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): **August 7, 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 August 7, 2008, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter ended June 30, 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 expense. These measures are provided as supplementary information and are not a substitute for financial measures calculated in accordance with GAAP. The Company reports these pro forma results to better enable financial statement users to assess 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. 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 August 7, 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: August 6, 2008

By: /s/ **B. LYNNE PARSHALL**
B. LYNNE PARSHALL
Chief Operating Officer,
Chief Financial Officer and Director

INDEX TO EXHIBITS

99.1 Press Release dated August 7, 2008.

ISIS REPORTS FINANCIAL RESULTS AND HIGHLIGHTS FOR SECOND QUARTER OF 2008

- **Isis ends the second quarter with more than $535 million in cash**
- **Conference Call Webcast Thursday, August 7, 8:30 a.m. EDT at www.isispharm.com**

CARLSBAD, Calif., August 7, 2008 - Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced its financial results for the second quarter ended June 30, 2008. The Company ended the quarter in the strongest financial position in its history with more than $535 million of cash and $873,000 of pro forma operating income in the second quarter.

"Over the last year we have added significant cash through our recent collaborations. More importantly, as our corporate alliances continue to be successful, we will continue to add cash to our balance sheet and revenue to our P&L. We remain on track to end 2008 with more than $450 million in cash and to meet our pro forma net operating loss guidance of less than $15 million for the year," commented B. Lynne Parshall, COO and CFO of Isis.

"Our strong financial position is a result of the successful execution of our business strategy, enabled by the efficiency of our antisense technology. The transactions we have completed balance both our short-term and long-term objectives. In addition, the maturation of our satellite companies is providing exactly the types of financial benefits for which they were created," continued Ms. Parshall. "Because of our partnering successes, we have reported our second profitable quarter in the past year. While we are not yet at the point of sustainable profitability and our quarter-to-quarter performance will continue to fluctuate based on one-time events such as the Teva-ATL license fee, our significant continuing revenue base coupled to our business model supports expansion of our pipeline while controlling our expenses, which we believe will lead to continuing strong financial performance."

Upcoming Key Milestones

- Initiate three trials in addition to the Phase 3 study in patients with heterozygous Familial Hypercholesterolemia (FH) announced this week, studying mipomersen in apheresis-eligible patients and high-risk high cholesterol patients
- Present liver imaging safety data on mipomersen
- Initiate Phase 1 clinical study on ISIS 353512, Isis' drug targeting CRP for the treatment of cardiovascular, renal and inflammatory diseases
- Report Phase 2 study data in type 2 diabetics treated with ISIS 113715 and sulfonylureas
- Complete Phase 1 study with ISIS 325568, targeting GCGR for the treatment of type 2 diabetes
- Initiate Phase 1 study on ISIS 333611, Isis' first CNS drug targeting SOD1 for the treatment of ALS
- Advance a second new drug candidate into development
- Potential acquisition of Ibis by Abbott

Financial Results

Isis had $873,000 of pro forma profit from operations in the second quarter of 2008 and a pro forma net operating loss (NOL) for the six months ended June 30, 2008 of $4.2 million, excluding compensation expense related to stock options, compared to an NOL of $17.3 million and $35.8 million during the same periods in 2007. On a GAAP basis, Isis recorded a loss from operations for the three and six months

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ended June 30, 2008 of $3.1 million and $12.0 million, respectively, compared to $19.7 million and $40.6 million for the same periods in 2007. The significant improvement in the Company's pro forma and GAAP operating results was driven primarily by the significant increase in revenue in 2008 from Isis' corporate partnerships. This was offset, in part, by higher expenses associated with the expansion of the companies' programs and, for Isis' GAAP results, an increase in non-cash stock compensation expense reflecting the increase in Isis' stock price over the same periods. The reconciliation of pro forma and GAAP measures is explained later in this release.

Revenue

Total revenue for the three and six months ended June 30, 2008 of $33.0 million and $54.3 million, respectively, was significantly higher than the revenue from the same periods in 2007 of $3.8 million and $6.3 million as a result of Isis' new collaborations. As part of Isis' strategic relationship with Genzyme Corporation, in the first quarter of 2008 Genzyme purchased $150 million of Isis stock at $30 per share and in the second quarter paid Isis a licensing fee of $175 million. Isis is amortizing the premium on the stock and the license fee into revenue through June 2012. Additionally, in the second quarter of 2008, Isis continued to recognize significant value from its partnerships, satellite companies and subsidiaries including:

- $2.0 million milestone payment from Bristol-Myers Squibb for a PCSK9 development candidate
- $4.6 million from Alnylam Pharmaceuticals, Inc.
- $1.4 million from Antisense Therapeutics Limited
- $3.3 million from Ibis representing a 72% increase from second half of 2007
- $656,000 of revenue from Regulus primarily from its GlaxoSmithKline (GSK) alliance

Operating Expenses

On a pro forma basis, operating expenses for the three and six months ended June 30, 2008 were $32.1 million and $58.5 million, respectively, compared to $21.1 million and $42.1 million for the same periods in 2007. The increase in operating expenses year over year is due to Isis' expanded clinical development programs as its drugs advance in development, an increase in Ibis' operating expenses to support the growth of its commercial business and the activities to achieve the Abbott milestones, and expenses for Regulus, which began in September 2007. On a GAAP basis, Isis' operating expenses for the three and six months ended June 30, 2008 were $36.1 million and $66.3 million, respectively, compared to $23.5 million and $46.8 million for the same periods in 2007,

including non-cash compensation expense related to stock options of $4.0 million and $7.8 million for the three and six months ended June 30, 2008 and $2.4 million and $4.8 million for the same periods in 2007.

Net Loss

Isis' net loss for the three and six months ended June 30, 2008 was $2.2 million and $6.5 million, respectively, compared to $11.0 million and $24.0 million for the same periods in 2007. Isis' net loss for the first half of 2008 was lower than the first half of 2007 primarily due to the decrease in the Company's loss from operations.

Balance Sheet

As of June 30, 2008, Isis had cash, cash equivalents and short-term investments of $537.0 million compared to $193.7 million at December 31, 2007. In 2008, Isis has received a significant amount of cash from its partners including:

- $325.0 million from Genzyme
- $40.5 million from Abbott
- $20.0 million from GSK

As of June 30, 2008, Isis had consolidated working capital of $428.1 million compared to $145.1 million at December 31, 2007. The cash Isis received in the first half of 2008 primarily led to the increase in Isis'

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consolidated working capital, offset by $68.9 million of deferred revenue from Genzyme and GSK that is included in current liabilities.

Based on Isis' existing and committed cash, not including the cash Isis could receive from Abbott if Abbott completes its purchase of Ibis, Isis remains on track to meet its cash guidance with a 2008 year end cash balance greater than $450 million, which the Company expects will last for at least five years.

Ibis Biosciences, Inc.

Ibis' revenue for the three and six months ended June 30, 2008 was $3.3 million and $6.2 million, respectively, compared to $1.9 million and $3.5 million for the same periods in 2007. Ibis' commercial revenue of $1.1 million and $2.3 million for the three and six months ended June 30, 2008 consisted of revenue from sales of Ibis T5000™ Biosensor Systems and assay kits, as well as revenue from Ibis' assay services business. In addition, Ibis' commercial revenue included revenue from the distribution agreement Ibis and Abbott entered into in March 2008. Ibis' revenue from government contracts was $2.2 million and $3.9 million for the three and six months ended June 30, 2008, and was driven primarily by contracts awarded in late 2007 and 2008 to date. Ibis was awarded $3.2 million of new contracts in the first half of 2008 that support Ibis' continued revenue growth by expanding the applications for the T5000 Biosensor System.

Excluding non-cash compensation expense related to stock options, operating expenses for Ibis were $8.2 million and $14.6 million for the three and six months ended June 30, 2008, compared to $4.4 million and $8.7 million for the same periods 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 $5.0 million and $8.4 million for the three and six months ended June 30, 2008, compared to $2.5 million and $5.2 million for the same periods in 2007. Ibis' non-cash compensation expense related to stock options was $466,000 and $942,000 for the three and six months ended June 30, 2008, compared to $406,000 and $815,000 for the same periods in 2007.

Regulus Therapeutics LLC

Regulus' revenue for the three and six months ended June 30, 2008 was $656,000 and $748,000 related primarily to revenue from its recently completed collaboration with GSK. As part of Regulus' strategic alliance with GSK, Regulus received a $15 million upfront fee, which it began amortizing into revenue in the second quarter of 2008 and will continue to amortize over its six-year period of performance under the agreement.

Excluding non-cash compensation expense related to stock options, operating expenses for Regulus were $1.8 million and $3.0 million for the three and six months ended June 30, 2008. With the recently announced strategic alliance with GSK, it is anticipated that Regulus' expenses will increase as Regulus continues to advance its research and development activities. The GSK alliance enhances Regulus' ability to expand operations and advance its programs. Regulus generated a loss from operations, excluding non-cash compensation expense related to stock options, of $1.2 million and $2.2 million for the three and six months ended June 30, 2008. Regulus' non-cash compensation expense related to stock options was $681,000 and $1.1 million for the three and six months ended June 30, 2008. Because Regulus was formed in the third quarter of 2007, it did not have operating results in the first half of 2007.

Quarterly Highlights

"Since the completion of our Genzyme collaboration, we've made great progress with mipomersen by initiating the first of four studies scheduled to begin by year end and receiving a patent allowance that gives the Isis-Genzyme apoB franchise broad protection of mipomersen and other antisense apoB compounds. In addition to the successes of our partnered drugs and satellite companies in the first half of

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the year, we continue to maximize the economic potential of our business model and our technology, while enabling the advancement of a broad portfolio of both partnered and internally developed drugs," concluded Ms. Parshall.

Cardiovascular Program

- Completed licensing transaction for mipomersen
- Finalized and announced 2008 mipomersen development plan with Genzyme
- Reported preclinical study in *Circulation* showing that mipomersen lowers Lp(a) and oxidized-LDL, independent risk factors for cardiovascular disease
- Initiated Phase 3 study in heterozygous FH subjects with coronary artery disease
- Granted broad patent coverage for antisense compounds targeting apolipoprotein B, U.S. Patent No. 7,407,943 entitled "Antisense modulation of Apolipoprotein B Expression"

Metabolic Program

- Highlighted our robust diabetes and obesity portfolio with nine presentations and posters at the American Diabetes Association meeting
  - Presented new preclinical data relating to ISIS 388626, Isis' drug targeting SGLT2
  - Presented results from eight research programs on novel targets that offer new mechanisms to address metabolic diseases, including obesity

Other Partnered Programs

- ATL and Teva reported encouraging Phase 2 results for ATL/TV1102, targeting VLA-4 in patients with multiple sclerosis
- Partnered oncology drugs highlighted at the American Society of Clinical Oncology demonstrate the potential of antisense technology to treat multiple cancers
  - OncoGenex reported encouraging Phase 2 results on OGX-011, targeting clusterin, in patients with hormone refractory prostate cancer
  - Eli Lilly and Company reported positive Phase 1 clinical trial results for LY2181308, targeting survivin
- Atlantic Healthcare received U.S. orphan drug designation for alicaforsen for the treatment of pouchitis
- Altair Therapeutics advanced AIR 645 into Phase 1 studies for the treatment of asthma

Regulus Therapeutics (microRNA Joint Venture)

- Entered into strategic alliance with GlaxoSmithKline
- Obtained exclusive rights from Stanford University to worldwide patent applications covering methods and compositions for antagonizing miR-181a
- Selected as one of the FierceBiotech's 'Fierce 15' for 2008

Ibis Biosciences

- Received an additional $20 million investment from Abbott for a total of 18.6 percent equity in Ibis, retaining Abbott's exclusive option to purchase remaining equity by June 30, 2009
- Extended government contracts that add to Ibis' revenue and fund the expansion of applications of the Ibis T5000 technology

Conference Call

At 8:30 a.m. Eastern Time today, August 7, 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 877-627-6585. 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, and its quarterly report on Form 10-Q for the quarter ended March 31, 2008, which are on file with the SEC. Copies of these and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries.

Isis Pharmaceuticals' Contacts:

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ISIS PHARMACEUTICALS, INC.
SELECTED FINANCIAL INFORMATION

Condensed Consolidated Statements of Operations
(In Thousands, Except Per Share Data)

	Three months ended,	Six months ended,

	June 30,		June 30,	
	2008	2007	2008	2007
	(unaudited)		(unaudited)	
Revenue:				
Research and development revenue under collaborative agreements	$ 26,814	$ 3,482	$ 47,499	$ 5,484
Licensing and royalty revenue	6,147	331	6,815	779
Total revenue	32,961	3,813	54,314	6,263
Expenses:				
Research and development	31,195	20,384	57,642	40,333
Selling, general and administrative	4,899	3,089	8,635	6,491
Total operating expenses	36,094	23,473	66,277	46,824
Loss from operations	(3,133)	(19,660)	(11,963)	(40,561)
Other income (expense):				
Investment income	560	3,053	5,515	6,454
Interest expense	(1,391)	(2,016)	(2,788)	(4,644)
Gain on investments, net	—	1,989	—	3,510
Loss on early retirement of debt	—	(1,993)	—	(3,212)
Loss attributed to noncontrolling interest in Symphony GenIsis, Inc.	—	7,603	—	14,409
Loss attributed to noncontrolling interest in Regulus Therapeutics LLC	965	—	1,848	—
Loss attributed to noncontrolling interest in Ibis Biosciences, Inc.	791	—	896	—
Net loss applicable to common stock	$ (2,208)	$ (11,024)	$ (6,492)	$ (24,044)
Basic and diluted net loss per share	$ (0.02)	$ (0.13)	$ (0.07)	$ (0.29)
Shares used in computing basic and diluted net loss per share	94,675	82,548	92,737	82,502

Isis Pharmaceuticals, Inc.

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

	Three months ended, June 30,		Six months ended, June 30,	
	2008	2007	2008	2007
	(unaudited)		(unaudited)	
As reported operating expenses according to GAAP	$ 36,094	$ 23,473	$ 66,277	$ 46,824
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(4,006)	(2,389)	(7,765)	(4,753)
Pro forma operating expenses	$ 32,088	$ 21,084	$ 58,512	$ 42,071
As reported loss from operations according to GAAP	$ (3,133)	$ (19,660)	$ (11,963)	$ (40,561)
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(4,006)	(2,389)	(7,765)	(4,753)
Pro forma income (loss) from operations	$ 873	$ (17,271)	$ (4,198)	$ (35,808)

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 income (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, June 30,		Six months ended, June 30,	
	2008	2007	2008	2007
	(unaudited)		(unaudited)	
Revenue:				
Commercial revenue (1)	$ 1,098	$ 810	$ 2,293	$ 1,441
Research and development revenue under collaborative agreements	2,160	1,081	3,944	2,026
Total revenue	3,258	1,891	6,237	3,467
Expenses:				

Cost of commercial revenue (2)	3,078	1,266	3,895	2,801
Research and development	3,572	2,460	8,128	4,647
Selling, general and administrative	2,024	1,035	3,527	2,023
Total operating expenses	8,674	4,761	15,550	9,471
Loss from operations	$ (5,416)	$ (2,870)	$ (9,313)	$ (6,004)

(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.

Regulus Therapeutics LLC
Statements of Operations
(In Thousands)

	Three Months Ended June 30, 2008	Six Months Ended June 30, 2008
Revenue:		
Research and development revenue under collaborative agreements	$ 656	$ 748
Total revenue	656	748
Expenses:		
Research and development	1,606	2,918
General and administrative	917	1,132
Total operating expenses	2,523	4,050
Loss from operations	$ (1,867)	$ (3,302)

Regulus was formed in the third quarter of 2007; therefore it does not have operating results for the first half of 2007.

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

	June 30, 2008 (unaudited)	December 31, 2007
Assets:		
Cash, cash equivalents and short-term investments	$ 536,969	$ 193,719
Other current assets	18,211	13,598
Property, plant and equipment, net	10,494	7,131
Other assets	43,725	44,410
Total assets	$ 609,399	$ 258,858
Liabilities, noncontrolling interest and stockholders' equity:		
Other current liabilities	$ 25,604	$ 29,000
Current portion of deferred contract revenue	101,507	33,205
2 5/8% convertible subordinated notes	162,500	162,500
Long-term obligations, less current portion	5,415	362
Long-term deferred contract revenue	214,202	23,548
Noncontrolling interest in Regulus Therapeutics LLC	7,523	9,371
Noncontrolling interest in Ibis Biosciences, Inc.	33,625	—
Stockholders' equity	59,023	872
Total liabilities, noncontrolling interest and stockholders' equity equity	$ 609,399	$ 258,858

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