

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

Date of report (Date of earliest event reported): **May 7, 2009**

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 May 7, 2009, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter ended March 31, 2009. In addition to disclosing results that are determined in accordance with Generally Accepted Accounting Principles (GAAP), the Company also discloses pro forma or non-GAAP results of operations, which are adjusted from GAAP to exclude non-cash compensation related to stock options. The Company is presenting pro forma information excluding non-cash compensation expense or benefit because the Company believes it is useful for investors in assessing the Company's operating results compared to the prior year. A copy of the release is furnished with this report as an exhibit pursuant to "Item 2.02. Results of Operations and Financial Condition" of Form 8-K in accordance with SEC Release Nos. 33-8216 and 34-47583.

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

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

99.1 Press Release dated May 7, 2009.

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

ISIS PHARMACEUTICALS, INC.

Dated: May 7, 2009

By: /s/ B. Lynne Parshall

B. LYNNE PARSHALL

Chief Operating Officer,

Chief Financial Officer and Director

INDEX TO EXHIBITS

99.1 Press Release dated May 7, 2009.



ISIS REPORTS STRONG FINANCIAL RESULTS AND HIGHLIGHTS FOR FIRST QUARTER OF 2009

Conference Call Webcast Thursday, May 7, 08:30 a.m. EDT at www.isispharm.com

CARLSBAD, Calif., May 7, 2009 - Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced its financial results for the quarter ended March 31, 2009. Primarily as a result of the \$171.8 million gain that Isis recognized from selling its Ibis Biosciences subsidiary to Abbott Molecular Inc. (AMI), Isis finished the first quarter of 2009 with pro forma net income of \$173.0 million. Isis also reported pro forma net operating income of \$2.1 million for the first quarter of 2009 compared to a net operating loss (NOL) of \$3.0 million in the first quarter of 2008. The improvement in Isis' operating results from the first quarter of 2008 was primarily due to an increase in revenue from its strategic alliance with Genzyme, which was completed in the second quarter of 2008. On a GAAP basis, Isis' net income of \$171.8 million and loss from operations of \$642,000 for the first quarter of 2009 also improved significantly from its net loss and loss from operations in the first quarter of 2008. The sale of Isis' diagnostic subsidiary, Ibis, not only was a substantial contributor to Isis' first quarter net income, but the \$175 million Isis received from completing the transaction also considerably increased Isis' cash position. Isis ended the quarter with \$652 million in cash, cash equivalents and short-term investments.

"We ended 2008 in the strongest financial position in our history, and our financial strength continued to improve this quarter. Already this year, we have received over \$200 million in cash, including the \$175 million we received at the beginning of the year from our sale of Ibis," said B. Lynne Parshall, COO and CFO of Isis. "Our strong financial position is a result of the execution of our business strategy both with our large pharmaceutical partners and our satellite companies, which enables us to build value through our successes and the successes of our partners. Over the last two years, we have added four new large pharmaceutical partners and five new satellite company partners. These partnerships not only result in financial benefit, but most importantly, they continue to expand and advance our pipeline. For instance, since 2007 together with our partners, we have added five new drugs to our pipeline, initiated clinical trials on seven of the drugs in our pipeline and presented positive clinical data on many of the drugs in our pipeline. Since 2007, we have also added more than \$750 million in cash from our partnerships. Because of these achievements, we have the financial strength and momentum to support continuing progress in 2009."

Upcoming Key Milestones

- Report data from a Phase 3 study evaluating mipomersen in homozygous Familial Hypercholesterolemia (FH) patients and from additional mipomersen studies in other patient populations
- Report data from a Phase 2 study evaluating ISIS 113715 in combination with sulfonylureas in patients with type 2 diabetes
- Begin clinical trials on one to three additional drugs in 2009; two clinical trials have already been initiated this year
- Expand pipeline by moving two to four additional drugs into development; one new drug has already been moved into development this year

Financial Results

As a result of selling Ibis to AMI, 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 the first quarter of 2009 also includes the \$171.8 million gain that Isis recognized on the sale net of taxes.

The improvement in the Company's pro forma and GAAP operating results was driven primarily by the increase in revenue in the first quarter of 2009 from Isis' corporate partnerships compared to the first quarter of 2008. This was offset, in part, by higher expenses associated with the expansion of the Company's programs as discussed in more detail in the "Operating Expenses" section below. Please refer to the reconciliation of pro forma and GAAP measures, which is explained later in this release.

Revenue

Revenue for the first quarter of 2009 was \$31.6 million compared to \$18.4 million in the first quarter of 2008. This substantial increase in Isis' revenue is primarily due to an increase in revenue from the Company's collaboration with Genzyme. As part of Isis' strategic relationship with Genzyme, in the first quarter of 2008 Genzyme purchased Isis stock at a significant premium to the then market price and in the second quarter of 2008 paid Isis a license fee. Isis is amortizing the premium on the stock and the license fee into revenue through June 2012. Revenue from Genzyme was higher in 2009 because the first quarter of 2008 only included revenue from amortization of the stock premium. Also contributing to the increase was the revenue Regulus Therapeutics earned from its strategic alliance with GlaxoSmithKline (GSK), which began in April 2008. Although not a material factor in the quarter to quarter change in revenue, Isis also earned revenue from the research and development it performed for its partners and from ongoing licensing agreements. Isis' satellite companies also continued to contribute to the Company's revenue from sublicensing fees, milestone payments and contract manufacturing. Although less predictable than the previously mentioned revenue sources, revenue from these sources contributes meaningfully to the Company's total revenue. Beginning in the second quarter, Isis will recognize revenue related to its recent license agreement with Alnylam, which will consist of the research funding and the amortization of the \$11 million upfront fee Isis will earn as part of the collaboration, as well as the milestone payment Isis earned when Alnylam initiated clinical trials on ALN-VSP.

Operating Expenses

On a pro forma basis, operating expenses for the first quarter of 2009 were \$29.5 million compared to \$21.3 million for the same period in 2008. Consistent with Isis' guidance, 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, the lead drug in Isis' cardiovascular franchise, and expenses for Regulus. Consistent with the Company's guidance, the broad Phase 3 program for mipomersen accounted for approximately 16% of the increase in Isis' operating expenses. On a GAAP basis, Isis' operating expenses from continuing operations for the first quarter of 2009 were \$32.2 million compared to \$24.6 million for the same period in 2008, including non-cash compensation expense related to stock options of \$2.7 million and \$3.3 million, respectively. During the remainder of 2009, Isis' operating expenses will increase modestly as Isis continues the development of mipomersen, as Regulus continues to build its core team, and as Isis expands its research and development efforts in different disease areas.

Interest Expense

In 2009, Isis adopted a new accounting standard, FASB Staff Position No. APB 14-1 (FSP 14-1), related to its 2 5/8% convertible notes. This new standard requires Isis to assign a value to its convertible debt equal to the estimated fair value of a similar debt instrument without the conversion feature, which results in Isis recording its convertible debt at a discount. FSP 14-1 then requires Isis to amortize the resulting debt discount over the expected life of the debt as additional non-cash interest expense. FSP 14-1 required retrospective application to all periods presented. Accordingly, the amount of interest expense Isis recorded in its statement of operations for the first quarter of 2009 and 2008 increased by \$1.7 million and \$1.5 million, respectively. 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 \$119.7 million and \$118.0 million at March 31, 2009 and December 31, 2008, respectively, with corresponding increases to shareholders' equity.

Net Loss from Continuing Operations, Net of Income Tax Benefit

Net loss from continuing operations, net of income tax benefit, for the first quarter of 2009 was \$814,000 compared to \$6.1 million in the first quarter of 2008. The improvement in Isis' net loss from continuing operations was primarily driven by the improvement in the Company's net operating results. Even though Isis finished the first quarter of 2009 with a net loss from continuing operations, Isis had taxable income, which is 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 earlier this year. Accounting rules require Isis to record an income tax benefit of \$717,000 on a line called "Income Tax Benefit" as part of its financial results from continuing operations because it will be using the tax benefits generated from its current year loss from continuing operations to offset a portion of its taxable income.

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 the first quarter of 2009 primarily consists of the \$202.5 million gain less income taxes. Accounting rules require Isis to allocate its 2009 tax expense between discontinued operations and continuing operations in its Consolidated Statement of Operations. Since the sale of Ibis to AMI was a discrete event that occurred in the first quarter of 2009, the accounting rules require Isis to record the total amount of its estimated income tax expense for discontinued operations in the first quarter of this year. Further, Isis is required to gross up this amount by the projected annual tax benefit it expects to record as part of its loss from continuing operations in 2009, which is described above. This means that in addition to the tax expense for the gain on the sale of Ibis, discontinued operations also includes the tax expense for other timing differences, which principally consists of the timing difference associated with the upfront funding Isis received from Genzyme. Accordingly, Isis has recorded tax expense of \$30.7 million in discontinued operations in the first quarter of 2009.

Net Income (Loss)

Isis' net income for the first quarter of 2009 was \$171.8 million, compared to a net loss of \$5.8 million in the first quarter of 2008. Basic and diluted net income per share for the first quarter of 2009 was \$1.76 per share and \$1.57 per share, respectively. Basic and diluted net loss per share for the first quarter of 2008 was \$0.06 per share. Isis' net income and net income per share in the first quarter of 2009 was significantly improved over Isis' net loss and net loss per share for the same period of 2008 primarily due to the gain Isis recognized when it sold Ibis to AMI.

Balance Sheet

As of March 31, 2009, Isis had cash, cash equivalents and short-term investments of \$652.2 million compared to \$491.0 million at December 31, 2008 and had consolidated working capital of \$527.2 million at March 31, 2009 compared to \$393.7 million at December 31, 2008. Isis received \$175 million from AMI in the first quarter 2009 for its sale of Ibis, which resulted in the significant increases in both of these amounts.

Regulus Therapeutics

Regulus' revenue for the first quarter of 2009 was \$638,000 compared to \$92,000 in the same period of 2008. The increase was primarily related to revenue from its collaboration with GSK.

Excluding non-cash compensation expense related to stock options, operating expenses for Regulus were \$2.8 million for the first quarter of 2009 compared to \$1.1 million in the same period of 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 \$2.2 million for the first quarter of 2009 compared to \$1.0 million in the same period of 2008.

Business Highlights

"2009 is looking very promising for Isis. Already this year, we have achieved three important goals related to our satellite company strategy, which maximizes the value of our inventions and technology. First, we have broadened our technology partnerships to maintain our leadership in all applications of antisense technology, announcing a new initiative with Alnylam to accelerate our efforts in single-stranded RNAi therapeutics. We benefit by having a partner to help us advance and fund development of the technology, while we have the opportunity to discover and develop ssRNAi antisense drugs ourselves. Second, our satellite company partners continue to advance antisense drugs that we discovered or drugs derived from technology that we created and licensed, which is broadening and maturing our pipeline, such as Achaogen's new aminoglycoside, ACHN-490. Finally, these partnerships continue to benefit us financially. Since the beginning of the year, we have earned over \$12 million from our partners at Alnylam for our single-stranded RNAi alliance, Alnylam's recent partnering activity with Cubist, and a milestone payment from Alnylam related to the initiation of clinical trials for ALN-VSP, plus a \$1 million milestone payment from Achaogen. Most importantly, we completed the sale of our diagnostics subsidiary, Ibis, to Abbott Molecular at the beginning of the year for a total price of \$215 million," added Ms. Parshall.

"Ibis is a great example of how we monetize our innovation for short-term significant financial gain while putting our diagnostics subsidiary in the hands of a partner that can maximize its commercial value, which we expect to continue to benefit from earn out payments on Ibis' commercial sales. This is the power of our business strategy; we capitalize on our technology and drug discovery platform to create not only short-term financial value but also sustainable value in the future as our assets advance," continued Ms. Parshall.

Drug Development Highlights

"Of course, our most significant upcoming milestone for this year is reporting the data from our Phase 3 study evaluating mipomersen in homozygous Familial Hypercholesterolemia patients. We expect top-line data from this study this quarter. This study is the first of four Phase 3 studies evaluating

mipomersen and we expect additional data as we complete additional studies on mipomersen. Moreover, we have many key milestones to look forward to in 2009, including data on many of the other drugs in our pipeline,” concluded Ms. Parshall.

Mipomersen, the most advanced drug in Isis’ cardiovascular pipeline, is being evaluated in a broad Phase 3 program in patients who cannot adequately control their cholesterol levels with current therapies and who need new treatment options.

- Isis and Genzyme initiated a Phase 3 study evaluating mipomersen in severe hypercholesterolemia patients. This latest mipomersen study is the fourth new clinical study initiated by Isis and Genzyme since the formation of the collaboration in early 2008.
- The regulatory strategy for European approval of mipomersen continues to evolve. Genzyme is planning an initial European submission for homozygous Familial Hypercholesterolemia (FH) with timing expected to be similar to that of the United States homozygous FH submission anticipated in the second half of 2010. Data from the severe hypercholesterolemia trial should be available at the time of this submission and may be basis for a broader indication. A potential second filing in Europe for patients with heterozygous FH could take place as early as late 2012. Genzyme will await data from an outcomes study prior to making additional submissions to potentially expand mipomersen’s indication.

Isis’ internal and partnered pipeline continues to mature as drugs in the pipeline advance in clinical development.

- Isis initiated a Phase 1 clinical study of ISIS-SGLT₂_{Rx} for the treatment of type 2 diabetes in healthy volunteers.
- Investigators participating in a Phase 1 study of iCo-007 presented data from an interim analysis of the study that showed iCo-007 appears to be well tolerated and demonstrates promising signs of activity in patients with diffuse diabetic macular edema.

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- OncoGenex reached an agreement with the FDA on the design of a second Phase 3 registration trial of OGX-011 that features durable pain palliation as the primary endpoint in patients with castrate resistant prostate cancer, via the Special Protocol Assessment process.

Isis broadened its pipeline with the addition of new drugs that Isis’ partners are developing including,

- A novel aminoglycoside drug, ACHN-490, which Achaogen is developing to treat bacterial infections.

Isis continues to expand its research and development activities including the evaluation of new and novel targets to treat diseases.

- Isis presented research at the American Association for Cancer Research (AACR) annual meeting demonstrating the potential of new RNA targets, including a class of non-coding RNAs, to treat cancer.
- Isis and its collaborators highlighted new antisense therapeutic programs and targets to treat cardiovascular disease and thrombosis at the Arteriosclerosis, Thrombosis and Vascular Biology (ATVB) annual conference, including data from a post-hoc analysis of a recently completed clinical study of mipomersen in which treatment with mipomersen resulted in a decrease in apoC-III.
- An Isis scientist was awarded the 2008 Ebert Prize for published research that provided the first proof-of-concept for the oral administration of antisense drugs in man.

Corporate Highlights

Isis continues to execute its business strategy by monetizing key assets with partners to continue the development and commercialization of the assets with attractive terms in upfront payments, milestone payments and participation in the commercial success of each asset.

- Isis sold its Ibis subsidiary to AMI for a total purchase price of \$215 million, plus up to 5% earn out on sales of assay kits and services.

Isis benefits financially as its partners advance drugs in development while also receiving upfront and royalty payments. This strategy provides cash to the Company while the drugs in Isis’ pipeline mature in clinical development.

- Isis received a \$1 million milestone payment from Achaogen for the filing of an IND for Achaogen’s aminoglycoside drug, ACHN-490.

Isis also benefits from its partnerships focused on developing and advancing certain RNA-based therapeutic technologies. These partnerships take advantage of Isis’ dominant intellectual property estate, expertise, and ongoing innovation and allow Isis to participate in newly emerging approaches to RNA-based therapeutics and augment its active programs in these areas.

- Isis received \$1 million from Alnylam related to Alnylam’s alliance with Cubist Pharmaceuticals, Inc.
- Isis also earned a milestone payment from Alnylam related to Alnylam’s clinical development of ALN-VSP in patients with advanced liver cancers.
- Isis co-exclusively licensed its single-stranded RNA interference (ssRNAi) technology to Alnylam as part of a new strategic initiative to continue to develop the ssRNAi platform.

Regulus Therapeutics, Isis’ and Alnylam’s jointly owned company, continues to make significant progress in all areas of its business. Isis continues to support Regulus as it translates one of the most important new discoveries in biology into a novel approach for treating disease.

- Regulus raised \$20 million in a Series A financing in which Isis and Alnylam were the sole and equal investors in the financing.

Conference Call

At 08:30 a.m. Eastern Time today, May 7, Isis will conduct a live webcast conference call to discuss this earnings release and related activities. Interested parties may access the webcast at www.isispharm.com, or listen to the call by dialing 877-591-4954. 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 19 drugs in development. Isis’ drug development programs are focused on treating cardiovascular

and metabolic diseases. Isis' partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. 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.

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, which is 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, March 31,	
	2009	2008 (1)
	(unaudited)	
Revenue:		
Research and development revenue under collaborative agreements	\$ 29,685	\$ 17,707
Licensing and royalty revenue	1,891	668
Total revenue	31,576	18,375
Expenses:		
Research and development	28,541	21,785
General and administrative	3,677	2,831
Total operating expenses	32,218	24,616
Loss from operations	(642)	(6,241)
Other income (expense):		
Investment income	2,192	3,035
Interest expense	(3,081)	(2,899)
Loss from continuing operations, before income tax benefit	(1,531)	(6,105)
Income tax benefit	717	—
Net loss from continuing operations, net of income tax benefit	(814)	(6,105)
Discontinued operations:		
Loss from discontinued operations	(29)	(564)
Gain on sale of Ibis Biosciences, Inc., net of tax	171,773	—
Net income (loss) from discontinued operations, net of tax	171,744	(564)
Net income (loss)	170,930	(6,669)
Net loss attributable to noncontrolling interest in Regulus Therapeutics Inc.	913	883
Net income (loss) attributable to Isis Pharmaceuticals, Inc. common stockholders	\$ 171,843	\$ (5,786)
Basic net income (loss) per share:		
Net income (loss) from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	\$ —	\$ (0.06)
Net income (loss) from discontinued operations	1.76	—
Basic net income (loss)	\$ 1.76	\$ (0.06)
Shares used in computing basic net income (loss) per share	97,521	90,799
Diluted net income (loss) per share:		
Net income (loss) from continuing operations attributable to Isis Pharmaceuticals, Inc. common stockholders	\$ 0.03	\$ (0.06)
Net income (loss) from discontinued operations	1.54	—
Diluted net income (loss)	\$ 1.57	\$ (0.06)
Shares used in computing diluted net income (loss) per share	111,274	90,799

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

	Three months ended, March 31,	
	2009	2008
	(unaudited)	
As reported operating expenses according to GAAP	\$ 32,218	\$ 24,616
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(2,703)	(3,283)
Pro forma operating expenses	<u>\$ 29,515</u>	<u>\$ 21,333</u>
As reported loss from operations according to GAAP	\$ (642)	\$ (6,241)
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(2,703)	(3,283)
Pro forma income (loss) from operations	<u>\$ 2,061</u>	<u>\$ (2,958)</u>
As reported net income (loss) according to GAAP	\$ 171,843	\$ (5,786)
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(1,145)	(3,759)
Pro forma net income (loss)	<u>\$ 172,988</u>	<u>\$ (2,027)</u>

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, March 31,	
	2009	2008
	(unaudited)	
Revenue:		
Research and development revenue under collaborative agreements	\$ 638	\$ 92
Total revenue	638	92
Expenses:		
Research and development	1,844	1,312
General and administrative	659	215
Total operating expenses	<u>2,503</u>	<u>1,527</u>
Loss from operations	<u>\$ (1,865)</u>	<u>\$ (1,435)</u>

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

	March 31, 2009	December 31, 2008 (1)
	(unaudited)	
Assets:		
Cash, cash equivalents and short-term investments	\$ 652,236	\$ 490,998
Other current assets	11,456	27,386
Property, plant and equipment, net	24,183	17,371
Other assets	<u>36,631</u>	<u>37,021</u>

Total assets	\$	724,506	\$	572,776
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Liabilities and stockholders' equity:				
Other current liabilities	\$	50,879	\$	32,037
Current portion of deferred contract revenue		85,581		92,662
2 ⁵ / ₈ % convertible subordinated notes		119,713		117,993
Long-term obligations, less current portion		11,370		9,938
Long-term deferred contract revenue		154,293		172,766
Stockholders' equity		302,670		147,380
Total liabilities and stockholders' equity	\$	724,506	\$	572,776

(1) Adjusted for the required retrospective adoption of FSP 14-1 and Statement of Financial Accounting Standards 160.

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