

# 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 9, 2010**

## ISIS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Charter)

**Delaware**

(State or Other Jurisdiction of Incorporation)

**000-19125**

(Commission File No.)

**33-0336973**

(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:

- 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 August 9, 2010, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter ended June 30, 2010. 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/benefit. 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 9, 2010.

**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.

Dated: August 9, 2010

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 9, 2010.



**ISIS IMPROVES FINANCIAL GUIDANCE AND REPORTS FINANCIAL RESULTS  
AND HIGHLIGHTS FOR SECOND QUARTER 2010**

· **Conference Call Webcast Monday August 9, 8:30 a.m. ET at [www.isispharm.com](http://www.isispharm.com)**

**CARLSBAD, Calif., August 9, 2010** - Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced its financial results for the quarter ended June 30, 2010. The Company finished the second quarter of 2010 with a pro forma net operating loss (NOL) of \$15.5 million and \$17.1 million for the three and six months ended June 30, 2010, respectively, compared to a pro forma net operating loss of \$1.3 million and pro forma net operating income of \$798,000 for the same periods of 2009.

Isis previously announced financial guidance for 2010, which included predicted revenue from existing partnerships but did not include cash and revenue from Isis' new partnership with GlaxoSmithKline (GSK). As a result, Isis is projecting improved financial performance and reducing its operating loss guidance for 2010 by approximately 10% to 20% to a pro forma net operating loss in the mid to high \$40 million range. Additionally, Isis expects to end the year with more than \$450 million in cash, a significant improvement over its previous cash guidance.

"We have been very successful with our partnerships, bringing in more than \$55 million in cash this year, including \$35 million from our recent partnership with GSK. Already this year, we have achieved the first milestone under our collaboration with GSK and earned an additional \$5 million, one of the factors that has allowed us to improve our guidance. Also contributing to our improved financial performance is revenue we received as a result of Regulus' newly formed alliance with sanofi-aventis and the milestone payments we earned from BMS and Achaogen. Our creation of Regulus with our partners at Alnylam to explore the exciting new area of microRNAs is an example of our continuing commitment and success in expanding our antisense technology platform," said B. Lynne Parshall, COO and CFO of Isis.

**Upcoming Key Milestones**

- Report full data from the positive Phase 3 study evaluating mipomersen in heterozygous FH patients at the upcoming ESC conference; top-line data reported in February 2010
- Report full data from the positive Phase 3 studies evaluating mipomersen in high-cholesterol patients at high risk for coronary heart disease and in patients with severe hypercholesterolemia
- Complete and report data from the Phase 1 study of ISIS-CRP<sub>Rx</sub> and begin a broad Phase 2 program
- Initiate the broad Phase 2 program of ISIS-EIF4E<sub>Rx</sub> in patients with cancer
- Altair to complete and report data from the Phase 2 study of AIR 645
- Excaliard to complete and report data from its remaining Phase 2 studies of EXC 001

**Financial Results**

On a GAAP basis, Isis reported a loss from operations of \$18.7 million and \$23.6 million for the three and six months ended June 30, 2010, respectively, compared to \$4.8 million and \$5.5 million for the same periods in 2009.

Beginning in the first quarter of 2010, as a result of adopting a new required accounting standard, Isis is no longer including Regulus' revenue and operating expenses in its operating results and no longer including Regulus' cash and debt on its balance sheet. Instead, Isis is presenting its share of Regulus' operating results on a separate line in its statement of operations called "Equity in net loss of Regulus"

Therapeutics Inc." On its balance sheet, Isis is presenting its investment in Regulus on a separate line called "Investment in Regulus Therapeutics Inc." This new standard improves the operating expenses and NOL reported in Isis' financial statements while not significantly affecting the Company's net loss. A reconciliation presenting Isis' 2009 operating results on a comparable basis to 2010 appears later in this release.

All pro forma amounts referred to in this press release exclude non-cash stock compensation. Please refer to the reconciliation of pro forma and GAAP measures, which is explained later in this release.

**Revenue**

Revenue for the three and six months ended June 30, 2010 was \$23.5 million and \$53.4 million, respectively, compared to \$31.0 million and \$62.6 million for the same periods in 2009. Isis' revenue fluctuates based on the nature and timing of payments under agreements with the Company's partners, including license fees, milestone-related payments and other payments. For example, in the first quarter of 2010 Isis recognized as revenue a \$6 million milestone payment it received from Bristol-Myers Squibb (BMS) for initiating Phase 1 studies on BMS-PCSK9<sub>Rx</sub>. And, in the second quarter of 2010, Isis began recognizing revenue from the \$35 million upfront payment it received from GSK. Additionally, Isis earned \$1.9 million from Regulus related to its recent strategic alliance with sanofi-aventis. Although Isis recognized new revenue from GSK, BMS and Regulus in the first half of 2010, its revenue compared to the first half of 2009 decreased slightly, primarily because the amortization of the upfront fee from the Company's Ortho-McNeil collaboration ended in the third quarter of 2009. Revenue for the first half of 2010 also decreased by \$1.8 million because Isis is no longer including Regulus' revenue in its 2010 revenue.

Recently, Isis earned a \$5 million milestone payment from GSK when it identified a drug development candidate to move forward in development under its GSK partnership. Because Isis achieved the milestone in July, the Company will recognize revenue from the milestone payment in the third quarter of 2010.

**Operating Expenses**

On a pro forma basis, operating expenses for the three and six months ended June 30, 2010 were \$39.0 million and \$70.5 million, respectively, compared to \$32.3 million and \$61.8 million for the same periods in 2009. The higher expenses in 2010 were primarily due to an increase in costs associated with advancing mipomersen toward its initial regulatory filings planned for the first half of next year offset in part by a \$5.3 million decrease because Isis is no

longer including Regulus' operating expenses in its 2010 operating expenses. On a GAAP basis, Isis' operating expenses from continuing operations for the three and six months ended June 30, 2010 were \$42.2 million and \$77.0 million, respectively, compared to \$35.8 million and \$68.0 million for the same periods in 2009.

#### **Net Loss from Continuing Operations Attributable to Isis Pharmaceuticals, Inc. Common Stockholders**

Net loss from continuing operations for the three and six months ended June 30, 2010 was \$25.2 million and \$34.8 million, respectively, compared to \$2.8 million and \$3.6 million for the same periods in 2009. The increase in Isis' net loss from continuing operations for the six months was primarily due to the following:

- \$18.1 million increase in Isis' net operating loss described above;
- \$7.2 million increase in net loss relating to the accounting treatment for Regulus;
- \$2.0 million decrease in investment income due to a lower average return on investments resulting from the current market conditions and a lower average cash balance; and
- \$2.5 million gain in 2009 from the sale of OncoGenex common stock that Isis owned, offset in part by \$880,000 in a non-cash loss related to the impairment of Isis' equity investment in Antisense Therapeutics Limited.

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#### **Net Income (Loss)**

Isis reported a net loss of \$25.2 million and \$34.8 million for the three and six months ended June 30, 2010, respectively, compared to a net loss of \$2.7 million for the three months ended June 30, 2009 and net income of \$183.5 million for the six months ended June 30, 2009. Basic and diluted net loss per share for the three and six months ended June 30, 2010 was \$0.25 per share and \$0.35 per share, respectively, compared to basic and diluted net loss per share of \$0.03 for the three months ended June 30, 2009 and net income per share of \$1.88 for the six months ended June 30, 2009. Net income and net income per share for the first six months of 2009 primarily consisted of the \$187.1 million gain, net of tax, which Isis recognized when it sold its subsidiary, Ibis Biosciences, to Abbott Molecular Inc. in the first quarter of 2009.

#### **Balance Sheet**

As of June 30, 2010, Isis had cash, cash equivalents and short-term investments of \$522.0 million compared to \$574.3 million at December 31, 2009 and had working capital of \$431.7 million at June 30, 2010 compared to \$484.7 million at December 31, 2009. The decrease in cash and working capital primarily relates to cash used in the first six months of 2010 for Isis' operations, including a \$7.7 million payment that Isis made for 2009 income taxes. Isis' cash and working capital also decreased because Isis is no longer including Regulus' cash, which was \$30.7 million at December 31, 2009, in Isis' cash balance. So far in 2010, Isis has received more than \$55 million from its corporate partnerships, including \$35 million from GSK.

#### **Business Highlights**

"Already this year, we have had many significant positive events, including the completion of the last two of the four Phase 3 studies planned to support the initial regulatory filings for this treatment. Across these four studies treatment with mipomersen produced promising results in patients who have persistently high LDL-C levels despite being treated on maximally tolerated lipid-lowering therapy," continued Ms. Parshall. "Last week, we reported the positive top-line results from two Phase 3 studies evaluating mipomersen in high-cholesterol patients at high risk for developing coronary heart disease and in patients with severe hypercholesterolemia. In all four of the Phase 3 studies we have completed, we have seen consistent and robust efficacy with a safety profile that supports our focused plan to target homozygous familial hypercholesterolemia and severe hypercholesterolemic patients for our initial filings. Together all of the Phase 3 studies will form a comprehensive filing package for our first regulatory filings for mipomersen, which Genzyme plans to file in both the U.S. and Europe in the first half of next year. We are excited by these positive Phase 3 results and look forward to continuing to successfully work with Genzyme to bring mipomersen to patients who are in need of a new and novel lipid-lowering agent."

"In addition to the successes we and Genzyme have reported for mipomersen, we have made substantial progress with many of the other drugs in our pipeline. For example, we and our partners have reported data on six clinical studies of antisense drugs in our pipeline, initiated clinical studies on two new novel drugs and our partners OncoGenex and Teva have initiated the first of three Phase 3 studies of OGX-011 in patients with cancer. Recently, we selected the first development candidate to move forward in our collaboration with GSK for the treatment of rare and infectious diseases. In addition, antisense drugs we and our partners are developing were featured prominently at recent scientific meetings, including the American Society of Clinical Oncology and the American Diabetes Association meeting. All of these achievements demonstrate the significant advances we have made this year in expanding and maturing our pipeline and bringing more antisense drugs into later-stage clinical development," added Ms. Parshall.

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#### **Drug Development Highlights**

- Mipomersen is being developed by Isis and Genzyme for patients with high cardiovascular risk who cannot adequately control their cholesterol levels with current therapies and who need new treatment options. Isis and Genzyme reported positive data from two Phase 3 studies evaluating mipomersen in patients with severe hypercholesterolemia and patients with high-cholesterol at high risk for coronary heart disease.
  - In a Phase 3 study evaluating mipomersen in patients with severe hypercholesterolemia, Isis and Genzyme reported that the study met its primary endpoint with a 36 percent reduction in LDL-C compared with a 13 percent increase in placebo.
  - In a Phase 3 study evaluating mipomersen in patients with high-cholesterol at high risk for developing coronary heart disease, Isis and Genzyme reported that the study met its primary endpoint with a 37 percent reduction in LDL-C compared with a 5 percent decrease in placebo.
  - In both studies all secondary endpoints were met.
  - In both studies, frequently observed adverse events were injection site reactions, flu-like symptoms and elevations in liver transaminases, as seen in previous studies.
- Isis reported new data from seven programs in its metabolic disease franchise at the American Diabetes Association's Scientific Sessions.
  - Isis reported the full data from a positive Phase 2 study evaluating ISIS 113715 in patients with type 2 diabetes whose glucose levels were uncontrolled despite being treated with maximum doses of sulfonylureas.

- Isis reported the full data from a positive Phase 1 study evaluating ISIS-GCGR<sub>Rx</sub> in patients who were given a glucagon challenge that doubled both plasma glucagon and glucose levels.
- Isis presented new data from the Company's obesity drug discovery program to a number of metabolic targets in a variety of animal models showing that antisense inhibition provided therapeutic benefit including reductions in fat mass and body weight and improved glucose metabolism.
- Isis added a new development candidate, ISIS-GSK1<sub>Rx</sub>, to its pipeline that was selected as part of its collaboration with GSK to develop therapeutic drugs to treat rare and infectious diseases for which Isis earned a \$5 million milestone payment.
- Achaogen initiated a Phase 2 study on ACHN-490, for which Isis earned a \$2 million milestone payment.
- Excaliard reported positive Phase 2 data demonstrating that treatment with EXC 001 reduced scarring in patients following elective abdominal surgery.
- iCo received approval to initiate a Phase 2 study on iCo-007 in patients with diabetic macular edema.
- OncoGenex and Teva initiated a Phase 3 study on OGX-011 in patients with prostate cancer.
- OncoGenex reported positive Phase 1 data on OGX-427 at the American Society of Clinical Oncology.

### Corporate Highlights

- Isis formed a new strategic alliance worth up to nearly \$1.5 billion with GSK to develop antisense drugs to treat rare and infectious diseases. Including the recently earned \$5 million milestone payment that GSK will pay to Isis in the third quarter, Isis will have received \$40 million of the potential \$155 million in pre-licensing payments.
- Regulus formed a new alliance with sanofi-aventis worth potentially over \$750 million to develop and commercialize microRNA therapeutics, including Regulus' leading fibrosis program targeting microRNA-21.
- Isis received \$1.9 million from Regulus, representing 7.5 percent of the \$25 million upfront payment Regulus received from sanofi-aventis.
- Isis and BMS extended their collaboration by two years and will continue to develop a follow-on drug to BMS-PCSK9<sub>Rx</sub> for franchise extension.

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### Conference Call

At 08:30 a.m. Eastern Time today, August 9, 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 866-700-6067 and refer to passcode "ISIS 2010," or access the webcast at [www.isispharm.com](http://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 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 23 drugs in development. Isis' drug development programs are focused on treating cardiovascular, metabolic, and severe neurodegenerative diseases and cancer. Isis' partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. Isis and Alnylam Pharmaceuticals are joint owners of Regulus Therapeutics Inc., a company focused on the discovery, development and commercialization of microRNA therapeutics. Isis also has made significant innovations beyond human therapeutics resulting in products that other companies, including Abbott, are commercializing. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of approximately 1,600 issued patents worldwide. Additional information about Isis is available at [www.isispharm.com](http://www.isispharm.com).

### Forward Looking Statements

This press release includes forward-looking statements regarding Isis Pharmaceuticals' business, the financial position and outlook for Isis as well as Regulus its majority-owned subsidiary, 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. 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, 2009 and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from the Company.

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

Isis Pharmaceuticals is a registered trademark of Isis Pharmaceuticals, Inc. Regulus Therapeutics is a trademark of Regulus Therapeutics Inc.

### **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, June 30,		Six months ended, June 30,	
2010	2009(1)	2010	2009(1)
(unaudited)	(unaudited)	(unaudited)	(unaudited)

<b>Revenue:</b>				
Research and development revenue under collaborative agreements	\$ 21,143	\$ 30,768	\$ 49,699	\$ 60,453
Licensing and royalty revenue	2,360	224	3,730	2,115
Total revenue	<u>23,503</u>	<u>30,992</u>	<u>53,429</u>	<u>62,568</u>
<b>Expenses:</b>				
Research and development	39,124	32,146	71,111	60,688
General and administrative	3,051	3,673	5,869	7,350
Total operating expenses	<u>42,175</u>	<u>35,819</u>	<u>76,980</u>	<u>68,038</u>
Loss from operations	(18,672)	(4,827)	(23,551)	(5,470)
<b>Other income (expense):</b>				
Equity in net loss of Regulus Therapeutics Inc.	(3,942)	—	(5,428)	—
Investment income	859	1,678	1,814	3,812
Interest expense	(3,263)	(3,155)	(6,500)	(6,236)
Gain (loss) on investments, net	(136)	2,612	(1,146)	2,671
Loss from continuing operations, before income tax benefit (expense)	(25,154)	(3,692)	(34,811)	(5,223)
Income tax benefit (expense)	—	11	—	(149)
Net loss from continuing operations	(25,154)	(3,681)	(34,811)	(5,372)
<b>Discontinued operations:</b>				
Loss from discontinued operations	—	—	—	(29)
Gain on sale of Ibis Biosciences, Inc., net of tax	—	94	—	187,119
Net income from discontinued operations, net of tax	—	94	—	187,090
Net income (loss)	(25,154)	(3,587)	(34,811)	181,718
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	—	857	—	1,770
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	<u>\$ (25,154)</u>	<u>\$ (2,730)</u>	<u>\$ (34,811)</u>	<u>\$ 183,488</u>
<b>Basic and diluted net income (loss) per share:</b>				
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	\$ (0.25)	\$ (0.03)	\$ (0.35)	\$ (0.03)
Net income from discontinued operations	—	—	—	1.91
Basic and diluted net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	<u>\$ (0.25)</u>	<u>\$ (0.03)</u>	<u>\$ (0.35)</u>	<u>\$ 1.88</u>
Shares used in computing basic and diluted net income (loss) per share	99,091	98,116	99,052	97,820

(1) During the preparation of the year end 2009 annual tax provision, Isis determined that certain tax items had been attributed to discontinued operations that are appropriately associated with continuing operations. As a result, Isis revised the tax provisions reflected in each of the first three quarters during 2009 to reflect the correction of this allocation. The historical condensed consolidated statements of operations for the three and six months ended June 30, 2009 reflect the revised tax provisions.

**Isis Pharmaceuticals, Inc.**  
**Reconciliation of Isis' 2009 Statement of Operations**  
**Adjusted for Regulus Therapeutics Inc.**  
**(In Thousands, Except Per Share Data)**  
**(unaudited)**

	Six months ended June 30, 2009 (as reported)	Adjustments for Regulus(1)	Six months ended June 30, 2009 (as adjusted)
<b>Revenue:</b>			
Research and development revenue under collaborative agreements	\$ 60,453	\$ (1,763)	\$ 58,690
Licensing and royalty revenue	2,115	—	2,115
Total revenue	<u>62,568</u>	<u>(1,763)</u>	<u>60,805</u>
<b>Expenses:</b>			
Research and development	60,688	(4,057)	56,631
General and administrative	7,350	(1,270)	6,080
Total operating expenses	<u>68,038</u>	<u>(5,327)</u>	<u>62,711</u>
Loss from operations	(5,470)	3,564	(1,906)
<b>Other income (expense):</b>			
Equity in net loss of Regulus Therapeutics Inc.	—	(3,606)	(3,606)
Investment income	3,812	(92)	3,720
Interest expense	(6,236)	81	(6,155)
Gain on investments	2,671	—	2,671
Income (loss) from continuing operations, before income tax expense	(5,223)	(53)	(5,276)
Income tax expense	(149)	—	(149)
Net income (loss) from continuing operations	(5,372)	(53)	(5,425)
<b>Discontinued operations:</b>			
Loss from discontinued operations	(29)	—	(29)
Gain on sale of Ibis Biosciences, Inc., net of tax	187,119	—	187,119
Net income from discontinued operations, net of tax	<u>187,090</u>	<u>—</u>	<u>187,090</u>
Net income	181,718	(53)	181,665

Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	1,770	(1,770)	—
Net income attributable to Isis Pharmaceuticals, Inc. common stockholders	<u>\$ 183,488</u>	<u>\$ (1,823)</u>	<u>\$ 181,665</u>
Basic and diluted net income (loss) per share:			
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	\$ (0.03)		\$ (0.05)
Net income from discontinued operations	1.91		1.91
Basic and diluted net income	<u>\$ 1.88</u>		<u>\$ 1.86</u>
Shares used in computing basic and diluted net income (loss) per share	<u>97,820</u>		<u>97,820</u>

(1) Assuming Isis would have adopted the new accounting standard retrospectively, these are the adjustments that would have been made to Isis' 2009 Statement of Operations.

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

	Three months ended, June 30,		Six months ended, June 30,	
	2010	2009	2010	2009
	(unaudited)		(unaudited)	
<b>As reported operating expenses according to GAAP</b>	\$ 42,175	\$ 35,819	\$ 76,980	\$ 68,038
Excluding compensation expense related to stock options	<u>(3,132)</u>	<u>(3,565)</u>	<u>(6,488)</u>	<u>(6,268)</u>
<b>Pro forma operating expenses</b>	<u>\$ 39,043</u>	<u>\$ 32,254</u>	<u>\$ 70,492</u>	<u>\$ 61,770</u>
<b>As reported loss from operations according to GAAP</b>	\$ (18,672)	\$ (4,827)	\$ (23,551)	\$ (5,470)
Excluding compensation expense related to stock options	<u>(3,132)</u>	<u>(3,565)</u>	<u>(6,488)</u>	<u>(6,268)</u>
<b>Pro forma income (loss) from operations</b>	<u>\$ (15,540)</u>	<u>\$ (1,262)</u>	<u>\$ (17,063)</u>	<u>\$ 798</u>

**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 income (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.

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

	June 30, 2010	December 31, 2009
	(unaudited)	
<b>Assets:</b>		
Cash, cash equivalents and short-term investments	\$ 522,028	\$ 574,312
Other current assets	14,857	21,814
Property, plant and equipment, net	36,071	27,338
Other assets	33,395	33,720
Total assets	<u>\$ 606,351</u>	<u>\$ 657,184</u>
<b>Liabilities and stockholders' equity:</b>		
Other current liabilities	\$ 27,946	\$ 35,763
Current portion of deferred contract revenue	77,268	75,681
2 5/8% convertible subordinated notes	128,907	125,100
Long-term obligations, less current portion	15,767	11,478
Investment in Regulus Therapeutics Inc.	4,070	—
Long-term deferred contract revenue	90,164	107,097
Stockholders' equity	262,229	302,065
Total liabilities and stockholders' equity	<u>\$ 606,351</u>	<u>\$ 657,184</u>

