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, 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 August 5, 2004.

Item 12. Results of Operations and Financial Condition.

On August 5, 2004, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter ended June 30, 2004. In addition to disclosing results that are determined in accordance with Generally Accepted Accounting Principles (GAAP), the Company also discloses pro forma results of operations, which are adjusted from GAAP to exclude certain expenses or benefits associated with non-cash compensation related to stock options and in 2003, a restructuring charge. The Company is presenting pro forma information excluding the effects of the non-cash compensation related to stock options and in 2003, a restructuring charge 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 4, 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 August 5, 2004.

Exhibit 99.1

Contact: Elizabeth Hougen, Vice President, Finance
Alison Trollope, Executive Director, Investor Relations
Isis Pharmaceuticals, 760-931-9200
http://www.isispharm.com

ISIS PHARMACEUTICALS REPORTS SECOND QUARTER 2004 FINANCIAL RESULTS AND HIGHLIGHTS

Company Provides Update on Product Development Plans

CARLSBAD, CA, August 5, 2004 — Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced financial results for the second quarter of 2004. The company's loss from operations was $21.3 million and $43.7 million for the three and six months ended June 30, 2004, respectively, compared to $19.5 million and $38.4 million for the same periods in 2003, according to generally accepted accounting principles (GAAP). The company's proforma loss from operations was $24.8 million and $43.9 million for the three and six months ended June 30, 2004, respectively, compared to $17.6 million and $36.5 million for the same periods in 2003, as adjusted from GAAP to exclude non-cash compensation related to stock options and in 2003, a restructuring charge. The company remains on-track to achieve its projected net operating loss in the mid-$80 millions, excluding non-cash compensation.

Revenue

The company's revenue for the three and six months ended June 30, 2004 was $9.8 million and $22.1 million, respectively, compared to $15.0 million and $29.0 million for the same periods in 2003**.** The decrease primarily reflects the completion of Isis' Phase 3 clinical trial of Affinitak™ and an associated reduction in revenue, which was offset in part by increased revenue from the company's TIGER biosensor program and Isis' recently established strategic alliance with Alnylam Pharmaceuticals, Inc.

Expenses

Isis' operating expenses were $31.2 million and $65.8 million for the three and six months ended June 30, 2004, respectively, compared to $34.5 million and $67.4 million for the same periods in 2003, according to GAAP. Included in operating expenses was non-cash compensation benefit related to stock options of $3.4 million and $183,000 for the three and six months ended June 30, 2004, respectively, compared to non-cash compensation expense of $123,000 and $132,000 for the same periods in 2003. Variable accounting for stock options can result in significant increases and decreases in non-cash compensation related to stock options as a result of the variability in the company's stock price.

As illustrated in the Selected Financial Information in this press release, the company's operating expenses on a proforma basis were $34.6 million and $66.0 million for the three and six months ended June 30, 2004, respectively, compared to $32.6 million and $65.5 million for the same periods in 2003. Operating expenses on a proforma basis were adjusted from GAAP to exclude non-cash compensation related to stock options and in 2003, restructuring expenses. The increase in operating expenses on a proforma basis for the three and six months ended June 30, 2004 was due primarily to increased spending to support the company's TIGER biosensor program, partially offset by planned expense reductions in other parts of the company that began in the second quarter of 2003.

Net Loss

The company's net loss applicable to common stock for the three and six months ended June 30, 2004 was $26.1 million or $0.47 per share**,** and $52.6 million or $0.94 per share**,** respectively, compared with a net loss applicable to common stock of $23.3 million or $0.42 per share, and $47.8 million or $0.86 per share, for the same periods in 2003**.** 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 second quarter with $147.3 million in cash and short-term investments and working capital of $140.2 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. In December 2003, Isis secured a $32 million term loan from Silicon Valley Bank, which was used to retire partner debt in 2003 and early 2004.

As part of Isis' ongoing efforts to streamline its balance sheet, in the second quarter of 2004 Isis entered into an agreement with a subsidiary of Elan Corporation, plc to acquire Elan's minority interest in Orasense™ and HepaSense™. Through this acquisition, Isis eliminated all future royalties to Elan related to the oral delivery platform developed within the Orasense collaboration. The agreement also eliminated all future royalties to Elan related to ISIS 14803, which is currently in Phase 2 clinical trials for the treatment of hepatitis C and was the focus of the HepaSense collaboration. In addition, the transaction allowed Elan to transfer its shares of Isis Series B preferred stock to a third party, which were converted to common stock. This eliminated dividend accretion of approximately $1.2 million between 2004 and 2006.

"We made solid progress this quarter across multiple important areas of our business. Our robust product pipeline continued to advance in development and we reported positive results of two clinical trials. We look forward to maintaining this momentum as we and our partners plan to report data from nine additional clinical trials before the end of 2004," said B. Lynne Parshall, Isis' Executive Vice President and CFO. "We also continue to enter into strategic partnerships that allow us to leverage our intellectual property portfolio and expertise to participate broadly in the success of multiple companies and products. The milestone payment from Eyetech and the payment from Alnylam associated with its newly announced collaboration with Merck this quarter illustrate that this strategy is providing financial value to our company and represent additional validation of Isis' technologies for creating important new drugs."

ISIS 104838 Development Update

The company is accelerating development of the oral formulation of ISIS 104838 for the treatment of rheumatoid arthritis (RA).

Isis' decision to pursue oral ISIS 104838 is based on:

- positive Phase 2 results reported earlier this year, in which the subcutaneous formulation of ISIS 104838 produced a statistically significant disease response (ACR 20) in patients with RA compared to placebo; combined with,

- recognition that the profile of injectible drugs to treat RA must be outstanding in light of the performance of competitive products; and

- the significant opportunity an oral TNF-alpha inhibitor presents in this otherwise highly competitive market.

Isis plans to initiate a Phase 2 trial comparing the oral and subcutaneous formulations of ISIS 104838 in patients with RA. In the planned study, which will be conducted outside the U.S., ISIS 104838 will be dosed in combination with methotrexate, a commonly used treatment for RA. Isis expects to initiate this trial in mid-2005.

To support oral dosing in the new trial, the company plans to complete ongoing oral delivery trials and conduct an additional preclinical safety study of oral ISIS 104838. In addition, to provide the U.S. Food and Drug Administration with additional information on the safety profile of ISIS 104838, Isis will conduct a preclinical safety study to reevaluate high dose toxicities and recovery from them. Isis will also conduct an additional preclinical study to evaluate nine months of dosing with ISIS 104838 to support longer dosing. Both studies are required to support further clinical trials in the U.S.

In order to move the oral formulation of ISIS 104838 forward aggressively and due to the number of promising drugs in development for psoriasis, Isis has decided not to initiate additional studies of ISIS 104838 for the treatment of psoriasis.

Pipeline Development Review

Isis' 10 drugs in development continue to advance. Second quarter highlights include:

- In June 2004, Isis and partner OncoGenex Technologies, Inc. reported results of a Phase 1 study of the second-generation anti-cancer drug OGX-011 (ISIS 112989) as presented at the 40th Annual Meeting of the Society of Clinical Oncology. In the trial, OGX-011 was well-tolerated, achieved excellent drug concentration in its target tissue, the prostate, and produced up to a 91 percent dose-dependent down-regulation of its target, clusterin. The inhibition of clusterin was also associated with the expected pharmacological outcome, the death of prostate cancer cells. OncoGenex and Isis plan to initiate trials of OGX-011 in combination with hormone therapy and chemotherapy in patients with prostate, breast and lung cancers in the second half of 2004.

- Also in June, Isis and its partner Antisense Therapeutics Limited (ATL) reported results of a dose-escalating Phase 1 study of the second-generation antisense drug ATL-1102 (ISIS 107248). Study findings showed that 6 mg/kg/week of ATL-1102 appeared well-tolerated, and is the proposed dose for Phase 2 development. ATL plans to initiate a Phase 2 clinical trial of ATL-1102 in patients with multiple sclerosis by the end of the year.

"With the clinical results reported this quarter, Isis and our partners have now reported positive data on five trials of second-generation drugs in the past 10 months. Cumulative data show that these drugs are working in man as expected," said Ms. Parshall. "Key advantages of our second-generation drugs include significantly higher potency, improved safety profiles compared to first-generation antisense drugs, and the potential to be delivered orally. Oral delivery would significantly increase patient convenience, broaden the range of diseases antisense drugs can treat and expand the market opportunities available to us."

Upcoming Pipeline Events

Isis and its partners plan to report data from nine clinical trials by the end of 2004. Specifically, Isis plans to report results of:

- Phase 3 studies of alicaforsen (target: ICAM-1) in patients with Crohn's disease

- Phase 2 studies of alicaforsen in patients with ulcerative colitis

- Preliminary Phase 2 study of ISIS 14803 (target: HCV) in combination with current therapy in patients with HCV infection who have failed current therapy

- Phase 2 trial of ISIS 113715 (target: PTP-1B) in patients with type 2 diabetes (late 04 or early 05)

- Phase 1 trial of ISIS 301012 (target: apoB-100), measuring safety and ability to reduce cholesterol in volunteers with elevated cholesterol

- Phase 3 trial of Affinitak™ (target: PKC-alpha) in patients with non-small cell lung cancer (conducted by our partner Eli Lilly and Company)

- Phase 1 trial of OGX-011 (target: clusterin) in combination with Taxotere® in patients with solid tumors (conducted by our partner OncoGenex)

Also in 2004, Isis and its partners plan to initiate:

- Phase 2 trial of ATL-1102 (target: VLA-4) in patients with multiple sclerosis (conducted by our partner ATL)

- Clinical trials of LY2181308 (target: survivin) in cancer patients (conducted by our partner Lilly)

- Additional Phase 2 trials of ISIS 113715 in patients with type 2 diabetes

- Additional Phase 2 trials of OGX-011 in combination with hormone therapy and chemotherapy in patients with prostate, breast and lung cancers (conducted by our partner OncoGenex)

Additional Second Quarter Highlights

In addition to advancing its clinical pipeline, Isis announced several achievements in drug discovery and business development in the second quarter of 2004:

Antisense Drug Discovery Advances:

- Reported, along with collaborators, data from multiple preclinical studies in metabolic disease as presented at the American Diabetes Association's 64th Scientific Sessions. Data from the studies demonstrated the utility of four second-generation antisense inhibitors in identifying new diabetes and related metabolic disease targets for drug discovery and as potential innovative treatments for these conditions.

- Announced that, in preclinical studies, an antisense drug suppressed the production of the mutant protein Cu/Zn superoxide dismutase (SOD-1), a molecule associated with an aggressive form of amyotrophic lateral sclerosis (ALS). Researchers believe that decreasing the amount of mutant SOD-1 in the brain of patients with this condition could potentially modify or halt the

progression of the disease. Leading neurodegenerative researchers conducted this study with funding from The ALS Association.

Business Development Progress:

- Earned a $1 million milestone from Eyetech Pharmaceuticals, Inc. associated with its filing of a New Drug Application with the U.S. Food and Drug Administration for Macugen™ for the treatment of wet age-related macular degeneration. Macugen is a non-antisense oligonucleotide (aptamer). In 2002, Eyetech licensed from Isis specific patents necessary to develop, manufacture and commercialize Macugen. Under the terms of the agreement, Isis may earn additional milestone and royalty payments from Eyetech.

- Earned a $500,000 license fee from Alnylam related to Alnylam's recently established alliance with Merck to develop and commercialize RNAi therapeutics for ocular diseases. This license fee was the first payment to Isis from its participation in fees from Alnylam's partnering programs under the companies' strategic alliance formed in March 2004 to develop and commercialize RNAi therapeutics. Under the terms of the agreement, Isis licensed to Alnylam its patent estate relating to antisense mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5 million technology access fee, participation in fees for Alnylam's partnering programs, as well as downstream milestone and royalty payments.

- Extended its anti-cancer antisense drug discovery collaboration with Lilly. 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. This oncology relationship, initiated in June 2002, builds on a broad, ongoing strategic alliance previously established by the companies in 2001 to discover antisense drugs in the areas of inflammatory and metabolic diseases.

Isis will conduct a live webcast conference call to discuss this earnings release on Thursday, August 5th at 10:00 am Eastern time. To participate over the Internet go to http://www.firstcallevents.com/service/ajwz408899305gf12.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 for its partners. The company has successfully commercialized the world's first antisense drug and has 10 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 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 1,400 issued patents worldwide. Additional information about Isis is available at 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, and quarterly report on Form 10-Q for the quarter ended March 31, 2004, which are on file with the U.S. Securities and Exchange Commission. Copies of these and other documents are available from the company.

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,	
	2004	2003	2004	2003
	(unaudited)		(unaudited)	
Revenue:				
Research and development revenue under collaborative agreements	$ 8,717	$ 14,900	$ 15,715	$ 28,681
Licensing revenue	1,126	116	6,431	316
Total revenue	9,843	15,016	22,146	28,997
Expenses:				
Research and development	32,036	30,179	60,983	60,439
General and administrative	2,568	2,431	5,021	5,054
Compensation related to stock options	(3,421)	123	(183)	132
Restructuring activities	—	1,803	—	1,803
Total operating expenses	31,183	34,536	65,821	67,428
Loss from operations	(21,340)	(19,520)	(43,675)	(38,431)
Investment and other income	842	1,167	1,975	2,803
Interest expense	(5,451)	(4,745)	(10,555)	(9,352)
Loss on investments	—	—	—	(2,438)
Net loss	(25,949)	(23,098)	(52,255)	(47,418)
Accretion of dividends on preferred stock	(180)	(172)	(361)	(343)
Net loss applicable to common stock	$ (26,129)	$ (23,270)	$ (52,616)	$ (47,761)
Basic and diluted net loss per share	$ (0.47)	$ (0.42)	$ (0.94)	$ (0.86)
Shares used in computing basic and diluted net loss per share	56,111	55,380	55,984	55,378

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

	Three months ended, June 30,		Six months ended, June 30,	
	2004	2003	2004	2003
	(unaudited)		(unaudited)	
As reported operating expenses according to GAAP	$ 31,183	$ 34,536	$ 65,821	$ 67,428
Excluding compensation related to stock options	(3,421)	123	(183)	132
Excluding restructuring activities	—	1,803	—	1,803
Proforma operating expenses	$ 34,604	$ 32,610	$ 66,004	$ 65,493
As reported loss from operations according to GAAP	$ (21,340)	$ (19,520)	$ (43,675)	$ (38,431)
Excluding compensation related to stock options	(3,421)	123	(183)	132
Excluding restructuring activities	—	1,803	—	1,803
Proforma loss from operations	$ (24,761)	$ (17,594)	$ (43,858)	$ (36,496)

Condensed Balance Sheets
(In Thousands)

	June 30, 2004	December 31, 2003
	(Unaudited)	
Assets:		
Current assets	$ 182,292	$ 239,561
Property, plant and equipment, net	32,172	34,790
Other assets	65,498	60,591
Total assets	$ 279,962	$ 334,942

Liabilities and stockholders' equity:		
Current liabilities	$ 42,132	$ 45,557
5.5% convertible subordinated notes	125,000	125,000
Long-term obligations, net of current portion	99,033	88,397
Long-term deferred revenue, net of current portion	2,186	8,810
Stockholders' equity	11,611	67,178
Total liabilities and stockholders' equity	$ 279,962	$ 334,942

####