

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, 2011**

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 February 28, 2011, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter and fiscal year ended December 31, 2010. 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 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 February 28, 2011.

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, 2011

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

INDEX TO EXHIBITS

99.1 Press Release dated February 28, 2011.



ISIS REPORTS FINANCIAL RESULTS AND HIGHLIGHTS FOR 2010

Conference Call Webcast Monday February 28, 4:30 p.m. ET at www.isispharm.com

CARLSBAD, Calif., February 28, 2011 - Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced its 2010 financial results and reviewed the highlights of the year. Isis improved upon its 2010 financial guidance with a pro forma net operating loss (NOL) of \$36.2 million, which is significantly better than the mid to high \$40 million range pro forma NOL the Company projected. Isis also exceeded its cash guidance by ending 2010 with \$472.4 million of cash, cash equivalents and short-term investments in excess of the \$450 million projected.

"2010 was another strong year for Isis. We exceeded our financial guidance for the year while continuing to significantly advance all areas of our business. Our most notable accomplishment was the successful completion of the initial Phase 3 program for mipomersen, which brings this important medicine closer to commercialization. In addition to progress on mipomersen, we expanded and advanced our drug pipeline, added an experienced partner for our severe and rare disease franchise and advanced our technology to help ensure that we remain the leader in antisense drug discovery and development," said B. Lynne Parshall, COO and CFO of Isis.

"Mipomersen's success sets the stage for an exciting year to come. 2011 will mark a turning point for us as we move mipomersen toward commercial markets, advance new drugs based on our next-generation chemistry and continue to progress our existing drugs through clinical trials toward the market. Our clinical development activities will remain an area of significant focus for us this year. Nevertheless, we expect our operating expenses to be similar to 2010. As our mipomersen expenses decrease, we expect to use the savings to increase our investment in the other drugs in our pipeline. We believe that our investments in our technology and pipeline can generate future value for our shareholders. We are projecting a pro forma NOL for 2011 in the low \$40 million range, an improvement over our guidance for last year. Based on our cash and committed cash, we expect to end 2011 with more than \$350 million in cash. As in 2010, our guidance is not based on the establishment of new partnerships so the addition of a new partner could favorably impact this guidance. As we did last year, we will continue to be selective in our partnering to maintain consistency with our goal of controlling our drugs until they reach key value points," added Ms. Parshall.

Upcoming Key Milestones

- Genzyme expects to file for marketing approval for mipomersen in Europe in the first half of 2011 and in the United States in 2011.
- Genzyme and Isis plan to report the full data from the positive Phase 3 study evaluating mipomersen in patients with severe hypercholesterolemia and in high-cholesterol patients at high risk for coronary heart disease.
- Isis plans to complete and report data from the Phase 1 study of ISIS-SGLT2_{Rx} and begin Phase 2 programs for ISIS-CRP_{Rx} and ISIS-SGLT2_{Rx}.
- Isis plans to begin clinical development for ISIS-GSK1_{Rx}, the first drug in development under Isis' partnership with GlaxoSmithKline (GSK).

Financial Results

On a GAAP basis, Isis reported a loss from operations of \$15.9 million and \$48.4 million for the three and twelve months ended December 31, 2010, respectively, compared to a loss from operations of \$11.7 million and \$27.5 million for the three and twelve months ended December 31, 2009, respectively.

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. 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 twelve months ended December 31, 2010 was \$26.4 million and \$108.5 million, respectively, compared to \$32.3 million and \$121.6 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. Isis recognized new revenue in 2010 in the form of an upfront fee from the Company's new partnership with GSK, which Isis is amortizing through the first quarter of 2015, milestone payments from GSK, Bristol-Myers Squibb and Achaogen, and sublicensing income from Regulus' collaboration with sanofi-aventis. Additionally, when Alnylam terminated the ssRNAi research program in November 2010, Isis recognized \$4.9 million of revenue from the upfront fee that Isis was amortizing into revenue over the research term. Isis' revenue for 2010 was less than in 2009 principally because the amortization of the upfront fee from the Company's Ortho-McNeil collaboration ended in the third quarter of 2009. In addition, Isis' revenue decreased by \$3.0 million because Isis is no longer including Regulus' revenue in its 2010 revenue.

Operating Expenses

On a pro forma basis, operating expenses for the three and twelve months ended December 31, 2010 were \$39.6 million and \$144.7 million, respectively, compared to \$40.4 million and \$135.8 million for the same periods in 2009. The higher expenses in 2010 were primarily due to increased costs related to advancing mipomersen towards its initial regulatory filings for marketing approval planned for 2011, maturing and expanding Isis' pipeline, and implementing generation 2.5 chemistry. The increase in costs was offset in part by an \$11.7 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 twelve months ended December 31, 2010 were \$42.3 million and \$156.8 million, respectively, compared to \$43.9 million and \$149.1 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 twelve months ended December 31, 2010 was \$14.0 million and \$61.3 million, respectively, compared to \$15.3 million and \$30.6 million for the same periods in 2009. The increase in Isis' net loss from continuing operations for 2010 compared to 2009 was primarily due to the following:

- \$29.6 million increase in net operating loss, excluding Regulus, as described above in revenue and operating expenses;
- \$2.1 million decrease in Isis' share of Regulus' net loss, which includes a \$4.7 million gain to reflect an increase in the valuation of Regulus and the change in Isis' ownership percentage due to the \$10 million investment sanofi-aventis made in Regulus valuing Regulus at more than \$130 million;
- \$3.0 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
- \$2.8 million decrease in gain (loss) on investments primarily due to a \$2.5 million gain Isis recognized in 2009 from the sale of OncoGenex common stock that it owned.

Net Income (Loss)

Isis reported a net loss of \$14.0 million and \$61.3 million for the three and twelve months ended December 31, 2010, respectively, compared to a net loss of \$16.8 million for the three months ended December 31, 2009 and net income of \$155.1 million for the twelve months ended December 31, 2009. Basic and diluted net loss per share for the three and twelve months ended December 31, 2010 was \$0.14 per share and \$0.62 per share, respectively, compared to basic and diluted net loss per share of \$0.17 for the three months ended December 31, 2009 and net income per share of \$1.58 for the twelve months ended December 31, 2009. Net income and net income per share for 2009 primarily consisted of the \$185.7 million gain, net of tax, Isis recognized when it sold its subsidiary, Ibis Biosciences, to Abbott Molecular Inc. in the first quarter of 2009.

Balance Sheet

As of December 31, 2010, Isis had cash, cash equivalents and short-term investments of \$472.4 million compared to \$574.3 million at December 31, 2009 and had working capital of \$377.2 million at December 31, 2010 compared to \$484.7 million at December 31, 2009. The decrease in cash and working capital primarily relates to cash used in 2010 for Isis' operations, including \$7.3 million that Isis paid 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.

2011 Goals

"We have many key events to look forward to in 2011, the most significant being the filings for marketing approval of mipomersen in the United States and Europe. In addition, we will continue to grow our pipeline. With the large number of drugs we and our partners are developing, we plan continuous news flow of clinical data and study initiations throughout the year. We are particularly excited by the activities adding breadth and depth to our pipeline. These activities include advancing and expanding our cardiovascular pipeline by approaching aspects of cardiovascular disease beyond lipid management, expanding our metabolic franchise to include obesity and growing our oncology franchise. We are also encouraged by our expanding new rare disease program that could offer new medicines to help patients in need," continued Ms. Parshall.

In 2011, Isis is planning to achieve the following goals itself and with its partners:

- Together with Genzyme, move mipomersen closer to the market for patients who cannot adequately control their cholesterol levels with current therapies.
 - File new drug applications for mipomersen marketing approval in the United States (NDA) and Europe (MAA).
 - Report detailed data from Phase 3 mipomersen studies in patients with severe hypercholesterolemia and patients with high cholesterol at high risk for coronary heart disease. (Top-line data reported in late 2010)
- Together with partners, report clinical data evaluating pharmacological effect and safety of multiple drugs in its pipeline.
- Continue to advance multiple drugs in Isis' pipeline into Phase 1 and Phase 2 development.
- Broaden Isis' pipeline by adding 3 to 5 new drugs.
- Identify a development candidate to move into Isis' pipeline that incorporates generation 2.5 chemistry.

Business Highlights

"2010 was a very busy year for us. We and Genzyme successfully completed the initial Phase 3 program for mipomersen to support filings for marketing approval in both the United States and Europe. We believe that the initial market for mipomersen represents a significant commercial opportunity. Also, the commercialization of mipomersen marks a significant milestone for our antisense drug discovery platform. We made substantial progress moving many of these drugs forward in development last year. For example, we advanced three of our drugs into Phase 1 studies and initiated a Phase 2 program on our anti-cancer drug. Our partner, Excaliard, presented results from three Phase 2 studies demonstrating that an antisense drug administered locally to scar tissue significantly reduced scar severity in patients. Finally, we added new drugs to our pipeline that broadens the therapeutic focus of our cardiovascular and metabolic programs, and added a new drug into our cancer franchise. As we move new drugs into development, we plan to integrate our new generation 2.5 chemistry, an exciting technology advance that could expand the therapeutic potential of our future drugs. Our progress this year positions us for a busy 2011, as we continue to advance the drugs in our pipeline. As a result, we will have many opportunities to highlight our drugs and their successes in detail," continued Ms. Parshall.

Drug Development Highlights

- Mipomersen continues to advance in clinical development and move closer to the market for patients with very high cholesterol, at high cardiovascular risk, who cannot reduce their LDL-C sufficiently with currently available lipid-lowering therapies. Isis and Genzyme successfully completed four Phase 3 studies that the companies plan to include in the initial United States and European filings for marketing approval for mipomersen. These filings will seek approval for the treatment of patients with homozygous familial hypercholesterolemia (FH) in the United States and Europe. The European filing may also include patients with severe heterozygous FH. Genzyme is also preparing for filings in markets beyond the United States and Europe.
 - The table below briefly summarizes the results of these studies. In all four studies, all primary, secondary and tertiary endpoints were met.

Phase 3 Study	Average Baseline LDL-C (mg/dL)	Average LDL-C Reduction (mg/dL)	Placebo Change in LDL-C (%)	Mipomersen Change in LDL-C (%)
Homozygous FH	426	-106	-3.3	-24.7
Severe Hypercholesterolemia	276	-101	+13	-36
Heterozygous FH	153	-46	+5	-28
High-Risk	123	-48	-5	-37

- In all studies, frequently observed adverse events were injection site reactions, flu-like symptoms and elevations in liver transaminases, as seen in previous studies.
- In all studies, patients maintained a regimen of maximally tolerated lipid-lowering therapy.
- Isis and its partners continued to advance the drugs in its pipeline and reported clinical results in a broad range of diseases, including positive clinical Phase 1 data on six drugs. Isis added three new drugs to its pipeline.
- Isis and its partners initiated Phase 1 clinical studies on four drugs, initiated seven Phase 2 studies on four drugs, and initiated two Phase 3 studies on OGX-011.

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. Isis received a \$35 million upfront payment and a \$5 million milestone payment related to the identification of ISIS-GSK1_{Rx}, the first drug selected as part of its collaboration with GSK.
- Isis and Bristol-Myers Squibb extended their collaboration by two years to discover a more potent PCSK9 drug to move into development.
- 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 miR-21. Isis received \$1.9 million, which represents 7.5 percent of the \$25 million upfront payment Regulus received from sanofi-aventis.
- sanofi-aventis invested \$10 million in Regulus valuing Regulus at more than \$130 million. From this investment sanofi-aventis acquired less than 10 percent ownership of Regulus' outstanding preferred shares, leaving Isis with 46 percent ownership.
- Regulus and GSK established a new collaboration to develop and commercialize microRNA therapeutics targeting microRNA 122, or miR-122, for hepatitis C viral infection.
- Isis earned in excess of \$15 million in milestone payments and sublicensing fees in 2010 as its partners advanced drugs in development.

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Conference Call

At 4:30 p.m. Eastern Time today, February 28, 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 866-825-3209 and refer to passcode "ISIS 2011," 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 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 24 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 has designed and executed a patent strategy that has provided the Company with strong and extensive protection for Isis' drugs and technology. Additional information about Isis is available at 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 jointly 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.

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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,	
	2010	2009	2010	2009
	(unaudited)		(unaudited)	
Revenue:				

Research and development revenue under collaborative agreements	\$ 25,437	\$ 21,716	\$ 102,921	\$ 108,131
Licensing and royalty revenue	983	10,545	5,552	13,469
Total revenue	<u>26,420</u>	<u>32,261</u>	<u>108,473</u>	<u>121,600</u>
Expenses:				
Research and development	39,333	40,104	145,160	134,623
General and administrative	2,944	3,830	11,669	14,515
Total operating expenses	<u>42,277</u>	<u>43,934</u>	<u>156,829</u>	<u>149,138</u>
Loss from operations	(15,857)	(11,673)	(48,356)	(27,538)
Other income (expense):				
Equity in net loss of Regulus Therapeutics Inc.	4,130	—	(2,228)	—
Investment income	780	1,061	3,370	6,361
Interest expense	(3,396)	(3,251)	(13,232)	(12,672)
Gain (loss) on investments, net	448	(651)	(713)	2,084
Loss from continuing operations, before income tax expense	(13,895)	(14,514)	(61,159)	(31,765)
Income tax expense	(90)	(2,318)	(92)	(3,191)
Net loss from continuing operations	(13,985)	(16,832)	(61,251)	(34,956)
Discontinued operations:				
Loss from discontinued operations	—	—	—	(29)
Gain (loss) on sale of Ibis Biosciences, Inc., net of tax	—	(1,496)	—	185,657
Net income (loss) from discontinued operations, net of tax	—	(1,496)	—	185,628
Net income (loss)	(13,985)	(18,328)	(61,251)	150,672
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	—	1,488	—	4,394
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	<u>\$ (13,985)</u>	<u>\$ (16,840)</u>	<u>\$ (61,251)</u>	<u>\$ 155,066</u>
Basic and diluted net income (loss) per share:				
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	\$ (0.14)	\$ (0.16)	\$ (0.62)	\$ (0.31)
Net income (loss) from discontinued operations	—	(0.01)	—	1.89
Basic and diluted net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	<u>\$ (0.14)</u>	<u>\$ (0.17)</u>	<u>\$ (0.62)</u>	<u>\$ 1.58</u>
Shares used in computing basic and diluted net income (loss) per share	99,267	98,467	99,143	98,109

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

	Year ended December 31, 2009 (as reported)	Adjustments for Regulus(1)	Year ended December 31, 2009 (as adjusted)
Revenue:			
Research and development revenue under collaborative agreements	\$ 108,131	\$ (3,013)	\$ 105,118
Licensing and royalty revenue	13,469	—	13,469
Total revenue	<u>121,600</u>	<u>(3,013)</u>	<u>118,587</u>
Expenses:			
Research and development	134,623	(8,981)	125,642
General and administrative	14,515	(2,755)	11,760
Total operating expenses	<u>149,138</u>	<u>(11,736)</u>	<u>137,402</u>
Loss from operations	(27,538)	8,723	(18,815)
Other income (expense):			
Equity in net loss of Regulus Therapeutics Inc.	—	(6,133)	(6,133)
Investment income	6,361	(172)	6,189
Interest expense	(12,672)	172	(12,500)
Gain on investments	2,084	(13)	2,071
Loss from continuing operations, before income tax expense	(31,765)	2,577	(29,188)
Income tax expense	(3,191)	141	(3,050)
Net loss from continuing operations	(34,956)	2,718	(32,238)
Discontinued operations:			
Loss from discontinued operations	(29)	—	(29)
Gain on sale of Ibis Biosciences, Inc., net of tax	185,657	—	185,657
Net income from discontinued operations, net of tax	<u>185,628</u>	<u>—</u>	<u>185,628</u>
Net income	150,672	2,718	153,390
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	4,394	(4,394)	—
Net income attributable to Isis Pharmaceuticals, Inc. common stockholders	<u>\$ 155,066</u>	<u>\$ (1,676)</u>	<u>\$ 153,390</u>
Basic and diluted net income (loss) per share:			
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc.	\$ (0.31)		\$ (0.33)

common stockholders		
Net income from discontinued operations	1.89	1.89
Basic and diluted net income	<u>\$ 1.58</u>	<u>\$ 1.56</u>
Shares used in computing basic and diluted net income (loss) per share	<u>98,109</u>	<u>98,109</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, December 31,		Years ended, December 31,	
	2010	2009	2010	2009
	(unaudited)		(unaudited)	
As reported operating expenses according to GAAP	\$ 42,277	\$ 43,934	\$ 156,829	\$ 149,138
Excluding compensation expense related to stock options	(2,712)	(3,571)	(12,159)	(13,385)
Pro forma operating expenses	<u>\$ 39,565</u>	<u>\$ 40,363</u>	<u>\$ 144,670</u>	<u>\$ 135,753</u>
As reported loss from operations according to GAAP	\$ (15,857)	\$ (11,673)	\$ (48,356)	\$ (27,538)
Excluding compensation expense related to stock options	(2,712)	(3,571)	(12,159)	(13,385)
Pro forma loss from operations	<u>\$ (13,145)</u>	<u>\$ (8,102)</u>	<u>\$ (36,197)</u>	<u>\$ (14,153)</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)

	December 31, 2010	December 31, 2009
Assets:		
Cash, cash equivalents and short-term investments	\$ 472,353	\$ 574,312
Other current assets	10,784	21,814
Property, plant and equipment, net	35,703	27,338
Other assets	31,637	33,720
Total assets	<u>\$ 550,477</u>	<u>\$ 657,184</u>
Liabilities and stockholders' equity:		
Other current liabilities	\$ 31,388	\$ 35,763
Current portion of deferred contract revenue	74,502	75,681
2 5/8% convertible subordinated notes	132,895	125,100
Long-term obligations, less current portion	15,867	11,478
Investment in Regulus Therapeutics Inc.	870	—
Long-term deferred contract revenue	50,413	107,097
Stockholders' equity	244,542	302,065
Total liabilities and stockholders' equity	<u>\$ 550,477</u>	<u>\$ 657,184</u>

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