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): **March 1, 2010**

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 March 1, 2010, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter and fiscal year ended December 31, 2009. 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 March 1, 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.

ISIS PHARMACEUTICALS, INC.

Dated: March 1, 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 March 1, 2010.

ISIS REPORTS STRONG FINANCIAL RESULTS AND HIGHLIGHTS FOR 2009

- **Reports Second Consecutive Year of Pro Forma Net Income**
- **Achieves All 2009 Financial Guidance Metrics**
- **Conference Call Webcast Monday, March 1, 8:30 a.m. EST at www.isispharm.com**

CARLSBAD, Calif., March 1, 2010 - Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced its 2009 financial results and reviewed the highlights of the year. Isis achieved its 2009 financial guidance with pro forma net income of $166.9 million and a pro forma net operating loss (NOL) of $14.2 million compared with its guidance for the year of pro forma net income of more than $145 million and a pro forma NOL in the low to mid $20 million range. Isis also achieved its cash guidance by ending 2009 with $574.3 million of cash, cash equivalents and short-term investments significantly in excess of the $550 million projected.

"We ended 2009 in a strong financial position. Our financial performance over the past four years reflects the value we are creating at Isis and the success of our business strategy. For the fourth consecutive year, we ended the year with a greater cash balance than that with which we began. With 22 drugs in development, including a broad Phase 3 program for mipomersen, we are nevertheless able to maintain a manageable cost structure and our partnership strategy provides us with a continuing revenue stream. We plan to continue to aggressively expand our pipeline and move drugs through the clinic to keep building the pipeline that has been the basis of our financial success to date," said B. Lynne Parshall, COO and CFO of Isis.

"2010 will be a very busy clinical development year for us. The development program ongoing for mipomersen is focusing not only on the first filings and indications, but also looking forward to broader future commercial opportunities. We are also anticipating significant activities in the rest of our pipeline. We plan to start Phase 2 clinical trials on at least three drugs, ISIS-CRP_{Rx}, ISIS-$SGLT2_{Rx}$, and the cancer drug we reacquired from Lilly, ISIS-$EIF4E_{Rx}$. We also expect to advance our three new drugs toward the clinic in exciting new therapeutic areas and to continue to expand the pipeline by adding three to five new drugs this year. In addition, we are making excellent progress toward the next major advance in antisense technology. Our goal is to designate a 'generation 2.5' chemistry this year, which we expect will make our drugs even more attractive. While we will continue to prudently manage our expenses, we believe these investments can generate significant value in the future. Because of our strong financial position, we are being highly selective in the types of partnerships that we are interested in. However, we have historically been successful in partnering and we may create new partnerships in 2010 if they are consistent with our goal of controlling our drugs through Phase 2 proof-of-concept," added Ms. Parshall.

"Due to the increase in the research and development activities we have planned for this year, we expect a modest increase in our operating expenses. In addition, while we will continue to generate revenue from our existing partnerships, we anticipate a reduction in revenue this year primarily due to the completion of the amortization of certain upfront fees. We will also no longer be consolidating Regulus' financial results into our own. All of these items impact our guidance. As such, we are projecting a 2010 pro forma net operating loss in the mid $50 million range. Additionally, we expect to end 2010 with more than $425 million in cash," continued Ms. Parshall.

Upcoming Key Milestones

- Report data from a Phase 3 study evaluating mipomersen in patients with severe high cholesterol (mid 2010)
- Report data from a Phase 3 study evaluating mipomersen in high-cholesterol patients at high risk for coronary heart disease (mid 2010)

Financial Results

On a GAAP basis, Isis reported a loss from operations of $11.7 million and $27.5 million for the three and twelve months ended December 31, 2009, respectively, compared to a loss from operations of $8.1 million and $13.1 million for the three and twelve months ended December 31, 2008, respectively. Isis' operating results in 2009 reflect higher expenses associated with the expansion of the Company's programs as discussed in more detail in the "Operating Expenses" section below, offset in part, by an increase in revenue in 2009 from Isis' corporate partnerships compared to 2008. Additionally, Isis reported a net loss of $16.8 million and net income of $155.1 million for the three and twelve months ended December 31, 2009, respectively, compared to a net loss of $10.3 million and $18.2 million for the same periods in 2008.

As a result of selling Isis' diagnostic subsidiary, Ibis Biosciences, to Abbott Molecular Inc. (AMI) in the first quarter of 2009, Isis is reporting Ibis' financial results as discontinued operations. Accordingly, Isis has presented all periods of Ibis' operating results in Isis' financial statements separately as discontinued operations. The discontinued operations line in 2009 also includes the $185.7 million gain that Isis recognized on the sale, net of taxes. A reconciliation summarizing the adjustments made to reflect the changes to Isis' 2008 historical statement of operations 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, 2009 was $32.3 million and $121.6 million compared to $29.6 million and $107.2 million in the same periods of 2008. Isis' revenue for the year ended December 31, 2009 was higher due in part to an increase in revenue from the Company's collaboration with Genzyme. 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, Isis' revenue in the fourth quarter of 2009 was significantly higher than the fourth quarter of 2008 primarily as a result of $10 million of sublicensing revenue that Isis earned in December 2009 from OncoGenex Pharmaceuticals, Inc. as a result of OncoGenex' license of OGX-011 to Teva Pharmaceutical Industries Ltd.

Operating Expenses

On a pro forma basis, operating expenses for the three and twelve months ended December 31, 2009 were $40.4 million and $135.8 million compared to $34.9 million and $107.0 million for the same periods in 2008. The higher expenses in 2009 were primarily due to the expansion of the Company's clinical development programs, including additional expenses associated with the broad Phase 3 clinical program for mipomersen, expenses for Regulus as it builds

its core team and expenses related to the Company's expansion of its drug discovery activities into new therapeutic areas. On a GAAP basis, Isis' operating expenses from continuing operations for the three and twelve months ended December 31, 2009 were $43.9 million and $149.1 million compared to $37.7 million and $120.3 million for the same periods in 2008, including non-cash compensation expense related to stock options of $3.6 million and $13.4 million for the three and twelve months ended December 31, 2009 and $2.9 million and $13.3 million for the same periods in 2008.

Interest Expense

In 2009, Isis adopted a new accounting standard for its 2 5/8% convertible notes, which required Isis to assign a value to its convertible debt without considering the conversion feature. As a result, Isis is recording its convertible debt at a discount, which Isis is amortizing over the expected life of the debt as additional non-cash interest expense. The new standard required retrospective application to all periods presented. Accordingly, the amount of interest expense Isis recorded in its statement of operations for the three and twelve months ended December 31, 2009 increased by $1.8 million and $6.8 million compared to an increase of $1.6 million and $6.2 million for the same periods in 2008. This new standard did not impact Isis' cash, cash equivalents and short-term investments but decreased the carrying value of Isis' $162.5 million convertible notes to $125.1 million and $118.0 million at December 31, 2009 and 2008, respectively, with corresponding increases to shareholders' equity. A reconciliation summarizing the adjustments made to reflect the changes to Isis' 2008 historical statement of operations appears later in this release.

Net Loss from Continuing Operations, including Income Tax Expense

Net loss from continuing operations for the fourth quarter of 2009 was $15.3 million compared to $7.8 million for the same period in 2008. For the years ended December 31, 2009 and 2008, net loss from continuing operations was $30.6 million and $9.8 million, respectively.

Even though Isis finished 2009 with a net loss from continuing operations, Isis had taxable income, which was primarily a result of the significant upfront payments that the Company received from its strategic alliance with Genzyme in 2008 and the gain it recognized on the sale of Ibis to AMI in early 2009. Accounting rules require Isis to allocate its 2009 tax expense of $20 million between continuing operations and discontinued operations in its Consolidated Statement of Operations. As a result, Isis recorded income tax expense of $3.2 million in 2009 as part of its financial results from continuing operations.

Isis' net loss from continuing operations also included a $2.5 million gain on investments that Isis recognized in the second quarter of 2009 when it sold the stock it held in OncoGenex. OncoGenex' stock price increased significantly in the second quarter of 2009 after announcing encouraging data from its clinical studies of OGX-011 and OGX-427. This gain demonstrates the value that Isis is recognizing from its satellite company strategy.

Net Income (Loss) from Discontinued Operations

The net income (loss) from discontinued operations represents the operating results of Ibis that are presented separately in Isis' financial statements as a result of the sale of Ibis to AMI in January 2009. Net income from discontinued operations in 2009 primarily consists of the $202.5 million gain less $16.8 million of income taxes. A reconciliation summarizing the adjustments made to reflect the changes to Isis' 2008 historical statement of operations appears later in this release.

Net Income (Loss)

Isis reported net income of $155.1 million for the year ended December 31, 2009 compared to a net loss of $18.2 million for 2008. Basic and diluted net income per share for the year ended December 31, 2009 was $1.58 per share, compared to basic and diluted net loss per share of $0.19 for 2008. The improvement in Isis' net income and net income per share in 2009 compared to 2008 was primarily due to the gain Isis recognized when it sold Ibis to AMI. For the three months ended December 31, 2009 and 2008, Isis reported a net loss of $16.8 million or $0.17 per share and $10.3 million or $0.11 per share, respectively. The increase in the net loss in the fourth quarter of 2009 compared to 2008 was primarily due to the increase in Isis' loss from continuing operations and $3.8 million of income tax expense recognized in the fourth quarter of 2009.

Regulus Therapeutics

Regulus' revenue for the three and twelve months ended December 31, 2009 was $625,000 and $3.0 million compared to $681,000 and $2.1 million for the same periods in 2008. The increase was primarily related to revenue from its collaboration with GlaxoSmithKline (GSK), including the discovery milestone payment that Regulus received from GSK in 2009.

Excluding non-cash compensation expense related to stock options, operating expenses for Regulus were $3.4 million and $11.6 million for the three and twelve months ended December 31, 2009 compared to $3.1 million and $7.6 million for the same periods in 2008. The increase is primarily related to Regulus' continued efforts to build its team to support its internal microRNA programs and its GSK collaboration. Regulus generated a loss from operations, excluding non-cash compensation expense related to stock options, of $2.7 million and $8.6 million for the three and twelve months ended December 31, 2009 compared to $2.4 million and $5.5 million for the same periods in 2008.

Beginning in the first quarter of 2010, as a result of a new accounting standard, Isis will no longer include Regulus' revenue and operating expenses in its operating results and no longer include Regulus' cash in Isis' balance sheet. Please see Isis' Form 8-K dated February 25, 2010 for a more detailed explanation of this change.

Balance Sheet

As of December 31, 2009, Isis had cash, cash equivalents and short-term investments of $574.3 million compared to $491.0 million at December 31, 2008 and had consolidated working capital of $484.7 million at December 31, 2009 compared to $393.7 million at December 31, 2008. Isis received $175 million from AMI in the first quarter of 2009 for its sale of Ibis, which resulted in the significant increases in both of these amounts. During 2009, Isis also received more than $35 million in cash from its corporate partnerships. Included on Isis' balance sheet at December 31, 2009 was $30.7 million of Regulus' cash.

Business Highlights

"We have had an excellent year. Not only have we continued to improve our financial position, we have reported successes across all areas of our business. The most notable of these was from our pipeline, with mipomersen at the top of the list. Over the past year, we have reported positive data from two Phase 3 studies on mipomersen, and we will complete and report data from the remaining Phase 3 studies later this year. These studies will form the basis of 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. It is exciting to be so close to completing this important step in mipomersen's development," added Ms. Parshall.

"Although mipomersen leads our development efforts, we made significant progress across our entire pipeline. We and our partners presented promising clinical data on a number of drugs this year, and we expanded our pipeline by adding four new drugs into development. We also reacquired our eIF-4E program to treat cancer from Lilly, which is a program that we are very excited about. In preclinical studies, we and Lilly demonstrated that antisense inhibition of eIF-4E reduced tumor growth in animals. We are encouraged by this early data and by the positive Phase 1 data of ISIS-EIF4E$_{Rx}$. We believe that ISIS-EIF4E$_{Rx}$ could have broad therapeutic implications in a number of cancers, and we will be initiating a Phase 2 program this year," continued Ms. Parshall.

"In addition to our pipeline advances, we continue to support our satellite companies by participating in their financings. And, we continue to see a strong interest in antisense technology from large pharmaceutical companies as evidenced by OncoGenex' licensing of OGX-011 to Teva Pharmaceuticals and Regulus' expanded alliance with GSK. As you can see, 2009 was a productive year and we believe that we will continue this momentum through 2010. With a pipeline of 22 drugs, we expect to have a steady stream of accomplishments as drugs move into the clinic, complete clinical studies and advance

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into Phase 2 and Phase 3 development. In summary, we are making excellent progress across all areas of our business. Our financial position remains strong and it enables us to invest in our business and our technology in ways that we believe will continue to generate value for our shareholders," concluded Ms. Parshall.

2010 Goals

In 2010, Isis is planning to achieve the following goals itself and with partners:

- Prepare for filing new drug applications for mipomersen in the United States (NDA) and Europe (MAA) in the first half of 2011with Genzyme
  - Complete and report remaining Phase 3 studies
- Report data on the following drugs:
  - ISIS-CRP$_{Rx}$ (Phase 1)
  - ISIS-SGLT2$_{Rx}$ (Phase 1)
  - iCo-007 (Phase 1 - iCo Therapeutics)
  - AIR645 (Phase 2 - Altair Therapeutics)
- Continue to advance its pipeline. Together with partners initiate the following clinical studies:
  - Phase 3 study on OGX-011 (OncoGenex and Teva)
  - Phase 2 studies on 5 drugs
  - Phase 1 studies on 2 drugs
- Broaden its pipeline by:
  - Expanding further into new therapeutic areas including neurodegenerative diseases and cancer
  - Adding 3 to 5 new drugs to its pipeline
- Advance antisense technology by:
  - Selecting the next generation antisense chemistry
- Add new partnership and/or satellite company relationships

Ortho-McNeil Collaboration

Isis' collaboration with Ortho-McNeil Janssen Pharmaceuticals (OMJP) has ended and Isis has regained the rights to drugs from both the glucagon receptor and glucocorticoid receptor programs. Isis reported positive Phase 1 data on ISIS-GCGR$_{Rx}$. Antisense inhibition of GCGR with ISIS-GCGR$_{Rx}$ improved blood glucose levels following a glucagon challenge with statistical significance at a dose of 400 mg/week and resulted in positive trends at lower doses. The drug was well tolerated at all doses. Isis intends to move a more potent inhibitor for its GCGR program forward that was identified as part of its collaboration with Ortho-McNeil. A more potent drug should enhance the therapeutic profile of the GCGR program and provide much greater commercial value. Isis also intends to move forward the GCCR program, which reduced blood glucose and demonstrated a dramatic and favorable effect on lipid levels including cholesterol and triglycerides, and reduced body fat in preclinical studies.

Drug Development Highlights

- Mipomersen continues to advance in clinical development and move closer to the market for patients 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 familial hypercholesterolemia (FH).
  - In a Phase 3 study evaluating mipomersen in patients with homozygous FH, Isis and Genzyme reported that the study met its primary endpoint with a 25% reduction in LDL-C after 26 weeks of treatment compared to a decrease of 3% for placebo ($p<0.001$), which constitutes an average reduction of LDL-C > 100 mg/dL, and also met all of its secondary and tertiary endpoints.
  - In a Phase 3 study evaluating mipomersen in patients with heterozygous FH, Isis and Genzyme reported that the study met its primary endpoint with a 28% reduction in LDL-C after 26 weeks of treatment compared to an increase of 5% for placebo ($p<0.001$) and also met all of its secondary endpoints. Patients treated with mipomersen had an average LDL-C level of 104

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mg/dL at the end of the study and 45% of the mipomersen-treated patients achieved LDL-C levels of less than 100 mg/dL.

- Isis reported positive Phase 2 data on ISIS 113715 in patients with type 2 diabetes on stable doses of sulfonylurea.
  - In this study, patients treated with 200 mg per week of ISIS 113715 for 13 weeks achieved consistent and statistically significant reductions in multiple short and intermediate measures of glucose control.
- Isis reported positive Phase 1 data in which ISIS-GCGR$_{Rx}$ produced a significant improvement in glucagon-induced blood glucose levels and was well tolerated.
- In addition, Isis and its partners continued to advance the drugs in Isis' pipeline and reported encouraging clinical results in a broad range of diseases.
  - Isis and its partners presented positive Phase 1 data on six drugs including, LY2181308, OGX-427, ISIS-GCGR$_{Rx}$, AIR645, iCo-007 and ACHN-490, and positive Phase 2 data on OGX-011.
- Isis and its partners added four new drugs to its pipeline including ISIS-FXI$_{Rx}$ to treat thrombosis, ISIS-SMN$_{Rx}$ to treat spinal muscular atrophy, ISIS-APOCIII$_{Rx}$ to treat cardiovascular disease, and ACHN-490 to treat severe bacterial infections.
- Isis and its partners initiated Phase 1 clinical studies on four drugs and initiated Phase 2 studies on two drugs including AIR645 and EXC 001.

Corporate Highlights

- Isis executed its business strategy by successfully monetizing a key asset.
  - Isis sold its Ibis subsidiary to AMI.
- Isis benefited financially as its partners advanced drugs in development.
  - Isis received $11 million in milestone payments and sublicensing fees .
- Isis also benefited from its partnerships focused on developing and advancing certain RNA-based therapeutic technologies, receiving nearly $13 million in total.
- Isis supported its satellite company partners who are developing antisense drugs discovered by Isis for the treatment of a broad range of diseases by participating in the financings of iCo Therapeutics, Altair Therapeutics, Excaliard Pharmaceuticals, and Regulus Therapeutics.
- Isis strengthened its intellectual property assets by obtaining patent grants and allowances that expand Isis' fundamental patents and increase protection of Isis' drugs in development.
  - Isis also exclusively licensed certain intellectual property from the University of Massachusetts to develop drugs to treat spinal muscular atrophy (SMA). Funding support for the University of Massachusetts' research program responsible for creating this intellectual property was provided in part by Families of SMA.
- Regulus formed a new alliance with GSK to develop and commercialize microRNA therapeutics targeting miR-122 for hepatitis C viral infection.

Conference Call

At 08:30 a.m. Eastern Time today, March 1, 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 866-730-5767 and refer to passcode "ISIS 2009," 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 22 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 over 1,600 issued patents worldwide. 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 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 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, 2008, 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' 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, December 31,		Years ended, December 31,	
	2009	2008	2009	2008
	(unaudited)			
Revenue:				
Research and development revenue under collaborative agreements	$ 21,716	$ 29,103	$ 108,131	$ 98,853
Licensing and royalty revenue	10,545	546	13,469	8,337
Total revenue	32,261	29,649	121,600	107,190
Expenses:				
Research and development	40,104	33,343	134,623	106,439
General and administrative	3,830	4,382	14,515	13,811
Total operating expenses	43,934	37,725	149,138	120,250
Loss from operations	(11,673)	(8,076)	(27,538)	(13,060)
Other income (expense):				

Investment income	1,061	2,514	6,361	11,318
Interest expense	(3,251)	(2,911)	(12,672)	(11,812)
Gain (loss) on investments, net	(651)	(965)	2,084	(965)
Loss from continuing operations, before income tax expense	(14,514)	(9,438)	(31,765)	(14,519)
Income tax expense	(2,318)	—	(3,191)	—
Loss from continuing operations, including income tax expense	(16,832)	(9,438)	(34,956)	(14,519)
Discontinued Operations:				
Loss from discontinued operations	—	(2,503)	(29)	(8,387)
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)	(2,503)	185,628	(8,387)
Net income (loss)	(18,328)	(11,941)	150,672	(22,906)
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	1,488	1,678	4,394	4,734
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (16,840)	$ (10,262)	$ 155,066	$ (18,172)
Basic and diluted net income (loss) per share:				
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.16)	$ (0.08)	$ (0.31)	$ (0.10)
Net income (loss) from discontinued operations	(0.01)	(0.03)	1.89	(0.09)
Basic and diluted net income (loss)	$ (0.17)	$ (0.11)	$ 1.58	$ (0.19)
Shares used in computing basic net income (loss) per share	98,467	96,889	98,109	94,566
Shares used in computing diluted net income (loss) per share	98,467	96,889	98,109	94,566

Isis Pharmaceuticals, Inc.
Reconciliation of Isis' 2008 Historical Statement of Operations
(In Thousands, Except Per Share Data)
(unaudited)

	Historical Isis Pharmaceuticals, Inc. Year ended December 31, 2008(1)	New Accounting Standard for Debt(2)	Adjusted year ended December 31, 2008
Revenue:			
Research and development revenue under collaborative agreements	$ 98,853	$ —	$ 98,853
Licensing and royalty revenue	8,337	—	8,337
Total revenue	107,190	—	107,190
Expenses:			
Research and development	106,439	—	106,439
General and administrative	13,811	—	13,811
Total operating expenses	120,250	—	120,250
Loss from operations	(13,060)	—	(13,060)
Other income (expense):			
Investment income	11,318	—	11,318
Interest expense	(5,603)	(6,209)	(11,812)
Loss on Investments, net	(965)	—	(965)
Net loss from continuing operations	(8,310)	(6,209)	(14,519)
Net loss from discontinued operations	(8,387)	—	(8,387)
Net loss	(16,697)	(6,209)	(22,906)
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	4,734	—	4,734
Net loss attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (11,963)	$ (6,209)	$ (18,172)
Basic and diluted net loss per share:			
Net loss from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	$ (0.04)		$ (0.10)
Net loss from discontinued operations	(0.09)		(0.09)
Basic and diluted net loss	$ (0.13)		$ (0.19)
Shares used in computing basic and diluted net loss per share	94,566		94,566

(1) The historical consolidated statement of operations reflects the required retrospective adoption of the accounting standard for non-controlling interests.

(2) Adjustment to reflect the required retrospective adoption of the accounting standard for debt.

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

	Three months ended, December 31,		Years ended, December 31,	
	2009	2008	2009	2008
As reported operating expenses according to GAAP	$ 43,934	$ 37,725	$ 149,138	$ 120,250
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(3,571)	(2,852)	(13,385)	(13,286)
Pro forma operating expenses	$ 40,363	$ 34,873	$ 135,753	$ 106,964
As reported loss from operations according to GAAP	$ (11,673)	$ (8,076)	$ (27,538)	$ (13,060)
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(3,571)	(2,852)	(13,385)	(13,286)
Pro forma income (loss) from operations	$ (8,102)	$ (5,224)	$ (14,153)	$ 226
As reported net income (loss) according to GAAP	$ (16,840)	$ (10,262)	$ 155,066	$ (18,172)
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(3,571)	(3,248)	(11,827)	(15,063)
Pro forma net income (loss)	$ (13,269)	$ (7,014)	$ 166,893	$ (3,109)

Reconciliation of GAAP to Pro Forma Basis

As illustrated in the Selected Financial Information in this press release, pro forma operating expenses, pro forma loss from operations and pro forma net income (loss) 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.

Regulus Therapeutics Inc.
Statements of Operations
(In Thousands)

	Three months ended, December 31,		Years ended, December 31,	
	2009	2008	2009	2008
	(unaudited)		(unaudited)	
Revenue:				
Research and development revenue under collaborative agreements	$ 625	$ 681	$ 3,013	$ 2,110
Total revenue	625	681	3,013	2,110
Expenses:				
Research and development	2,699	2,344	8,981	7,180
General and administrative	773	1,067	2,755	2,851
Total operating expenses	3,472	3,411	11,736	10,031
Loss from operations	$ (2,847)	$ (2,730)	$ (8,723)	$ (7,921)

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

	December 31, 2009	December 31, 2008
Assets:		
Cash, cash equivalents and short-term investments	$ 574,312	$ 490,998
Other current assets	21,814	27,386
Property, plant and equipment, net	27,338	17,371
Other assets	33,720	37,021
Total assets	$ 657,184	$ 572,776
Liabilities and stockholders' equity:		
Other current liabilities	$ 35,763	$ 32,037
Current portion of deferred contract revenue	75,681	92,662
2 5/8% convertible subordinated notes	125,100	117,993
Long-term obligations, less current portion	11,478	9,938
Long-term deferred contract revenue	107,097	172,766

Stockholders' equity	302,065	147,380
Total liabilities and stockholders' equity	$ 657,184	$ 572,776

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