SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

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

Date of report (Date of earliest event reported): **February 10, 2004**

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.)

2292 Faraday Avenue
Carlsbad, CA 92008
(Address of Principal Executive Offices and Zip Code)

Registrant's telephone number, including area code: **(760) 931-9200**

Item 7. Financial Statements and Exhibits.

(c) Exhibits.

99.1 Press Release dated February 10, 2004.

Item 12. Results of Operations and Financial Condition.

On February 10, 2004, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter and year ended December 31, 2003. 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 that exclude certain adjustments associated with restructuring activities and non-cash compensation expense or benefit, as applicable. 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 12. 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.

SIGNATURE

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

ISIS PHARMACEUTICALS, INC.

Dated: February 10, 2004

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

INDEX TO EXHIBITS

99.1	Press Release dated February 10, 2004.

Contacts: Elizabeth Hougen, Vice President, Finance
Karen Lundstedt, Vice President, Corporate Communications
Isis Pharmaceuticals, Inc. 760-931-9200
http://www.isispharm.com

ISIS PHARMACEUTICALS REPORTS FINANCIAL RESULTS AND HIGHLIGHTS FOR 2003

CARLSBAD, Calif., February 10, 2004 — Isis Pharmaceuticals, Inc. (Nasdaq: ISIS), today announced its financial results for the year-ended December 31, 2003. The company's loss from operations for 2003 was $79.0 million compared to $50.8 million in 2002, according to generally accepted accounting principles (GAAP). Consistent with its guidance, the company's loss from operations for 2003 on a proforma basis was $76.3 million, which is adjusted from GAAP to exclude non-cash compensation charges of $913,000 and restructuring charges of $1.8 million. This compared to a proforma loss from operations in 2002 of $52.4 million, which excludes $3.0 million in non-cash compensation benefit and restructuring charges of $1.4 million.

Revenue

Total revenue for the quarter and year-ended December 31, 2003 was $9.7 million and $50.0 million, respectively, compared to $21.9 million and $80.2 million for the same periods in 2002. The decrease in revenue was primarily due to the reduction in revenue associated with the clinical development of Affinitak™ and the conclusion of Elan Corporation plc.'s participation in the HepaSense™ and Orasense™ collaborations. In late 2002, Isis terminated its collaborations with Elan and reacquired rights to
ISIS 14803 and the oral formulation of ISIS 104838. The decrease in revenue was offset in part by new sources of revenue not present in 2002, including the achievement of milestones in the discovery and development of drugs for our partners Eli Lilly and Company, Amgen, and the Industrial Research Institute of Taiwan (ITRI), in addition to increased revenue related to our TIGER diagnostic program.

Expenses

As illustrated in the Selected Financial Information in this press release, operating expenses on a proforma basis for the quarter and year-ended December 31, 2003 were $31.2 million and $126.3 million, respectively, compared to $31.7 million and $132.6 million for the same periods in 2002. These decreases were attributed primarily to planned expense reductions during 2003.

Total operating expenses for the year-ended December 31, 2003 included a charge of approximately $913,000 in non-cash compensation expense due to variable accounting for stock options associated primarily with the employee stock option exchange program that was offered in the second quarter of 2003. For the year-ended 2002, the company reported compensation benefit of $3.0 million associated primarily with an employee option exchange program offered in January 2000. All options in the 2000 program were

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either exercised or cancelled by the end of 2002 and had no impact on the company's financial statements in 2003. Variable stock options can result in significant non-cash increases and decreases in compensation expense as a result of the variability in the company's stock price.

The 2003 year-to-date operating expenses included a restructuring charge of $1.8 million related to Isis' expense reduction plan, which included a small reduction in its workforce, as compared to restructuring charges of approximately $1.4 million in 2002 related to Isis' termination of the Genetrove ™ database product and write down of certain intellectual property.

Net Loss

Thope company's net loss applicable to common stock for the quarter and year-ended December 31, 2003 was $25.6 million, or $0.46 per share, and $95.7 million, or $1.73 per share, respectively, compared with a net loss applicable to common stock of $16.0 million, or $0.29 per share, and $73.3 million, or $1.35 per share, for the same periods last year. The increase in the net loss applicable to common stock was primarily a result of the increase in loss from operations.

Balance Sheet

Isis maintained a strong balance sheet at the end of the year with $215.5 million in cash and short-term investments and working capital of $194.0 million. At December 31, 2002, Isis had cash and short-term investments of $289.4 million and working capital of $244.2 million. Cash and short-term investments and working capital decreased primarily as a result of cash used in operations.

Isis' 2003 and Recent Highlights

"In 2003, we reported our first clinical results with two second-generation antisense drugs, ISIS 104838 in rheumatoid arthritis and ISIS 113715 for type 2 diabetes. The positive data indicate that second-generation drugs are an important improvement over first-generation antisense, particularly in terms of potency, side effect profile, patient convenience and cost of therapy. We also initiated clinical trials with our first cardiovascular compound, ISIS 301012, which was shown to be a potent cholesterol- lowering agent in preclinical studies," stated B. Lynne Parshall, Isis' Executive Vice President and CFO. "As evidence of our steady progress in antisense drug development, we plan to report data from clinical trials of eight different antisense drugs across all phases of development during the course of 2004. Our strategy of developing a broad pipeline gives us many opportunities for clinical success. Importantly, we have the financial resources to aggressively advance the development of our products."

"Beyond our pipeline, we continue to realize value from other key assets, including our intellectual property estate. The progress of MacugenÔ for the treatment of age-related macular degeneration illustrates the value within our patent estate, given Isis' royalty position in this drug. In 2003, Pfizer and Eyetech reported encouraging Phase 3 data for Macugen that will serve as the basis for an NDA, with commercialization of the drug expected in 2005. Eyetech licensed several Isis chemistry patents for the development of Macugen, an aptamer. Assuming successful commercialization of Macugen, Isis has the opportunity to earn milestone payments and royalties that will be

meaningful to us," continued Ms. Parshall. "We are committed to further exploiting our leadership position in RNA-based drug discovery and development for the benefit of our shareholders."

Advanced Antisense Drug Development:

- Reported results from eight clinical trials:
    - Rheumatoid Arthritis (RA): in a Phase 2 study, ISIS 104838 produced a statistically significant disease response in evaluable patients with RA that received the two highest doses; an initial study showed the drug was distributed to synovial tissue and reduced TNF-alpha mRNA levels in synovium in a dose-dependent manner
    - Hepatitis C (HCV): in a Phase 2 single-agent study, ISIS 14803 decreased viral levels in a dose-dependent manner in patients who failed previous treatment
    - Type 2 Diabetes: in a Phase 1 study, ISIS 113715 decreased the amount of insulin required by normal volunteers to normalize blood glucose tolerance tests following a glucose challenge
    - Pouchitis/Ulcerative Colitis (UC): in a Phase 2 study of patients with pouchitis, alicaforsen (ISIS 2302) enema improved clinical disease symptoms with remissions that lasted up to nine months
    - Anticancer studies including a Phase 3 trial of Affinitak in combination with chemotherapy in patients with non-small cell lung cancer, which resulted in data that were not sufficient to support single-study registration of the drug, and two Phase 2 studies of ISIS 2503 in combination with chemotherapy that suggested activity in patients with pancreatic and breast cancers
- Began five new clinical initiatives on its own or with partners:
    - Phase 1 trial of ISIS 301012 for cardiovascular disease
    - Phase 1 trial of ISIS 107248 (ATL 1102) for multiple sclerosis with partner Antisense Therapeutics Limited (ATL)
    - Phase 2 trial of ISIS 14803 in addition to standard HCV treatments
    - Phase 2 program for ISIS 113715 in patients with type 2 diabetes
    - Second Phase 2 trial of Alicaforsen for the treatment of ulcerative colitis

Expanded RNA-Based Drug Discovery Efforts:

- Received a grant and subsequently achieved two milestones in its antisense drug discovery partnership with ITRI of Taiwan, focused on the coronavirus associated with Severe Acute Respiratory Syndrome (SARS)
- Received a grant from the Singapore Economic Development Board to support the broadening of two of Isis' RNA-based drug discovery and development programs: micro-RNA drug discovery and antisense drug discovery targeting the coronavirus associated with SARS
- Expanded drug discovery partnership with OncoGenex Technologies Inc. to include the development of OGX-225, a second-generation antisense anti-cancer drug that is designed to inhibit the production of two related proteins simultaneously
- Initiated a multi-year collaboration to discover antisense drugs that regulate alternative RNA splicing with Ercole Biotech, Inc. Ercole licensed Isis' Bcl-x preclinical antisense drug as its lead development compound
- Achieved a $1.5 million milestone from Lilly for the selection of LY2181308 for clinical development. LY2181308 is an antisense inhibitor of survivin and a product of the antisense drug discovery collaboration between Isis and Lilly
- Achieved a second milestone in its antisense drug discovery collaboration with Amgen
- Entered into a target validation agreement with Pfizer, Inc., in which Pfizer obtained access to Isis' antisense inhibitors and acquired a license to specific patents within Isis' intellectual property estate for use in its internal antisense-based functional genomics program

Furthered Ibis Diagnostic Program:

- Received a three-year grant for $6 million from the Centers for Disease Control and Prevention (CDC) to develop and apply Ibis' diagnostic technology to the surveillance of infectious disease in the U.S.

Strengthened Isis' Financial Position

- Retired approximately $32 million in partner debt using a new five-year, secured 4% variable rate term loan. The retired convertible partner debt was due from 2003 to 2005 and carried interest rates ranging from 8.5% to 12%.

- Reached a mutually beneficial renegotiation of Isis' manufacturing relationship with Lilly. Lilly waived repayment of the $21 million manufacturing loan it provided Isis to build Isis' second manufacturing facility. Lilly also agreed to allow Isis to use the facility to manufacture other drugs. In exchange, Isis released Lilly from its obligations to purchase additional Affinitak from Isis and to pay for the costs of maintaining an idle manufacturing suite

2004 Clinical Goals — Isis Products

- Report results of Phase 3 studies of alicaforsen in Crohn's disease — second half 2004
- Report results of Phase 2 studies of alicaforsen in ulcerative colitis — second half 2004
- Report results of Phase 2 trial of ISIS 113715 in type 2 diabetes — second half 2004 or early 2005
- Report preliminary results of Phase 2 study of ISIS 14803 in combination with current HCV therapies — second half 2004
- Report results of Phase 1 study of ISIS 301012 in cardiovascular disease — second half 2004
- Initiate Phase 2 clinical trial of ISIS 104838 in patients with rheumatoid arthritis to refine dose and schedule — second half 2004

2004 Clinical Goals - Isis' Partnered Products

- Report results of Lilly's Phase 3 study of Affinitak in non-small cell lung cancer — second half 2004
- Report Phase 1 / 2 results of ISIS 112989 (OGX-011) in prostate cancer and other tumor types (OncoGenex) — first half 2004
- Report final Phase 1 results of ISIS 107248 (ATL 1102) in multiple sclerosis (ATL) — mid 2004; initiate Phase 2 trial — second half 2004
- Initiate clinical trials of LY2181308, an antisense inhibitor of survivin, for cancer (Lilly) — mid 2004

Isis will conduct a live webcast conference call to discuss this earnings release on Tuesday, February 10 at 8:30 am Eastern time. To participate over the Internet go to http://www.isispharm.com or http://www.firstcallevents.com/service/ajwz398765671gf12.html. A replay of the webcast will be available at these addresses for up to 30 days.

Isis Pharmaceuticals, Inc., is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs. The company has successfully commercialized the world's first antisense product, and has 11 antisense products in development. In the company's GeneTrove™ program, Isis uses antisense technology as a tool to determine the function of genes and uses that information to direct the company's internal drug discovery research and that of its corporate partners. Through its Ibis TherapeuticsÒ program, Isis is developing a novel diagnostic tool to detect infectious organisms and is focused on the discovery of small molecule drugs that bind to RNA. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of

more than 1,300 issued patents worldwide. Additional information about Isis is available at www.isispharm.com

This press release contains forward-looking statements concerning the financial position and clinical goals of Isis Pharmaceuticals, Inc., the planned development activities and therapeutic potential for our products in our pipeline, and the potential value of the company's functional genomics, drug discovery and diagnostics technology platforms, as well as its licensing efforts. Any statement describing a goal, expectation, intention or belief of the company 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 financing such activities. Actual results could differ materially from those projected in this release. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' research and development programs are described in additional detail in the company's Annual Report on Form 10-K, for the year ended December 31, 2002 and Form 10-Q for the period ended September 30, 2003, which are on file with the U.S. Securities and Exchange Commission, copies of which are available from the company.

- Financial Data to Follow —

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

	Three months ended, December 31,		Years ended, December 31,	
	2003	2002	2003	2002
	(Unaudited)		(Unaudited)	
Revenue:				
Research and development revenue under collaborative agreements	$ 9,523	$ 18,240	$ 49,467	$ 67,820
Research and development revenue from joint ventures	—	3,508	—	11,942
Licensing revenue	176	111	523	417
Total revenue	9,699	21,859	49,990	80,179
Expenses:				
Research and development	29,114	30,091	116,963	124,074
General and administrative	2,088	1,632	9,289	8,547
Compensation (benefit) related to stock options	(23)	9	913	(3,002)
Restructuring activities	—	1,373	1,803	1,373
Total operating expenses	31,179	33,105	128,968	130,992
Loss from operations	(21,480)	(11,246)	(78,978)	(50,813)
Equity in loss of affiliates	—	(2,831)	—	(16,011)
Investment and other income	1,120	2,219	5,100	8,462
Interest expense	(5,015)	(3,971)	(18,680)	(16,562)
Loss on investments	—	—	(2,438)	—
Loss on repayment of debt	—	—	—	(2,294)
Gain on repayment of debt	—	—	—	4,976
Net loss	(25,375)	(15,829)	(94,996)	(72,242)
Accretion of dividends on preferred stock	(176)	(168)	(694)	(1,060)
Net loss applicable to common stock	$ (25,551)	$ (15,997)	$ (95,690)	$ (73,302)
Basic and diluted net loss per share	$ (0.46)	$ (0.29)	$ (1.73)	$ (1.35)
Shares used in computing basic and diluted net loss per share	55,555	55,155	55,463	54,480

(more)

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

	Three months ended, December 31,		Years Ended December 31,	
	2003	2002	2003	2002
	(Unaudited)		(Unaudited)	
As reported operating expenses according to GAAP	$ 31,179	$ 33,105	$ 128,968	$ 130,992
Excluding compensation expense (benefit) related to stock options	(23)	9	913	(3,002)
Excluding restructuring activities	—	1,373	1,803	1,373
Proforma operating expenses	$ 31,202	$ 31,723	$ 126,252	$ 132,621
As reported loss from operations according to GAAP	$ (21,480)	$ (11,246)	$ (78,978)	$ (50,813)
Excluding compensation expense (benefit) related to stock options	(23)	9	913	(3,002)
Excluding restructuring activities	—	1,373	1,803	1,373
Proforma loss from operations	$ (21,503)	$ (9,864)	$ (76,262)	$ (52,442)

Condensed Balance Sheets
(In Thousands)

	December 31, 2003	December 31, 2002
	(Unaudited)	
Assets:		
Current assets	$ 239,561	$ 320,180
Property, plant and equipment, net	34,790	59,094

Other assets	60,591	59,409
Total assets	$ 334,942	$ 438,683
Liabilities and stockholders' equity:		
Current liabilities	$ 45,557	$ 75,950
5.5% convertible subordinated notes	125,000	125,000
Long-term obligations, net of current portion	88,397	67,893
Long-term deferred revenue, net of current portion	8,810	14,363
Stockholders' equity	67,178	155,477
Total liabilities and stockholders' equity	$ 334,942	$ 438,683

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