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 2, 2006**

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 May 2, 2006, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter ended March 31, 2006. 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 and costs associated with restructuring activities. The Company is presenting pro forma information excluding the effects of the restructuring activities and 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 2, 2006.

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 2, 2006

By: /s/ **B. LYNNE PARSHALL**
B. LYNNE PARSHALL
Executive Vice President,
Chief Financial Officer and Director

INDEX TO EXHIBITS

99.1	Press Release dated May 2, 2006.

Elizabeth Hougen, Vice President, Finance
Navjot Rai, Assistant Director, Corporate Communications
Isis Pharmaceuticals, 760-603-2331
http://www.isispharm.com

ISIS PHARMACEUTICALS REPORTS FINANCIAL RESULTS AND HIGHLIGHTS FOR FIRST QUARTER OF 2006

- Isis Secures $75 Million to Advance Development of ISIS 301012
- Isis Reports Positive Phase 2 Data on ISIS 301012 for the Treatment of High Cholesterol and Cardiovascular Disease
- Ibis Division Ships Biosensor System to Naval Health Research Center

CARLSBAD, Calif., May 2, 2006 /PRNewswire-FirstCall/ — Isis Pharmaceuticals, Inc. (Nasdaq: ISIS), today announced its financial results for the quarter ended March 31, 2006. The Company's pro forma loss from operations decreased significantly and was $14.6 million for the three months ended March 31, 2006, compared to the pro forma loss from operations of $17.1 million for the same period in 2005. The Company's loss from operations for the three months ended March 31, 2006 also decreased significantly and was $16.0 million compared to $23.5 million for the same period in 2005, according to GAAP. The Company's significant decrease in loss from operations in the first quarter of 2006 compared to the same period in 2005 was principally a result of cost savings from focusing resources on key programs. The cost savings achieved through the Company's reorganization in the first quarter of 2005 led to a decrease in R&D and G&A expenses of $4.9 million. A decrease in restructuring activities of $7.0 million from the first quarter of 2005 to the same period in 2006 also contributed to the reduction in loss from operations. The adjustment from GAAP to pro forma loss from operations is discussed under "Expenses" below and illustrated in the Selected Financial Information included in this press release.

Revenue

Total revenue for the three months ended March 31, 2006 was $5.0 million compared to $7.4 million for the same period in 2005. Isis' revenue frequently fluctuates based on the timing of activities and achievements under various contracts. The decrease in revenue reflects a decrease in revenue from collaborations of $3.4 million offset by an increase in Isis' Ibis division revenue. Revenue from collaborations was less in the first quarter of 2006 than in the same period in 2005 primarily due to a decrease in revenue associated with Isis' collaboration with Eli Lilly and Company, which was extended in August 2005 to focus on a select number of targets. The increase in Ibis' revenue primarily relates to an increase in the number and size of active government contracts that Ibis scientists were working on in the first quarter of 2006 compared to the same period in 2005. A more detailed explanation follows below under "Isis' Ibis Division".

Expenses

Isis' operating expenses on a pro forma basis for the quarter ended March 31, 2006 decreased to $19.6 million from $24.5 million for the same period in 2005. These results represent a decrease of 20% in the Company's expenses for 2006 compared to 2005. The decrease in operating expenses on a pro forma basis for the quarter ended March 31, 2006 compared to the same period in 2005 reflects the impact of the Company's reorganization in the first quarter of 2005. In addition, Isis' pro forma operating expenses were approximately 10% below the average of the previous two quarters reflecting the continued impact of the Company's cost containment measures. Isis expects pro forma operating expenses to increase slightly during 2006 as the Company advances the development of ISIS 301012 and the two preclinical diabetes drugs funded through Isis' collaboration with Symphony GenIsis, Inc. as well as ISIS 113715.

The Company expects pro forma operating expenses to be flat compared to the annualized rate of the last two quarters of 2005, or approximately $88 million. Isis' operating expenses, according to GAAP, also decreased and were $21.0 million for the three months ended March 31, 2006, reduced from $30.9 million for the same period in 2005.

As illustrated in the Selected Financial Information in this press release, Isis' pro forma operating expenses and loss from operations were adjusted from GAAP to exclude non-cash compensation related to stock options and costs associated with restructuring activities. Isis believes the excluded items are not indicative of its operating results or cash flows of its operations. The presentation of Isis' pro forma results is consistent with how Isis' management internally evaluates the performance of its operations. Beginning in the first quarter of 2006, Isis included in its operating results non-cash compensation expense related to stock options as required by SFAS No. 123(R), which, for the first quarter of 2006, was $1.4 million. Prior to that, the Company's operating expenses included non-cash compensation benefit or expense as a result of variable accounting for stock options, which, for the first quarter of 2005, was a benefit of $633,000. The adjustment to pro forma operating expenses and loss from operations for the quarter ended March 31, 2006 and 2005 also included $36,000 and $7.1 million, respectively, of costs associated with restructuring activities.

Net Loss

Isis' net loss applicable to common stock for the three months ended March 31, 2006 was $17.5 million, or $0.24 per share, compared with a net loss applicable to common stock of $29.7 million, or $0.52 per share, for the same period in 2005. In August 2005, Isis issued 12 million shares of common stock in a private placement that raised net proceeds of $48 million. Also in August 2005, Isis issued 2.5 million shares to Lilly in connection with the conversion of the Company's $100 million Lilly loan. These additional shares were the primary reason for the significant decrease in net loss per share from the first quarter of 2005 to the same period in 2006. The decrease in the net loss applicable to common stock was the result of a decrease in Isis' loss from operations and a decrease in interest expense. The decrease in interest expense was primarily due to the effect of a lower debt balance during the first quarter of 2006 compared to the same period in 2005 as a result of the conversion of the Company's Lilly loan in the third quarter of 2005, which was interest free requiring Isis to impute interest expense.

Isis' Ibis Division

To develop the Ibis biosensor system and related applications, previously referred to by the government acronym T.I.G.E.R., or Triangulation Identification for Genetic Evaluation of Risk, Isis' Ibis division receives contracts and grants from U.S. government agencies. To date, Ibis has delivered its first three biosensor systems to its government partners for use in biowarfare defense, epidemiological surveillance and forensics. These deliveries represent Ibis' initial steps in commercializing its biosensor system and related applications-specific infectious organism ID kits. In 2005 and continuing through the first quarter of 2006, Ibis scientists advanced application development for the Ibis biosensor system through new and existing contracts with its government partners in the

areas of biowarfare defense, epidemiological surveillance, microbial forensics and pharmaceutical process control. This work is valuable because Ibis can apply much of the application development to non-government commercial opportunities. Further, this shift from basic instrument and system development to application development reflects the progression of Ibis from technology development to commercial viability. Ibis generated revenue from its government contracts and grants of $3.2 million for the three months ended March 31, 2006, compared to revenue of $2.3 million for the same period in 2005. The 39% increase in revenue was a result of an increase in the number and size of government contracts awarded to Ibis during 2005 that extend into 2006. Further, these new contracts contributed to an increase in the utilization of internal labor on government funded contracts as opposed to internal research and development projects. Excluding $217,000 of non-cash compensation expense related to stock options under SFAS 123(R), Ibis' operating expenses for the quarter ended March 31, 2006 of $3.5 million were essentially flat compared to the quarter ended March 31, 2005 of $3.4 million. Ibis generated a loss from operations of $531,000 for the

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quarter ended March 31, 2006 compared to $1.1 million for the same period in 2005. The decrease in loss from operations was primarily attributable to the increase in revenue offset by the non-cash compensation expense related to stock options. Ibis continued to improve its quarterly loss from operations in the first quarter of 2006 compared to 2005.

Balance Sheet

In April 2006, Isis continued its successful efforts to strengthen its balance sheet by entering into a $75 million product development collaboration with Symphony GenIsis, Inc. The collaboration will support ISIS 301012 through the completion of registration-supporting clinical studies in patients with familial hypercholesterolemia and the completion of Phase 2b clinical trials in patients with high cholesterol. The financing will also support development of two novel diabetes drugs through initial proof of concept in human clinical trials. The $75 million proceeds from this collaboration will be consolidated into Isis' balance sheet in the second quarter of 2006. The Symphony GenIsis collaboration combined with the steps Isis took during the second half of 2005 to fortify its financial position, including raising over $48 million in its August 2005 financing and converting its $100 million loan from Lilly into 2.5 million shares of stock, provide Isis with the financial strength to continue to successfully execute its 2006 goals.

Isis ended the first quarter of 2006 with cash, cash equivalents and short-term investments of $78.6 million and working capital of $69.9 million. At December 31, 2005, Isis had cash, cash equivalents and short-term investments of $94.4 million and working capital of $82.1 million. The decrease in cash, cash equivalents and short-term investments primarily reflects cash used in operations, including cash received from contracts, and cash received from stock option exercises. Operating cash usage decreased from $21.1 million in the first quarter of 2005 to approximately $15.5 million for the same period in 2006. This 27% decrease in cash usage reflects the impact of Isis' reorganization in the first quarter of 2005.

"We have entered 2006 building on our focus from 2005 with continuing successes in all areas of our business. Our two most important assets, ISIS 301012 to treat patients with high cholesterol and ISIS 113715 to treat patients with Type 2 diabetes, are progressing well. The data announced last week from our Phase 2 single-agent study of ISIS 301012 continue to support the therapeutic potential of this drug to produce statin-like reductions in LDL with concomitant reductions in triglycerides. This is the third study in which we have confirmed this potential, and we are very excited about this drug," said Lynne Parshall, Executive Vice President and CFO of Isis. "Maintaining control of the development of ISIS 301012 was a key motivation for our recently announced transaction with Symphony GenIsis. Obtaining $75 million to support the development of ISIS 301012 along with two promising preclinical-stage metabolic disease drugs helps ensure that ISIS 301012 will be aggressively developed and supports the development of two novel diabetes drugs to clinical proof of concept. We believe that as we continue to make progress with ISIS 301012 and the two diabetes drugs, we will continue to create shareholder value and maximize the value of each of these assets. Based on reasonable assumptions for new sources of revenue and cash, we believe we have sufficient resources to meet our anticipated requirements through at least the end of 2008."

"We expect, in 2006, a full year of benefit from the focus and expense reductions we implemented last year," Ms. Parshall continued. "This will result in a net operating loss, excluding non-cash compensation expense and restructuring costs, in the high $50 million range. Operating expenses will be flat compared to the annualized rate of the last two quarters of 2005, or approximately $88 million, including increases in spending on ISIS 301012 and the two new metabolic disease drugs in the Symphony GenIsis collaboration."

"As we continue through 2006, we are looking forward to additional progress in our clinical pipeline as well as that of our partners," Ms. Parshall concluded.

2006 First Quarter Highlights and Recent Accomplishments

Isis Advances Development of Second-generation Antisense Drugs

Isis continues to advance its most promising drugs to treat cardiovascular, metabolic and inflammatory diseases.

ISIS 301012 (Targeting apoB-100 for the treatment of high cholesterol)

Additional data from clinical studies of ISIS 301012 continue to broaden the potential profile for the drug to treat patients with cardiovascular disease.

Phase 2 Data

- Initial data from the low-dose cohorts of a Phase 2 clinical trial of ISIS 301012 as a single-agent in patients with high cholesterol produced rapid, dose-dependent and prolonged reductions of its target, apoB-100, with concomitant reductions in low density lipoprotein (LDL), very low density lipoprotein (VLDL), total cholesterol and triglycerides. At a dose of 200 mg/wk for three months, ISIS 301012 achieved a median percent reduction from baseline of 47% in apoB-100, 42% in LDL, 34% in total cholesterol and 46% in triglycerides at day 99. ISIS 301012 was well tolerated in this study.

Phase 1 Data

- ISIS 301012 significantly reduced triglycerides in a Phase 1 study of ISIS 301012 in normal volunteers with borderline elevated cholesterol. ISIS 301012 also produced rapid, dose-dependent, and prolonged reductions of its target, apoB-100, with concomitant reductions in LDL, VLDL, and total cholesterol levels.

- In a drug-drug interaction study, ISIS 301012 did not interact with simvastatin or ezetimibe, currently available lipid lowering drugs with which ISIS 301012 may be dosed in combination.

- In a Phase 1 study of an oral capsule formulation of ISIS 301012, the drug demonstrated oral bioavailability, and significantly reduced apoB-100 and LDL.

Animal Data

- ISIS 301012 reduced atherosclerotic plaques, apoB-100, and circulating inflammatory cytokines in an animal model of atherosclerosis. Reducing atherosclerotic plaques in animals confirms that ISIS 301012 has the potential to benefit patients who already have atherosclerosis.

Clinical Development Update

- Initiated Phase 2 development program of ISIS 301012 in patients with familial hypercholesterolemia (FH), potentially providing an accelerated pathway to commercialization because of the unmet medical need in patients with FH.

Isis adds new drugs to its development pipeline

ISIS 325568 (Targeting GCGR for the treatment of diabetes)

- Initiated development activities of ISIS 325568, a generation 2.2 antisense drug, for the treatment of type 2 diabetes.

ISIS 353512 (Targeting CRP for the treatment of cardiovascular & inflammatory diseases)

- Initiated development activities of ISIS 353512, a generation 2.2 antisense drug, for the treatment of cardiovascular disease and inflammatory diseases.

Isis Supports Advancement of its Partners' Pipelines and Expands Licensing and Partnerships

Isis continues to expand its drug discovery and development programs and capitalize on its extensive patent estate through a combination of corporate partnerships, satellite company relationships and licensing transactions. The Company announced several achievements demonstrating the successful execution of this partnering strategy.

Collaborations
Symphony GenIsis

- Completed a transaction with Symphony Capital Partners, L.P. and a group of co-investors to provide $75 million to fund the development of Isis' cholesterol-lowering drug, ISIS 301012, and two novel drugs from Isis' metabolic disease program. In addition to providing the financial support to move these drugs forward aggressively, the transaction allows Isis to continue to control and manage the development of ISIS 301012 and two potentially valuable diabetes drugs through key development milestones.

Lilly
LY2275796 (Targeting eIF-4E for the treatment of cancer)

- Lilly initiated clinical trials of LY2275796 in cancer patients. This is the second anti-cancer antisense drug that Lilly has taken into the clinic. Lilly paid Isis a $750,000 milestone payment as a result of advancing LY2275796 into clinical trials.

Satellite Company Relationships

Isis' satellite company relationships exemplify an important part of Isis' partnering strategy in which it identifies high quality biotechnology companies with which to closely collaborate to advance drugs and technologies.

ALS Association
ISIS 333611 (Targeting SOD1 for the treatment of amyotrophic lateral sclerosis)

- ISIS 333611, a second-generation antisense drug, is being developed by investigators at the Center for Neurologic Study and the Ludwig Institute at the University of California, San Diego with funding from the ALS Association (ALSA), as well as grants from the NIH and the Scripps Research Institute. ALSA is funding a safety study in rhesus monkeys to confirm the safety of ISIS 333611 to support clinical testing.

Antisense Therapeutics Ltd. (ATL)
ATL1102 (Targeting VLA-4 for the treatment of multiple sclerosis)

- ATL re-initiated its Phase 2 trial of ATL1102 for patients with relapsing-remitting multiple sclerosis.

Achaogen

- Licensed Isis' proprietary aminoglycosides program to Achaogen for $1.5 million paid in Achaogen stock. Achaogen is solely responsible for the continued development of the aminoglycoside program and products.

ImQuest Pharmaceuticals
ISIS 5320 (Targeting HIV for the treatment of AIDS)

- Licensed ISIS 5320 to ImQuest. ISIS 5320 is a compound that has been shown *in vitro* and *in vivo* to be a potent and specific inhibitor of HIV, the virus that causes AIDS.

Rosetta Genomics

- Entered into joint research collaboration with Rosetta Genomics to discover and develop antisense drugs that regulate microRNAs for the treatment of the most prevalent type of liver cancer, hepatocellular carcinoma.

Isis Continues to Strengthen its Intellectual Property Estate

As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of approximately 1,500 issued patents worldwide. To date, Isis has generated over $76 million from its intellectual property estate.

- Issuance of U.S. Patent 7,015,315 by the United States Patent and Trademark Office covering antisense drugs with modified sugars, frequently called "chimeric" oligonucleotides or "gapmers", including Isis' proprietary second-generation chemistry, generation 2.2 chemistry, and numerous other sugar-modified antisense compounds. Because this newly issued patent does not expire until March 2023, it significantly extends the duration of Isis' control over antisense drug chemistry and design, and most importantly, the patent life of Isis' second-generation antisense drugs.

Isis' Ibis Division Executes Commercialization Plans for IBIS T-5000 Biosensor System

Isis' Ibis division meets major business milestones and continues applications development with government funding.

- Executed commercialization plans by delivering an IBIS biosensor system to the Naval Health Research Center for use in epidemiological surveillance.

- Ibis has delivered IBIS biosensor systems to the Department of Homeland Security's National Bioforensic Analysis Center for use in microbial forensics and to the United States Army Medical Research Institute for Infectious Disease for use in biowarfare defense.

Isis will conduct a live webcast conference call to discuss this earnings release on Tuesday, May 2, at 5:00 pm Eastern time. To participate over the Internet go to http://www.videonewswire.com/event.asp?id=33542 or http://www.isispharm.com. A replay of the webcast will be available at these addresses for a limited time.

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 15 drugs in development. Isis' drug development programs are aimed at treating cardiovascular, metabolic and inflammatory diseases. Isis' partners are focused in disease areas such as inflammatory, ocular, viral and neurodegenerative diseases, and cancer. In its Ibis division, Isis is developing and commercializing the Ibis biosensor system, a revolutionary system to identify infectious organisms. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of approximately 1,500 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release includes forward-looking statements regarding Isis Pharmaceuticals' business, the financial position of Isis, and the therapeutic and commercial potential of the Company's technologies and products in development. Any statement describing Isis' goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, in developing and commercializing systems to identify infectious organisms that are effective and commercially attractive, and in the endeavor of building a business around such products. Isis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis.

As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2005, which is on file with the U.S. Securities and Exchange Commission (SEC) and available from the Company.

ISIS PHARMACEUTICALS, INC.
SELECTED FINANCIAL INFORMATION
(In Thousands, Except Per Share Data)
Condensed Consolidated Statements of Operations

Three months ended,

	March 31,	
	2006	2005
	(unaudited)	
Revenue:		
Research and development revenue under collaborative agreements	$ 4,468	$ 7,135
Licensing revenue	490	307
Total revenue	4,958	7,442
Operating expenses:		
Research and development (including non-cash compensation expense related to stock options of $1.2 million and $0 in 2006 and 2005, respectively)	18,372	22,361
General and administrative (including non-cash compensation expense related to share-based payments of $221,000 and $0 in 2006 and 2005, respectively)	2,566	2,137
Compensation related to the variable accounting of stock options	—	(633)
Restructuring activities	36	7,084
Total operating expenses	20,974	30,949
Loss from operations	(16,016)	(23,507)
Investment and other income	811	504
Interest expense	(2,275)	(6,655)
Net loss applicable to common stock	$ (17,480)	$ (29,658)
Basic and diluted net loss per share	$ (0.24)	$ (0.52)
Shares used in computing basic and diluted net loss per share	72,377	57,521

Ibis Division Statements of Operations
(In Thousands)

	Three months ended, March 31,	
	2006	2005
	(unaudited)	
Revenue	$ 3,198	$ 2,325
Operating expenses	$ 3,729	$ 3,437
Loss from operations	$ (531)	$ (1,112)

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

	Three months ended, March 31,	
	2006	2005
	(unaudited)	
As reported operating expenses according to GAAP	$ 20,974	$ 30,949
Excluding compensation benefit related to variable accounting of stock options	—	633
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(1,374)	—
Excluding restructuring activities	(36)	(7,084)
Pro forma operating expenses	$ 19,564	$ 24,498
As reported loss from operations according to GAAP	$ (16,016)	$ (23,507)
Excluding compensation benefit related to variable accounting of stock options	—	633
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(1,374)	—
Excluding restructuring activities	(36)	(7,084)
Pro forma loss from operations	$ (14,606)	$ (17,056)

Condensed Consolidated Balance Sheets
(In Thousands)

	March 31, 2006	December 31, 2005
	(Unaudited)	
Assets:		
Current assets	$ 90,731	$ 105,858
Property, plant and equipment, net	8,208	9,130
Other assets	51,698	51,385
Total assets	$ 150,637	$ 166,373
Liabilities and stockholders' equity (deficit):		
Current liabilities	$ 20,845	$ 23,793
5.5% convertible subordinated notes	125,000	125,000

Long-term obligations, net of current portion	12,942	14,915
Stockholders' equity (deficit)	(8,150)	2,665
Total liabilities and stockholders' equity (deficit)	$ 150,637	$ 166,373