SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K/A

(Amendment No.2)

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 5, 2005**

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 5, 2005, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter ended March 31, 2005. 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 certain expenses or benefits associated with non-cash compensation related to stock options and restructuring charges. 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.

Item 2.05. Costs Associated With Exit or Disposal Activities.

On January 10, 2005, the Company issued a press release and filed a Form 8-K announcing that it had reorganized and refocused the Company's resources to advance its most promising second-generation antisense drug candidates and to continue its development of antisense technology (the "Restructuring").

On March 1, 2005 the Company issued a press release announcing the Company's financial results for the year ended December 31, 2004. The press release contained additional information regarding the Restructuring.

On May 5, 2005 the Company issued a press release announcing the Company's financial results for the quarter ended March 31, 2005. The press release contained additional information regarding the Restructuring. This press release is attached to this Current Report as Exhibit 99.1 and is incorporated herein by reference.

Item 9.01. Financial Statements and Exhibits.

(c) Exhibits.

99.1 Press Release dated May 5, 2005.

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 5, 2005

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 5, 2005.

Exhibit 99.1

Contact: Elizabeth Hougen, Vice President, Finance
Claudine Prowse, Ph.D., Director, Investor Relations
Isis Pharmaceuticals, 760-603-2331
http://www.isispharm.com

ISIS PHARMACEUTICALS REPORTS FINANCIAL RESULTS AND HIGHLIGHTS FOR THE FIRST QUARTER 2005

Company Reviews 2005 Goals

CARLSBAD, CA, May 5, 2005 — Isis Pharmaceuticals, Inc. (Nasdaq: ISIS), today announced its financial results for the quarter ended March 31, 2005. The Company's proforma loss from operations was $17.1 million for the three months ended March 31, 2005, compared to a proforma loss from operations of $19.1 million for the same period in 2004. The Company's loss from operations for the three months ended March 31, 2005 was $23.5 million, compared to $22.3 million for the same period in 2004, according to GAAP. The Company's decrease in proforma loss from operations in 2005 was principally a result of cost savings related to the Company's recent strategic decision to reorganize and refocus its resources to advance its most promising second-generation drugs. The Company expects to achieve additional cost savings during the remainder of 2005 as a result of its recent restructuring activities and, consistent with previous guidance, expects that its 2005 proforma loss from operations will be in the low $50 million range.

Isis' proforma loss from operations is adjusted from GAAP to exclude a non-cash compensation benefit of $633,000 and costs associated with restructuring activities of $7.1 million in the first quarter of 2005, and a non-cash compensation expense of $3.2 million for the same period in 2004.

Revenue

Total revenue for the three months ended March 31, 2005 was $7.4 million compared to $12.3 million for the same period in 2004. Isis' revenue may fluctuate from period to period based on the nature and timing of license fees and milestones earned, and other deliverables under agreements with its partners. For example, Isis earned a one time $5 million license fee from Alnylam Pharmaceuticals Inc. in the first quarter of 2004 in connection with Isis' strategic alliance with Alnylam, which primarily accounts for the decrease in revenue from 2004 to 2005.

Expenses

As illustrated in the Selected Financial Information in this press release, operating expenses on a proforma basis for the three months ended March 31, 2005 were $24.5 million compared to $31.4 million for the same period in 2004, which represents a substantial decrease of more than 20%. The decrease in first quarter operating expenses on a proforma basis compared to the same period in 2004 reflects the impact of the Company's cost containment measures implemented during the first quarter of 2005. Operating expenses on a proforma basis were adjusted from GAAP to exclude non-cash compensation related to stock options and costs associated with restructuring activities.

Isis' operating expenses were $30.9 million for the three months ended March 31, 2005 compared to $34.6 million for the same period in 2004, according to GAAP. The Company's first quarter 2005 operating expenses included $7.1 million in charges for restructuring activities, primarily associated with employee termination costs, building consolidation costs and the closure of Isis' Singapore laboratory.

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Total operating expenses for the three months ended March 31, 2005 included a non-cash compensation benefit of approximately $633,000 related to variable accounting for stock options, compared to a non-cash compensation expense of $3.2 million for the same period in 2004. Variable accounting for stock options can result in significant increases and decreases in non-cash compensation expense related to stock options as a result of the variability in the Company's stock price.

Net Loss

The Company's net loss applicable to common stock for the three months ended March 31, 2005 was $29.7 million, or $.52 per share, compared with a net loss applicable to common stock of $26.5 million, or $.47 per share, for the same period in 2004. The increase in the net loss applicable to common stock was the result of an increase in interest expense primarily due to the effect of a higher debt balance in 2005 compared to 2004 and a decrease in investment income due to the Company's lower average cash balance in 2005 compared to 2004, offset in part by a decrease in loss from operations.

Isis' Ibis Division

To develop TIGER technology and applications, Isis' Ibis division has received contracts from a number of government agencies, including the Defense Advanced Research Projects Agency (DARPA), the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), the Federal Bureau of Investigation (FBI), and the Department of Homeland Security (DHS). Ibis generated revenue from these contracts of $2.3 million for the three months ended March 31, 2005, compared to revenue of $2.8 million for the same period in 2004. Operating expenses for Ibis were $3.4 million for the three months ended March 31, 2005 compared to $3.9 million for the same period in 2004. Ibis' revenue and operating expenses may fluctuate on a quarter to quarter basis due primarily to the timing of equipment purchased in support of its government contracts. In general, when Ibis purchases equipment, it records expenses associated with the purchase and corresponding revenue. During 2004, Ibis was acquiring the necessary equipment components to build the TIGER systems that Ibis expects to deploy to its government partners this year. As a result, the first quarter of 2004 included $1.0 million in revenue and associated expense related to these equipment purchases, compared to $283,000 for the same period in 2005. This variance in revenue and expense related to equipment purchases is the primary reason for the decrease in revenue and operating expenses from first quarter 2004 to first quarter 2005. During the three months ended March 31, 2005, Ibis generated a net operating loss of $1.1 million, which was slightly improved over the $1.2 million operating loss for the same period in 2004.

Balance Sheet

Isis ended the quarter with cash, cash equivalents and short-term investments of $82.7 million and working capital of $60.9 million. At December 31, 2004, Isis had cash, cash equivalents and short-term investments of $103.9 million and working capital of $82.2 million. Cash, cash equivalents and short-term investments decreased primarily as a result of cash used in operations. The cost containment measures the Company implemented during the first quarter of 2005 should significantly decrease its cash use throughout the remainder of 2005.

“Early this year, we initiated a restructuring to enable us to strategically invest our resources in our most promising antisense drug candidates and technologies while reducing the Company’s cash usage,” said B. Lynne Parshall, Isis’ Executive Vice President and CFO. “As a result of the measures we took, our cash burn decreased significantly to $21.2 million compared to $34.6 million for the first quarter last year. In addition, we are also benefiting from a reduction in expenses, and we remain on-track to achieve our projected net operating loss in the low $50 million dollar range”.

“In the first quarter, we made progress in key areas of the Company: advancing Isis’ products through development, expanding our efforts in RNA-based drug discovery through partnering, and advancing the TIGER biosensor technology. A significant development during the quarter was the initiation of an oral clinical trial with our cholesterol-lowering compound, ISIS 301012, which was shown to be a potent cholesterol-lowering agent in Phase 1 studies. This year we will continue to aggressively advance clinical development of ISIS 301012 with the initiation of multiple Phase 2 clinical trials. In addition, we will report final Phase 1 results for the drug at the upcoming American Diabetes Association meeting in June. Phase 2 data for our type 2 diabetes drug, ISIS 113715, will also be highlighted at ADA, in addition to several other examples of our broad metabolics program,” Ms. Parshall said.

“Also this quarter, we added Sarissa to our list of satellite company partners in addition to expanding our existing drug discovery collaboration with our partner OncoGenex. Our satellite company relationships exemplify an important part of our partnering strategy where we identify very high quality biotech companies with whom we collaborate closely to move drugs of interest through clinical development. This strategy enables us to progress as many drugs as possible in the clinic, not only in our hands, but in the hands of our partners,” continued Ms. Parshall.

“Beyond our pipeline, we continued to advance our TIGER biosensor system and have hired Mike Treble to help us prepare for TIGER product commercialization. Mike has over 25 years experience in product development and in commercializing technologies in diagnostic and life science companies. TIGER is essentially fully funded by the government and recently received two new government contracts for $1.5 million from the Department of Homeland Security for microbial forensics. The year ahead promises to be important for TIGER as we transition the system from the research phase towards commercialization.” Ms. Parshall said.

“In summary, we believe that the operating plan we have implemented early this year leaves us poised to successfully execute our goals for 2005,” concluded Ms. Parshall.

Isis’ 2005 First Quarter and Recent Highlights

Following are updated 2005-2006 goals and timelines as announced in April 2005:

Isis’ 2005-2006 Goals and Timelines

Relatively Near-Term Opportunities:

Alicaforsen Enema:

- Identify a partner and prepare a Phase 3 development plan (2nd Half)

ISIS 301012:

- Demonstrate that oral ISIS 301012 reduces cholesterol in normal volunteers (2nd Half)
- Initiate single agent Phase 2 studies to define dose and schedule (2nd Qtr)
- Initiate combination studies with atorvastatin and other cholesterol-lowering drugs (2nd Half)
- Initiate studies in patients with familial hypercholesterolemia (2nd Half)

Longer-Term Opportunities:

ISIS 113715

- Demonstrate activity of ISIS 113715 as a single agent in patients with type 2 diabetes (4th Qtr)
- Define the optimal dose and schedule for future clinical trials (4th Qtr)
- Advance into longer term (12 week) trials (2nd Half)
- Initiate combination trials with other anti-diabetic agents (2nd Half)

Partner Development Pipelines

- LY2181308, an anticancer drug that targets survivin, is currently in Phase 1 trials. It is being developed by Isis’ partner Eli Lilly and Company. Isis’ goal is to support Lilly’s ongoing development program for LY2181308.
- OGX-011, an anticancer drug that targets clusterin, is currently in Phase 1/2 clinical trials. It is being developed by Isis’ partner OncoGenex. Isis’goal is to support OncoGenex’s ongoing development plans for OGX-011 through the initiation of Phase 2 studies in patients with a variety of solid tumors.

Ibis' TIGER Biosensor Program

- Deploy first TIGER system to government partner (2nd Qtr)
- Complete business plan and describe it to shareholders (2nd Half)
- Add new government contracts for developing and advancing the TIGER biosensor system (2nd Half)
- Broaden applications for the TIGER biosensor system (2005)
- Prepare Ibis to perform as an independent entity (2005)
- Create non-government partnerships to advance applications of the TIGER biosensor system (4th Qtr)

2005 First Quarter and Recent Highlights

Expanded RNA-Based Drug Discovery Efforts:

- Announced the expansion of Isis' antisense drug discovery and development collaboration in cancer with OncoGenex. The broadened relationship allows for the development of two additional second-generation antisense anti-cancer drug candidates. OncoGenex will be solely responsible for the preclinical and clinical development of the added anti-cancer drugs. Recently, OncoGenex selected its first drug candidate under this expansion, OGX-427. OGX-427 targets heat shock protein 27 (Hsp27), a protein that is overexpressed in numerous tumor types and is associated with treatment resistance through its ability to help cancer cells survive stress-induced injury.

  This oncology relationship was initiated in December 2001 to co-develop OGX-011, a drug currently in Phase 1/2 development for the treatment of prostate, breast and lung cancers. In 2003, OncoGenex and Isis added a second drug to their collaboration, OGX-225, which is in the research phase of development.

- Licensed a second-generation drug targeting thymidylate synthase (TS) to Sarissa, Inc., a newly-formed company spun out of the University of Western Ontario. TS is a well-known drug target that protects cancer cells from the effects of chemotherapy. Sarissa paid Isis a $1.0 million upfront fee in exchange for the exclusive, worldwide license to the TS antisense drug. The upfront fee is in the form of a convertible note which will convert into Sarissa stock upon its successful completion of a venture capital financing. Sarissa will also pay Isis milestone payments for key clinical and regulatory achievements and royalties on product sales. Sarissa will be solely responsible for preclinical and clinical development of the drug.

- Phase 1 study of an oral capsule formulation of ISIS 301012. This drug is a second-generation antisense inhibitor of apoB-100, for the lowering of high cholesterol. The subcutaneous form of the drug is completing a Phase 1 study and is expected to enter Phase 2 clinical trials later this year. Data previously reported from the Phase 1 trial showed that subcutaneously administered ISIS 301012 produced rapid and prolonged reductions of its target as well as low density lipid (LDL), very low density lipid (VLDL) and total cholesterol in healthy volunteers with elevated cholesterol. ApoB-100 is the sole lipoprotein of LDL cholesterol, the "bad" lipid involved in heart disease. Final data from this study will be presented at the American Diabetes Association's (ADA) 65th Scientific Sessions in San Diego, June 10th-14th.

- Results from clinical trials evaluating ISIS 113715 for type 2 diabetes and data on several late-stage preclinical antisense inhibitors in development for the treatment of metabolic diseases will also be presented at the ADA. Data presented at ADA will expand upon presentations made by Isis' scientists and collaborators at the 4th International Metabolic Diseases Drug Discovery World Summit in San Diego in April.

- Scientists from Isis and collaborators from academia and industry presented research findings that, in aggregate, demonstrate the effectiveness of second-generation antisense drugs and the power of antisense technology in identifying, characterizing, and validating new targets for the treatment of cancer at the 96th Annual Meeting of the American Association for Cancer Research. Results from multiple preclinical studies demonstrated that second-generation antisense agents selectively inhibit novel cancer targets and improve survival in cancer cell and animal models.

- Initiated development activities on its first drug for the treatment of asthma and related pulmonary diseases. The drug, ISIS 369645, is a second-generation antisense inhibitor of the alpha subunit of the interleukin 4 receptor, IL4R-alpha. Inhibiting the production of the IL4R-alpha inhibits the activity of two important cytokines in asthma, IL4 and IL13, which regulate inflammation, mucus overproduction and airway hyperresponsiveness.

Ibis' TIGER* (Triangulation Identification for Genetic Evaluation of Risks) *Biosensor Program

- Hired Michael Treble as Isis Vice President and Head of Ibis. Mr. Treble and David J. Ecker, Ph.D., Vice President and Scientific Head of Ibis, will be responsible for spearheading the strategic direction and commercialization of the Company's TIGER biosensor system. Mr. Treble has over 25 years experience in product development and in commercializing technologies and diagnostics. Additionally, he has founded five biotech/life science start-up companies in the last 15 years.

- Received two contracts totaling $1.5 million for the development of a new TIGER biosensor system microbial forensics application for use in investigating crimes involving infectious agents, by comparing the genetic "fingerprint" of an infectious agent to that of a potential source. The new awards also support further enhancement of the Microbial Rosetta Stone (MRS) database to include additional genetic information on infectious agents. The MRS database is a key component of the TIGER biosensor system. These new contracts broaden TIGER's commercial applications and product opportunities for use by government and non-government customers.

Business Activities

- Supported Kinovate Life Sciences' official launch of the NittoPhase™ solid support for oligonucleotide synthesis. The joint development of this solid phase support product was announced on November 8th, 2004 by Kinovate's sole shareholder, Nitto Denko Corporation (Osaka, Japan), a leading multi-national polymer synthesis company and Isis. NittoPhase™ has great potential to decrease oligonucleotide manufacturing costs due to its significantly lower unit cost, as well as potentially higher yield and full length purity, reducing cost-of-goods.

Corporate Reorganization

- Provided guidance on new corporate structure and research and development programs for 2005. Isis reorganized and refocused the Company's resources to advance its most promising second-generation antisense drug candidates and continue its development of antisense technology. As a result of this strategic reorganization, the Company reduced its workforce by approximately 40% with commensurate expense savings. These measures significantly reduced the Company's cash usage.

Isis will conduct a live webcast conference call to discuss this earnings release on Thursday, May 5th at 11:00 am Eastern time. To participate over the Internet go to http://www.firstcallevents.com/service/ajwz405840956gf12.html or http://www.isispharm.com. A replay of the webcast will be available at these addresses for up to 30 days.

About Isis Pharmaceuticals, Inc.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs for its pipeline and for its partners. The Company has successfully commercialized the world's first antisense drug and has 11 antisense products in development to treat metabolic, cardiovascular and inflammatory diseases, and cancer. Through its Ibis division, Isis is developing a biosensor system to identify infectious organisms. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of more than 1,500 issued patents worldwide. Additional information about Isis is available at http://www.isispharm.com.

This press release includes forward-looking statements regarding our business, the financial position of Isis Pharmaceuticals, and the therapeutic and commercial potential of our technologies and products in development. Any statement describing our 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' clinical 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 technology and systems used to identify infectious agents, and in the endeavor of building a business around such products and services. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in Isis' Annual Report on Form 10-K for the year ended December 31, 2004, which is on file with the U.S. Securities and Exchange Commission (SEC), and available from the Company.

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FINANCIAL TABLES

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

	Three months ended, March 31,	
	2005	2004
	(unaudited)	
Revenue:		
Research and development revenue under collaborative agreements	$ 7,135	$ 6,998
Licensing and royalty revenue	307	5,305
Total revenue	7,442	12,303
Expenses:		
Research and development	22,361	28,947
General and administrative	2,137	2,453
Compensation expense (benefit) related to stock options	(633)	3,238
Restructuring activities	7,084	—
Total operating expenses	30,949	34,638
Loss from operations	(23,507)	(22,335)
Investment and other income	504	1,133
Interest expense	(6,655)	(5,104)
Net loss	(29,658)	(26,306)
Accretion of dividends on preferred stock	—	(181)
Net loss applicable to common stock	$ (29,658)	$ (26,487)

Basic and diluted net loss per share	$ (0.52)	$ (0.47)
Shares used in computing basic and diluted net loss per share	57,521	55,858

Ibis Division Statements of Operations

	Three months ended, March 31,	
	2005	2004
	(unaudited)	
Revenue	$ 2,325	$ 2,797
Operating expenses	3,437	3,953
Loss from operations	(1,112)	(1,156)

Reconciliation of GAAP to Proforma Basis:
Operating Expenses and Loss From Operations

	Three months ended, March 31,	
	2005	2004
	(unaudited)	
As reported operating expenses according to GAAP	$ 30,949	$ 34,638
Excluding compensation benefit (expense) related to stock options	633	(3,238)
Excluding restructuring activities	(7,084)	—
Proforma operating expenses	$ 24,498	$ 31,400
As reported loss from operations according to GAAP	$ (23,507)	$ (22,335)
Excluding compensation expense (benefit) related to stock options	(633)	3,238
Excluding restructuring activities	7,084	—
Proforma loss from operations	$ (17,056)	$ (19,097)

Condensed Balance Sheets
(In Thousands)

	March 31, 2005	December 31, 2004
	(unaudited)	
Assets:		
Current assets	$ 96,991	$ 125,609
Property, plant and equipment, net	26,665	28,454
Other assets	51,992	54,362
Total assets	$ 175,648	$ 208,425
Liabilities and stockholders' equity:		
Current liabilities	$ 36,062	$ 43,416
5.5% convertible subordinated notes	125,000	125,000
Long-term obligations, net of current portion	118,358	111,611
Long-term deferred revenue, net of current	378	531
Stockholders' deficit	(104,150)	(72,133)
Total liabilities and stockholders' equity	$ 175,648	$ 208,425