $50 million of proceeds as stockholders' equity.

Quarterly Highlights

"The momentum we created in 2007 continued in full force into the first quarter of 2008 with more partnering successes and advances in our pipeline. The highlight of the quarter was our strategic relationship with Genzyme focused on the licensing of mipomersen and a research relationship. Together with Genzyme, we have made significant progress in revising mipomersen's development plans to be responsive to the FDA's

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recent guidance. We remain confident the deal will be completed this quarter on terms that are attractive to both companies," continued Ms. Parshall. "As evidenced from our recent partnering successes, we continue to benefit from our business strategy that enables us to discover and develop drugs and technologies, nurturing them until the right time to progress them to partners or to satellite companies. This strategy has provided us with the financial strength and the diverse pipeline of drugs that we have today. Looking forward, we expect to grow our pipeline this year, adding two to four new drugs; already we have added the first drug with PSCK9, our development candidate with Bristol-Myers Squibb. In addition, we will be presenting clinical data from some of our most advanced drugs and moving exciting new drugs into clinical studies. We are on target to meet our financial goals for 2008, including ending the year with over $450 million in cash that will enable us to continue to exploit our efficient drug discovery platform and to lead innovation in RNA-based technologies."

- ***Mipomersen***

  Mipomersen, the most advanced drug in Isis' cardiovascular pipeline, will be evaluated in a broad Phase 3 program in patients with high cholesterol at high risk for cardiovascular disease including an ongoing Phase 3 study in patients with homozygous Familial Hypercholesterolemia (FH).

  - Isis reported updated safety data on mipomersen from an ongoing open-label extension study in 20 patients with FH that showed that mipomersen continues to be well tolerated and maintains activity in longer-term treatment.
  - Isis reported the results of two preclinical studies in which the lowering of apoB-100 resulted in the dramatic reduction of atherosclerotic plaques in murine models of atherosclerosis.
  - In April, Isis received guidance from the FDA on approval requirements for mipomersen.
  - Isis licensed mipomersen to Genzyme as part of a strategic alliance for which the contracts are being finalized and the transaction is expected to be completed this quarter. The deal included:

    - A $175 million mipomersen licensing fee
    - A $150 million equity investment (at $30 per share)
    - Over $1.5 billion in milestone payments for mipomersen
    - A share of profits on mipomersen and follow-on drug(s) ranging from 30 to 50 percent of all commercial sales.
    - A preferred partner relationship for the development and commercialization of antisense drugs for CNS and certain rare diseases.

- ***Pipeline Highlights***

  - Isis expanded its cardiovascular disease franchise with the addition of a development candidate that targets PCSK9.

    - Isis received a $2 million milestone payment with the selection of an antisense drug candidate to advance into development.

  - OncoGenex reported encouraging Phase 2 data of OGX-011, an antisense drug in clinical studies in patients with advanced prostate or lung cancers.
  - Antisense Therapeutics licensed TV-1102 (formerly ATL1102), an antisense drug in Phase 2 clinical development for patients with multiple sclerosis, to Teva Pharmaceuticals.
  - Altair Therapeutics has advanced AIR 645, an antisense drug discovered by Isis and licensed to Altair in 2007, into Phase 1 studies. AIR 645 is the first inhaled antisense drug to enter clinical development for the treatment of asthma.
  - Lilly has advanced an antisense drug, LY2181308, which targets survivin for the treatment of cancer, into Phase 2 trials.

- ***Ibis Biosciences***

  - Ibis, Isis' majority-owned subsidiary, has developed and is commercializing its biosensor technology to revolutionize the way that infectious disease pathogens are identified. At the beginning of the year, Ibis completed a transaction with Abbott in which:

    - Abbott invested $20 million in Ibis and now owns 10.25 percent equity in Ibis at a post money valuation of $215 million, with the option to invest an additional $20 million in Ibis by July 31, 2008.

- Abbott also acquired the option to purchase the remaining shares of Ibis for a total purchase price of $215 to $230 million. If Abbott exercises its option to acquire Ibis, Isis will receive earn out payments tied to the achievement of specific cumulative sales.

- Ibis entered into a distribution relationship under which Abbott will be selling Ibis products.

- Ibis was also awarded up to approximately $2.8 million in government contracts and grants.

- ***Regulus Therapeutics***

  - Regulus, Isis' joint venture formed in September 2007, is focused on developing microRNA therapeutics, as a new approach to target the pathways of human disease. Last month, Regulus entered into a strategic alliance with GSK that could provide up to nearly $600 million to Regulus to develop microRNA-targeted therapeutics to treat inflammatory disease.

    - Regulus received a $20 million upfront payment, including a $15 million option fee and payment for a $5 million note that will convert into Regulus common stock under certain circumstances.
    - The alliance provides GSK with an option to license drug candidates directed at four different inflammatory disease microRNA targets.
    - Regulus will receive up to $144.5 million in development, regulatory and sales milestone payments for each microRNA-targeted drug discovered and developed as part of the collaboration.
    - Regulus will also receive tiered royalties up to double digits on sales of drugs resulting from the alliance.

Conference Call

At 08:30 a.m. Eastern Time today, May 12, Isis will conduct a live webcast conference call to discuss this earnings release and related activities. Interested parties may access the webcast at www.isispharm.com, or listen to the call by dialing 877-548-7906. A webcast replay will be available for a limited time at the same address.

About Isis Pharmaceuticals, Inc.

Isis is exploiting its expertise in RNA to discover and develop novel drugs for its product pipeline and for its partners. The Company has successfully commercialized the world's first antisense drug and has 18 drugs in development. Isis' drug development programs are focused on treating cardiovascular and metabolic diseases. Isis' partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. Ibis Biosciences, Inc., Isis' majority-owned subsidiary, is developing and commercializing the Ibis T5000™ Biosensor System, a revolutionary system to identify infectious organisms. Isis is a joint owner of Regulus Therapeutics LLC, a joint venture focused on the discovery, development and commercialization of microRNA therapeutics. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of over 1,500 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release includes forward-looking statements regarding Isis Pharmaceuticals' business, the financial position and outlook for Isis as well as its Ibis Biosciences subsidiary and its Regulus joint venture, and the therapeutic and commercial potential of the Company's 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, including those statements that are described as Isis' goals or projections. 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, in developing and commercializing systems to identify infectious organisms that are effective and commercially attractive, and in the endeavor of building a business around such products. 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, 2007, 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.

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,

	March 31,	
	2008	2007
	(unaudited)	
Revenue:		
Research and development revenue under collaborative agreements	$ 20,686	$ 2,002
Licensing and royalty revenue	668	448
Total revenue	21,354	2,450
Expenses:		
Research and development	26,449	19,949
Selling, general and administrative	3,736	3,402
Total operating expenses	30,185	23,351
Loss from operations	(8,831)	(20,901)
Other income (expense):		
Investment income	4,956	3,401
Interest expense	(1,398)	(2,628)
Gain on investments	—	1,521
Loss on early retirement of debt	—	(1,219)
Loss attributed to noncontrolling interest in Symphony GenIsis, Inc.	—	6,806
Loss attributed to noncontrolling interest in Regulus Therapeutics LLC	883	—
Loss attributed to noncontrolling interest in Ibis Biosciences, Inc.	105	—
Net loss applicable to common stock	$ (4,285)	$ (13,020)
Basic and diluted net loss per share	$ (0.05)	$ (0.16)
Shares used in computing basic and diluted net loss per share	90,799	82,456

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

	Three months ended, March 31,	
	2008	2007
	(unaudited)	
As reported operating expenses according to GAAP	$ 30,185	$ 23,351
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(3,759)	(2,364)
Proforma operating expenses	$ 26,426	$ 20,987
As reported loss from operations according to GAAP	$ (8,831)	$ (20,901)
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(3,759)	(2,364)
Proforma loss from operations	$ (5,072)	$ (18,537)

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.

Ibis Biosciences, Inc.
Statements of Operations
(In Thousands)

	Three months ended, March 31,	
	2008	2007
	(unaudited)	
Revenue:		
Commercial revenue (1)	$ 1,195	$ 631
Research and development revenue under collaborative agreements	1,784	945

Total revenue	2,979	1,576
Expenses:		
Cost of commercial revenue (2)	817	718
Research and development	4,556	3,005
Selling, general and administrative	1,503	988
Total operating expenses	6,876	4,711
Loss from operations	$ (3,897)	$ (3,135)

(1) Ibis' commercial revenue has been classified as research and development revenue under collaborative agreements on Isis' condensed consolidated statement of operations.

(2) Ibis' cost of commercial revenue has been classified as research and development expenses on Isis' condensed consolidated statement of operations.

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Isis Pharmaceuticals, Inc.
Condensed Consolidated Balance Sheets
(In Thousands)

	March 31, 2008	December 31, 2007
	(unaudited)	
Assets:		
Cash, cash equivalents and short-term investments	$ 338,415	$ 193,719
Other current assets	14,436	13,598
Property, plant and equipment, net	8,274	7,131
Other assets	44,299	44,410
Total assets	$ 405,424	$ 258,858
Liabilities, noncontrolling interest and stockholders' equity:		
Current liabilities	$ 80,260	$ 62,205
2 5/8% convertible subordinated notes	162,500	162,500
Long-term obligations, net of current portion	85,189	23,910
Noncontrolling interest in Regulus Therapeutics LLC	8,488	9,371
Noncontrolling interest in Ibis Biosciences, Inc.	14,366	—
Stockholders' equity	54,621	872
Total liabilities, noncontrolling interest and stockholders' equity equity	$ 405,424	$ 258,858

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