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): **August 5, 2003**

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 August 5, 2003.

Item 12. Results of Operations and Financial Condition.

On August 5, 2003, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter ended June 30, 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: August 5, 2003

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

INDEX TO EXHIBITS

99.1	Press Release dated August 5, 2003.

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ISIS PHARMACEUTICALS REPORTS SECOND QUARTER 2003 HIGHLIGHTS AND FINANCIAL RESULTS

CARLSBAD, Calif., August 5, 2003 — Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced its financial results for the second quarter of 2003. The company's loss from operations was $19.5 million and $38.4 million for the three and six months ended June 30, 2003, respectively, compared to $12.3 million and $22.1 million for the same periods in the previous year. Excluding restructuring expenses and non-cash compensation expense or benefit, the company's proforma loss from operations was $17.6 million and $36.5 million for the three and six months ended June 30, 2003, respectively, compared to $13.9 million and $25.2 million for the same periods in the previous year.

Total revenue for the three and six months ended June 30, 2003 was $15.0 million and $29.0 million, respectively, compared to $20.1 million and $38.0 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 product rights to ISIS 14803 for hepatitis C and the oral formulation of ISIS 104838. As a result, Isis no longer earns revenue from these collaborations. The decrease in revenue was offset in part by new sources of revenue not present in the same period of 2002, including the achievement in April 2003 of a milestone in the development of the anticancer drug ISIS 23722 from Isis' drug discovery collaboration with Eli Lilly and Company, the addition of new GeneTroveä relationships in late 2002 and early 2003 and the achievement of a second milestone in February 2003 in the company's antisense drug discovery collaboration with Amgen.

As illustrated in the Selected Financial Information in this press release, operating expenses on a proforma basis for the three and six months ended June 30, 2003 were $32.6 million and $65.5 million, respectively, compared to $34.0 million and $63.2 million for the same periods in 2002. The decrease in the second quarter ended June 30, 2003 compared to the same period in 2002 was primarily due to planned expense reductions. The expenses for the first half of 2003 were higher than in the same period last year, primarily due to the company's continued investment in advancing the development of its pipeline of products and the full implementation of its research collaboration with Lilly.

Total operating expenses for the three and six months ended June 30, 2003 included approximately $123,000 and $132,000, respectively, in non-cash compensation expense due to variable accounting for stock options associated with the employee stock

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option exchange program that was initiated in the second quarter of 2003. In the three and six month periods of the previous year, the company reported compensation benefit of $1.6 million and $3.1 million, respectively, associated primarily with an option exchange program offered to non-officer employees in January 2000. All remaining options in this program were either exercised or cancelled in December 2002. 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.

In the second quarter of 2003, Isis recorded a one-time restructuring charge of $1.8 million related to its expense reduction plan, which included a small reduction in its workforce. There were no restructuring charges in the same period of 2002.

The company's net loss applicable to common stock for the three and six months ended June 30, 2003 was $23.3 million, or $0.42 per share, and $47.8 million, or $0.86 per share, respectively, compared with a net loss applicable to common stock of $21.2 million, or $0.39 per share, and $39.5 million, or $0.73 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.

Isis strengthened its balance sheet in the second quarter of 2003 with the reduction of $21.2 million in notes payable through the renegotiation of its manufacturing agreement with Lilly. Additionally, the company ended the quarter with $255.9 million in cash and short-term investments and working capital of $216.7 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 use of cash in operations.

"We are pleased with our overall financial position. Our second quarter operating expenses decreased, as expected, with the implementation of our expense reduction plan. We are on track to meet our 2003 financial goal. We have a strong cash balance, which enables us to continue to invest in the development of our pipeline and our technologies," said B. Lynne Parshall, Isis' Executive Vice President and CFO.

"We continue to make steady progress in the development of our antisense drugs. During the quarter we initiated three new clinical studies in ulcerative colitis with alicaforsen (ISIS 2302), in hepatitis C with ISIS 14803 and in diabetes with ISIS 113715. We also reported encouraging clinical data from an ongoing Phase II study of alicaforsen in ulcerative colitis/pouchitis and from Phase II studies of ISIS 2503 in pancreatic and breast cancers," said Ms. Parshall.

"We have further executed our business strategy and expanded the reach of antisense technology with the initiation of two new drug discovery collaborations in the second quarter," continued Ms. Parshall. "We are applying the efficiency and speed of antisense technology to discover antisense drugs to combat SARS with our partner, ITRI, in Taiwan. In addition, we have collaborated with Ercole to exploit the unique ability of antisense to regulate alternative RNA splicing. Antisense is the only drug discovery technology able to target a gene's messenger RNA in a sequence-specific fashion to direct splicing. Our goal is to discover antisense drugs that work through this mechanism, which other classes of drugs cannot exploit. We are pleased with the ongoing momentum

of our business and are focused on capitalizing on our strong position in RNA-based technologies to bring new products to patients and generate value for shareholders."

Isis' Second Quarter 2003 Highlights

Clinical Development

- Reported results from three studies of its anticancer antisense drugs at the Annual Meeting of the American Society of Clinical Oncology (ASCO). Data presented included results from a Phase III trial of Affinitak in combination with chemotherapy in patients with non-small cell lung cancer, a summary of which had previously been reported by Isis. Also presented were final results from two Phase II studies of ISIS 2503 in combination with chemotherapy in patients with pancreatic and breast cancers.

- Initiated a Phase II clinical trial to assess the benefit of adding ISIS 14803 to standard treatments for hepatitis C. In the study, ISIS 14803 will be administered to patients who have not achieved an early response to treatment with pegylated interferon and ribavirin.

- Reported at the 2003 Digestive Disease Week (DDW) meeting results of a Phase II clinical trial in patients with pouchitis, a condition related to ulcerative colitis. Patients experienced an improvement in clinical disease symptoms after receiving treatment with alicaforsen enema.

- Initiated a Phase I clinical trial of ISIS 113715, a second-generation antisense drug for Type 2 diabetes, designed to improve defective insulin signaling by targeting the gene, PTP-1B. PTP-1B reduces insulin's ability to manage blood sugar levels.

- Achieved a milestone in the development of ISIS 23722, as part of its broad antisense drug discovery collaboration with Lilly, which resulted in a $1.5 million payment to Isis. ISIS 23722 is the first compound from the partnership to be selected for clinical development by Lilly.

- Initiated a second Phase II clinical trial of alicaforsen in people with active ulcerative colitis. The placebo-controlled study will compare the safety and efficacy of different dosing-regimens of alicaforsen enema.

Antisense Research and Drug Discovery

- Initiated a collaboration with the Industrial and Technology Research Institute (ITRI) of Taiwan to identify antisense drugs targeting the coronavirus associated with Severe Acute Respiratory Syndrome (SARS).

- Initiated a multi-year collaboration with Ercole Biotech, Inc. to discover antisense drugs that regulate alternative RNA splicing. Defects in the splicing process play a central role in disease and can be uniquely modified by antisense technology.

Strengthening Isis' Financial Position

- 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.

Isis will conduct a live webcast conference call to discuss this press release on Tuesday, August 5 at 11:00 am Eastern time. To participate over the Internet, go to www.isispharm.com or to ***www.firstcallevents.com/service/*ajwz386662695gf12*.html*** . A replay of the webcast will be available at this address 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 commercialized its first product, Vitravene(R) (fomivirsen), to treat CMV-induced retinitis in AIDS patients. In addition, Isis has 13 antisense products in its development pipeline, with two in late-stage development and five in Phase II human clinical trials. Affinitak(TM) (formerly called LY900003 and ISIS 3521), an inhibitor of PKC-alpha, is in Phase III development for non-small cell lung cancer, and alicaforsen (ISIS 2302), an ICAM-1 inhibitor, is in Phase III clinical trials for Crohn's disease. Isis has a broad patent estate, as the owner or exclusive licensee of more than 1,200 issued patents worldwide. Isis' GeneTrove(TM) program uses antisense to assist pharmaceutical industry partners in validating and prioritizing potential gene targets through customized services. The Ibis Therapeutics(TM) program is focused on the detection of infectious organisms and the discovery of small molecule drugs that bind to RNA. 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 products in the company's pipeline, and the potential value of the company's functional genomics and drug discovery technology platform. 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, which is 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, June 30,		Six months ended, June 30,	
	2003	2002	2003	2002
	(unaudited)		(unaudited)	
Revenue:				
Research and development revenue under collaborative agreements	$ 14,900	$ 17,889	$ 28,681	$ 32,603
Research and development revenue from affiliates	—	2,087	—	5,121
Licensing revenue	116	85	316	296
Total revenue	15,016	20,061	28,997	38,020
Expenses:				
Research and development	30,179	31,530	60,439	58,513
General and administrative	2,431	2,444	5,054	4,671
Compensation (benefit) related to stock options	123	(1,574)	132	(3,106)
Restructuring activities	1,803	—	1,803	—
Total operating expenses	34,536	32,400	67,428	60,078
Loss from operations	(19,520)	(12,339)	(38,431)	(22,058)
Equity in loss of affiliates	—	(3,960)	—	(9,726)
Investment and other income	1,167	1,892	2,803	4,036
Interest expense	(4,745)	(4,164)	(9,352)	(8,795)
Loss on prepayment of debt	—	(2,294)	—	(2,294)
Loss on investments	—	—	(2,438)	—
Net loss	(23,098)	(20,865)	(47,418)	(38,837)
Accretion of dividends on preferred stock	(172)	(335)	(343)	(670)
Net loss applicable to common stock	$ (23,270)	$ (21,200)	$ (47,761)	$ (39,507)
Basic and diluted net loss per share	$ (0.42)	$ (0.39)	$ (0.86)	$ (0.73)
Shares used in computing basic and diluted net loss per share	55,380	54,117	55,378	54,022

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

	Three months ended, June 30,		Six months ended, June 30,	
	2003	2002	2003	2002
	(unaudited)		(unaudited)	
As reported operating expenses according to GAAP	$ 34,536	$ 32,400	$ 67,428	$ 60,078
Excluding compensation expense (benefit) related to stock options	123	(1,574)	132	(3,106)
Excluding restructuring activities	1,803	—	1,803	—
Proforma operating expenses	$ 32,610	$ 33,974	$ 65,493	$ 63,184
As reported loss from operations according to GAAP	$ (19,520)	$ (12,339)	$ (38,431)	$ (22,058)
Excluding compensation expense (benefit) related to stock options	123	(1,574)	132	(3,106)
Excluding restructuring activities	1,803	—	1,803	—
Proforma loss from operations	$ (17,594)	$ (13,913)	$ (36,496)	$ (25,164)

ISIS PHARMACEUTICALS, INC.
SELECTED FINANCIAL INFORMATION
(In Thousands, Except Per Share Data)
Condensed Balance Sheets

	June 30, 2003	December 31, 2002
	(unaudited)	
Assets:		
Current assets	$ 271,954	$ 320,180
Property, plant and equipment, net	39,269	59,094
Other assets	59,633	59,409
Total assets	$ 370,856	$ 438,683
Liabilities and stockholders' equity:		

Current liabilities	$ 55,208	$ 75,950
5.5% Convertible subordinated notes	125,000	125,000
Long-term obligations, net of current portion	65,221	67,893
Long-term deferred revenue, net of current portion	12,592	14,363
Stockholders' equity	112,835	155,477
Total liabilities and stockholders' equity	$ 370,856	$ 438,683

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