
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): **November 4, 2003**

ISIS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Charter)

Delaware

(State or Other Jurisdiction of Incorporation)

000-19125
(Commission File No.)

33-0336973
(IRS Employer Identification No.)

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 November 4, 2003.

Item 12. Results of Operations and Financial Condition.

On November 4, 2003, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter ended September 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.

2

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: November 4, 2003

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

INDEX TO EXHIBITS

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 THIRD QUARTER 2003 HIGHLIGHTS AND FINANCIAL RESULTS

CARLSBAD, Calif., November 4, 2003 — Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced its financial results for the third quarter of 2003. The company's loss from operations was \$19.1 million and \$57.5 million for the three and nine months ended September 30, 2003, respectively, compared to \$17.5 million and \$39.6 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 \$18.3 million and \$54.8 million for the three and nine months ended September 30, 2003, respectively, compared to \$17.4 million and \$42.6 million for the same periods in the previous year.

Revenue

Total revenue for the three and nine months ended September 30, 2003 was \$11.3 million and \$40.3 million, respectively, compared to \$20.3 million and \$58.3 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. The decrease in revenue was offset in part by new sources of revenue not present in the same nine month period of 2002, including the achievement of milestones in the discovery and development of drugs for our partners Eli Lilly and Company and Amgen.

Expenses

As illustrated in the Selected Financial Information in this press release, operating expenses on a proforma basis for the three and nine months ended September 30, 2003 were \$29.6 million and \$95.1 million, respectively, compared to \$37.7 million and \$100.9 million for the same periods in 2002. The decrease in the third quarter ended September 30, 2003 compared to the same period in 2002 was primarily due to planned expense reductions.

Total operating expenses for the three and nine months ended September 30, 2003 included approximately \$804,000 and \$936,000, respectively, in non-cash compensation expense due to variable accounting for stock options associated with the employee stock option exchange program that was offered in the second quarter of 2003. In the respective three and nine month periods of the previous year, the company reported compensation expense of \$95,000 and 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 either exercised or cancelled by the end of 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.

The 2003 year-to-date operating expenses include a one-time restructuring charge of \$1.8 million related to Isis' expense reduction plan, which included a small reduction in its workforce. There were no restructuring charges in the same period of 2002.

Net Loss

The company's net loss applicable to common stock for the three and nine months ended September 30, 2003 was \$22.4 million, or \$0.40 per share, and \$70.1 million, or \$1.27 per share, respectively, compared with a net loss applicable to common stock of \$17.8 million, or \$0.33 per share, and \$57.3 million, or \$1.06 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 in the third quarter of 2003 by ending the quarter with \$234.8 million in cash and short-term investments and working capital of \$195.6 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.

"Our third quarter financial results are in line with our expectations and on track to meet our 2003 financial goal. Our cash position is strong and we are continuing to invest aggressively in the development of our product pipeline. We have reported positive results from several clinical programs over the past two months, including exciting data on second-generation antisense drugs, and we are approaching many key clinical milestones in the coming months," said B. Lynne Parshall, Isis' Executive Vice President and CFO.

"In addition, we have continued to engage in strategic alliances that will expand the application of our technologies and our proprietary position in them. We've recently been awarded grants from the U.S. Centers for Disease Control and the Singapore Economic Development Board to advance our Ibis diagnostic program, called TIGER, and our micro-RNA research, respectively," stated Ms. Parshall. "We expanded our relationship with OncoGenex, adding another second-generation antisense drug for the treatment of cancer. Together, these alliances are worth up to \$14 million to Isis over three years. We will continue to generate value for shareholders through strategic partnering."

Isis' Third Quarter 2003 and Recent Highlights

Clinical Data Highlights

- As described in more detail in a separate press release issued last week, Isis reported positive data from the following clinical programs:

- ISIS 113715 for Type 2 Diabetes: in a Phase 1 study, ISIS 113715 decreased the amount of insulin required to normalize blood glucose tolerance tests in normal volunteers following a glucose challenge.
- ISIS 104838 for Rheumatoid Arthritis: in a Phase 2 study, ISIS 104838 distributed to synovial tissue and reduced TNF-alpha mRNA levels in synovium in a dose-dependent manner.
- Alicaforsen (ISIS 2302) for Pouchitis/Ulcerative Colitis: in a Phase 2 study of patients with pouchitis, treatment with alicaforsen enema improved clinical disease symptoms with remissions that lasted up to nine months.
- ISIS 14803 for Hepatitis C: in a Phase 2 single-agent study, ISIS 14803 decreased viral levels in a dose-dependent manner in patients that had failed previous treatment.
- Additionally, Isis' partner, Antisense Therapeutics Limited, initiated a Phase 1 study of ISIS 107248, for the treatment of multiple sclerosis.

Business Activity

- Expanded our 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. OGX-225 targets two molecules involved in the development of metastatic disease in hormone-regulated tumors such as prostate and breast cancers.
- Received a three year grant for up to \$6 million from the Centers for Disease Control and Prevention (CDC) to develop and apply Ibis' diagnostic technology to the surveillance of human and animal infectious disease in the U.S.
- Received a grant from the Singapore Economic Development Board which will 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 Severe Acute Respiratory Syndrome (SARS).

Isis will conduct a live webcast conference call to discuss this earnings release on Tuesday, November 4 at 9:30 am Eastern time. To participate over the Internet go to <http://www.isispharm.com>. 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 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 Therapeutics™

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 and drug discovery technology platforms. 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 June 30, 2003, which are on file with the U.S. Securities and Exchange Commission, copies of which are available from the company.

GeneTrove® and Ibis Therapeutics® are trademarks of Isis Pharmaceuticals, Inc

- Financial Data to Follow –

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

	Three months ended, September 30,		Nine months ended, September 30,	
	2003	2002	2003	2002
	(unaudited)		(unaudited)	
Revenue:				
Research and development revenue under collaborative agreements	\$ 11,263	\$ 16,977	\$ 39,944	\$ 49,580

Research and development revenue from affiliates	—	3,313	—	8,434
Licensing and royalty revenue	31	10	347	306
Total revenue	11,294	20,300	40,291	58,320
Operating Expenses:				
Research and development	27,410	35,470	87,849	93,983
General and administrative	2,147	2,244	7,201	6,915
Compensation (benefit) related to stock options	804	95	936	(3,011)
Restructuring activities	—	—	1,803	—
Total operating expenses	30,361	37,809	97,789	97,887
Loss from operations	(19,067)	(17,509)	(57,498)	(39,567)
Equity in loss of affiliates	—	(3,454)	—	(13,180)
Investment and other income	1,177	2,207	3,980	6,243
Interest expense	(4,313)	(3,796)	(13,665)	(12,591)
Loss on prepayment of 14% notes	—	—	—	(2,294)
Gain on prepayment of 12% notes	—	4,976	—	4,976
Loss on investments	—	—	(2,438)	—
Net loss	(22,203)	(17,576)	(69,621)	(56,413)
Accretion of dividends on preferred stock	(175)	(222)	(518)	(892)
Net loss applicable to common stock	\$ (22,378)	\$ (17,798)	\$ (70,139)	\$ (57,305)
Basic and diluted net loss per share	\$ (0.40)	\$ (0.33)	\$ (1.27)	\$ (1.06)
Shares used in computing basic and diluted net loss per share	55,540	54,708	55,418	54,253

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

	Three months ended, September 30,		Nine months ended, September 30,	
	2003 (unaudited)	2002 (unaudited)	2003 (unaudited)	2002 (unaudited)
As reported operating expenses according to GAAP	\$ 30,361	\$ 37,809	\$ 97,789	\$ 97,887
Excluding compensation expense (benefit) related to stock options	804	95	936	(3,011)
Excluding restructuring activities	—	—	1,803	—
Proforma operating expenses	\$ 29,557	\$ 37,714	\$ 95,050	\$ 100,898
As reported loss from operations according to GAAP	\$ (19,067)	\$ (17,509)	\$ (57,498)	\$ (39,567)
Excluding compensation expense (benefit) related to stock options	804	95	936	(3,011)
Excluding restructuring activities	—	—	1,803	—
Proforma loss from operations	\$ (18,263)	\$ (17,414)	\$ (54,759)	\$ (42,578)

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

	September 30, 2003 (unaudited)	December 31, 2002
Assets:		
Current assets	\$ 255,242	\$ 320,180
Property, plant and equipment, net	37,880	59,094
Other assets	60,424	59,409
Total assets	\$ 353,546	\$ 438,683
Liabilities and stockholders' equity:		
Current liabilities	\$ 59,639	\$ 75,950
5.5% Convertible subordinated notes	125,000	125,000
Long-term obligations, net of current portion	64,390	67,893
Long-term deferred revenue, net of current portion	11,003	14,363
Stockholders' equity	93,514	155,477
Total liabilities and stockholders' equity	\$ 353,546	\$ 438,683

