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# 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 6, 2004**

## 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**

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#### Item 7. Financial Statements and Exhibits.

(c) Exhibits.

99.1 Press Release dated May 6, 2004.

#### Item 12. Results of Operations and Financial Condition.

On May 6, 2004, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter ended March 31, 2004. 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 non-cash compensation expense related to stock options. The Company is presenting pro forma information excluding the effects of the non-cash compensation expense related to stock options 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.

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#### 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 6, 2004

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

INDEX TO EXHIBITS



Contact: Elizabeth Hougen, Vice President, Finance  
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## ISIS PHARMACEUTICALS REPORTS FINANCIAL RESULTS AND HIGHLIGHTS FOR THE FIRST QUARTER 2004

**CARLSBAD, CA, May 6, 2004** — Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced its financial results for the first quarter of 2004. The company's revenue for the three months ended March 31, 2004 was \$12.3 million compared to \$14.0 million for the same period in 2003. The decrease reflects the completion of Isis' Phase 3 clinical trial of Affinitak™ and an associated reduction in revenue, offset by revenue earned in connection with the Alnylam Pharmaceuticals, Inc. alliance for RNAi therapeutics and an increase in revenue from the company's TIGER biosensor program.

### Expenses

Isis' operating expenses were \$34.6 million for the first quarter of 2004 compared to \$32.9 million for the same period in 2003, according to generally accepted accounting principles (GAAP). Included in operating expenses was non-cash compensation expense related to stock options of \$3.2 million for the first quarter of 2004 and \$9,000 for the same period in 2003. Variable accounting for stock options can result in significant increases and decreases in non-cash compensation expense as a result of the variability in the company's stock price. The company's stock price increased 19.4% between December 31, 2003 and March 31, 2004.

As illustrated in the Selected Financial Information in this press release, the company's operating expenses on a proforma basis were \$31.4 million for the first quarter of 2004 compared to \$32.9 million for the same period in 2003. Operating expenses on a proforma basis were adjusted from GAAP to exclude non-cash compensation expense related to stock options. The decrease in operating expenses on a proforma basis was the result of planned expense reductions that began in the second quarter of 2003, offset in part by increased spending to support the development of other products in the company's pipeline and the company's TIGER biosensor program.

### Loss from Operations

Isis' loss from operations was \$22.3 million for the first quarter of 2004 compared to \$18.9 million for the same period in 2003, according to GAAP. The company's loss from operations for the first quarter of 2004 on a proforma basis was \$19.1 million compared to \$18.9 million for the same period in 2003. Loss from operations on a proforma basis remained relatively flat for the first quarter of 2004 compared to the same period in 2003. Loss from operations, according to GAAP, increased due to the non-cash compensation expense recorded in the first quarter of 2004.

### Net Loss

The company's net loss applicable to common stock for the quarter-ended March 31, 2004 was \$26.5 million, or \$0.47 per share, compared with a net loss applicable to common stock of \$24.5 million, or \$0.44 per share, for the same period 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 first quarter with \$180.9 million in cash and short-term investments and working capital of \$169.2 million. At December 31, 2003, Isis had cash and short-term investments of \$215.5 million and working capital of \$194.0 million. Cash and short-term investments and working capital decreased primarily as a result of cash used in operations, Isis' equity investment in Alnylam and the retirement of partner debt.

### Isis' 2004 First-Quarter and Recent Highlights

"Isis owns a number of key assets that are capable of generating near-term revenue and value. Specifically, we recently initiated an alliance with Alnylam Pharmaceuticals, which is focused on discovering new RNAi drugs. This relationship exemplifies our ability to leverage our leading patent estate to generate revenue. Furthermore, this demonstrates our ability to successfully execute our business strategy of engaging in RNA-based drug discovery collaborations that increase the use of our technology and allow us to participate in the commercial upside of our partners' successes," said B. Lynne Parshall, Isis' Executive Vice President and CFO. "We also recently received a government contract for up to \$19.5 million to continue the development of our novel biosensor. We are planning for its commercialization."

"We also made progress in the development of our antisense drugs. In January, we announced data from a Phase 2 study of ISIS 104838 in patients with rheumatoid arthritis, which demonstrated the drug is active," continued Ms. Parshall. "The company's pipeline, our most valuable asset, will reach a number of major development milestones in the second half of the year as we expect to report data from eight clinical trials. We look forward to this year of momentum for the company and our technology."

#### *Expanded RNA-Based Drug Discovery Efforts:*

- Announced the extension of Isis' antisense drug discovery collaboration in cancer with Eli Lilly and Company. During this extension, Isis and Lilly will continue to characterize and develop RNase H, siRNA, and splicing modulating inhibitors for the treatment of cancer using second and third generation chemistries. An important component of this extension will be the exploration of potential new anticancer drug targets using RNA-directed technologies. This oncology relationship, initiated in June 2002, builds on a broad, ongoing strategic alliance previously established by the companies to discover antisense drugs in the areas of inflammatory and metabolic diseases.
- Formed a strategic alliance with Alnylam Pharmaceuticals, the leading RNAi therapeutics company, to accelerate the development and commercialization of RNAi therapeutics. The alliance combines Isis' intellectual property and drug

development expertise with Alnylam's intellectual property and research expertise in RNAi therapeutics.

- Announced the achievement of two milestones in its antisense drug discovery partnership with Industrial Technology Research Institute (ITRI) of Taiwan, focused on the coronavirus associated with Severe Acute Respiratory Syndrome (SARS). The milestones relate to the identification of potent, second-generation antisense drugs that inhibit SARS virus replication and the successful completion of preclinical studies evaluating aerosol and parenteral delivery of antisense drugs as specified under the agreement. The achievement of these milestones resulted in payments to Isis.

*Progress in Antisense Drug Discovery and Development:*

- In a Phase 2 clinical trial of Isis' proprietary second-generation antisense drug ISIS 104838, evaluable rheumatoid arthritis patients who received the two highest doses studied experienced a positive disease response. An initial biomarker study showed the drug distributed to synovial tissue and reduced TNF-alpha mRNA levels in synovium in a dose-dependent manner. ISIS 104838 is an antisense inhibitor of TNF-alpha.
- In preclinical studies, an antisense drug suppressed the production of the mutant protein Cu/Zn superoxide dismutase (SOD1), a molecule associated with an aggressive form of amyotrophic lateral sclerosis (ALS). Leading neurodegenerative researchers conducted this study with funding from The ALS Association. Researchers believe that decreasing the amount of mutant SOD1 in the brain of patients with this condition could potentially modify or halt the progression of the disease.

*Granted New Funding for TIGER Biosensor Program:*

- Received a two-year contract providing up to \$19.5 million for the continued development of the company's TIGER biosensor system to identify infectious agents in biological warfare attacks. This new funding is from the Defense Advanced Research Projects Agency (DARPA) under a subcontract from San Diego-based Science Applications International Corporation (SAIC). In a single test, TIGER can rapidly and accurately identify essentially all infectious organisms contained in a sample. The company has completed proof-of-concept studies, and is currently planning for the initial commercialization of this technology within government markets.

Isis will conduct a live webcast conference call to discuss this earnings release on Thursday, May 6<sup>th</sup> at 10:00 am Eastern time. To participate over the Internet go to <http://www.firstcallevts.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.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs for its pipeline and its partners. The company has successfully commercialized the world's first antisense drug and has 11 antisense products in development to treat metabolic, cardiovascular, inflammatory and viral diseases and cancer. Through its Ibis Therapeutics® program, Isis is developing a biosensor to identify infectious organisms, and is discovering 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](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 developing technology and systems used to identify infectious agents, in discovering and commercializing drugs that are safe and effective for use as human therapeutics and in the endeavor of building a business around such products and services. Actual results could differ materially from those discussed in this press 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 Isis' Annual Report on Form 10-K for the year ended December 31, 2003, which is on file with the U.S. Securities and Exchange Commission. Copies of this and other documents are available from the company.

Ibis Therapeutics is a registered trademark 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, March 31,	
	2004	2003
	(unaudited)	
<b>Revenue:</b>		
Research and development revenue under collaborative agreements	\$ 6,998	\$ 13,780
Licensing revenue	5,305	200
<b>Total revenue</b>	<b>12,303</b>	<b>13,980</b>

Expenses:			
Research and development		28,947	30,261
General and administrative		2,453	2,622
Compensation related to stock options		3,238	9
Total operating expenses		<u>34,638</u>	<u>32,892</u>
Loss from operations		(22,335)	(18,912)
Investment and other income		1,133	1,636
Interest expense		(5,104)	(4,608)
Loss on investments		<u>—</u>	<u>(2,438)</u>
Net loss		(26,306)	(24,322)
Accretion of dividends on preferred stock		<u>(181)</u>	<u>(171)</u>
Net loss applicable to common stock		<u>\$ (26,487)</u>	<u>\$ (24,493)</u>
Basic and diluted net loss per share		<u>\$ (0.47)</u>	<u>\$ (0.44)</u>
Shares used in computing basic and diluted net loss per share		<u>55,858</u>	<u>55,375</u>

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

	Three months ended, March 31,	
	2004	2003
	(unaudited)	
<b>As reported operating expenses according to GAAP</b>	\$ 34,638	\$ 32,892
Excluding compensation expense related to stock options	<u>3,238</u>	<u>9</u>
<b>Proforma operating expenses</b>	<u>\$ 31,400</u>	<u>\$ 32,883</u>
<b>As reported loss from operations according to GAAP</b>	\$ (22,335)	\$ (18,912)
Excluding compensation expense related to stock options	<u>3,238</u>	<u>9</u>
<b>Proforma loss from operations</b>	<u>\$ (19,097)</u>	<u>\$ (18,903)</u>

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**Condensed Balance Sheets  
(In Thousands)**

	March 31, 2004	December 31, 2003
	(Unaudited)	
<b>Assets:</b>		
Current assets	\$ 208,881	\$ 239,561
Property, plant and equipment, net	32,721	34,790
Other assets	71,124	60,591
Total assets	<u>\$ 312,726</u>	<u>\$ 334,942</u>
<b>Liabilities and stockholders' equity:</b>		
Current liabilities	\$ 39,643	\$ 45,557
5.5% convertible subordinated notes	125,000	125,000
Long-term obligations, net of current portion	94,558	88,397
Long-term deferred revenue, net of current portion	5,971	8,810
Stockholders' equity	47,554	67,178
Total liabilities and stockholders' equity	<u>\$ 312,726</u>	<u>\$ 334,942</u>

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