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): **October 27, 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**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

o Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

o Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

o Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

o Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Item 2.02. Results of Operations and Financial Condition.

On October 27, 2004, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter ended September 30, 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, 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 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 2.02. 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.

Item 9.01. Financial Statements and Exhibits.

(c) Exhibits.

99.1 Press Release dated October 27, 2004.

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: October 26, 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 October 27, 2004.

ISIS PHARMACEUTICALS REPORTS THIRD QUARTER 2004 FINANCIAL RESULTS AND HIGHLIGHTS

Company Reports Lilly-Sponsored Phase 3 Clinical Trial of Affinitak for Non-small Cell Lung Cancer Does Not Meet Primary Endpoint

CARLSBAD, Calif., October 27, 2004 — Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced financial results for the third quarter of 2004. The company's loss from operations was $22.4 million and $66.1 million for the three and nine months ended September 30, 2004, respectively, compared to $19.1 million and $57.5 million for the same periods in 2003, according to generally accepted accounting principles (GAAP). The company's proforma loss from operations was $22.8 million and $66.7 million for the three and nine months ended September 30, 2004, respectively, compared to $18.3 million and $54.8 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 nine months ended September 30, 2004 was $9.1 million and $31.2 million, respectively, compared to $11.3 million and $40.3 million for the same periods in 2003. The decrease in revenue primarily reflects the completion of Isis' Phase 3 clinical trial of Affinitak(TM) with an associated reduction in revenue, offset in part by increased revenue from the company's alliances, particularly with: government agencies relating to its TIGER biosensor program; Alnylam Pharmaceuticals, Inc; and Eli Lilly and Company.

Expenses

Isis' operating expenses were $31.5 million and $97.3 million for the three and nine months ended September 30, 2004, respectively, compared to $30.4 million and $97.8 million for the same periods in 2003, according to GAAP. Included in operating expenses was non-cash compensation benefit related to stock options of $466,000 and $649,000 for the three and nine months ended September 30, 2004, respectively, compared to non-cash compensation expense of $804,000 and $936,000 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 $31.9 million and $97.9 million for the three and nine months ended September 30, 2004, respectively, compared to $29.6 million and $95.1 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, a restructuring charge. The nominal increase in operating expenses on a proforma basis was primarily due 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 nine months ended September 30, 2004 was $32.7 million or $0.57 per share, and $85.3 million or $1.51 per share, respectively, compared with a net loss applicable to common stock of $22.4 million or $0.40 per share, and $70.1 million or $1.27 per share, for the same periods in 2003. The increase in the net loss applicable to common stock was the result of the increase in loss from operations, as well as a non-cash loss on investments of $5.1 million principally related to the impairment of the company's equity investment in Alnylam. The impairment reflects the decrease in the market value of Alnylam's stock, which we believe is primarily a result of current financial market conditions related to biotechnology companies. The impairment does not reflect any change in Isis' confidence that Alnylam w ill continue to be the center of excellence in RNAi or in our belief that the combination of Isis' intellectual property and development expertise and Alnylam's intellectual property and research expertise in RNAi therapeutics will make significant progress in developing promising RNAi drugs. The alliance, established in 2004, provides Isis with an opportunity to realize substantial value from its pioneering work in antisense mechanisms and oligonucleotide chemistry and is an example of Isis' strategy to participate in all areas of RNA-based drug discovery. Isis licensed to Alnylam its patents relating to antisense mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5 million technology access fee, participation in fees from Alnylam's partnering programs, as well as downstream milestone and royalty payments. In the second quarter of 2004, Isis earned $500,000 from Alnylam related to Alnylam's alliance with Merck, the first payment to Isis from Alnylam's partnering programs under the strategic alliance.

Balance Sheet

Isis ended the third quarter with $125.6 million in cash and short-term investments and working capital of $116.5 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 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. The proceeds from this loan were used to retire partner debt in 2003 and early 2004.

"We are on-track to achieve our financial goals for 2004 and remain in a solid financial position that will allow us to continue to strategically invest our resources in our most promising antisense drug candidates and technologies," said B. Lynne Parshall, Chief Financial Officer of Isis.

"Our broad collaboration with Lilly continues its strong momentum and in the third quarter of 2004, Lilly licensed an additional second-generation anti-cancer drug resulting from this alliance. We also reported additional compelling data from Isis' pipeline of second-generation drugs this quarter, and were pleased to add an exciting new drug to our proprietary anti-cancer franchise. We look forward to the achievement of multiple key milestones in our pipeline before the end of 2004," continued Ms. Parshall.

Lilly-Sponsored Phase 3 Affinitak Lung Efficacy Registration Trial (ALERT)

Isis reported today the results of a Phase 3 clinical trial of Affinitak in combination with Gemzar® (gemcitabine HCl) and cisplatin in patients with non-small cell lung cancer (NSCLC). Findings from this trial, which was sponsored by Eli Lilly and Company (NYSE: LLY), are similar to the results of an initial Isis-sponsored Phase 3 study of Affinitak for NSCLC reported by the companies in 2003. In this latest study, patients in both treatment arms, those receiving Affinitak along with Gemzar and cisplatin and those receiving the chemotherapy alone, experienced equivalent median survival, the primary endpoint of the trial, of approximately 10 months. The addition of Affinitak to Gemzar and cisplatin was adequately tolerated. The safety profile of Affinitak in combination with the chemotherapy regimen was consistent with that observed in the previous Phase 3 trial.

Lilly Collaboration Strong and Advances an Additional Second-Generation Antisense Drug

The Lilly / Isis broad strategic collaboration to discover new antisense drugs continues to succeed in moving drugs forward in development:

- In September 2004, Lilly licensed a second antisense anti-cancer drug from Isis, LY2275796. LY2275796 targets eukaryotic initiation factor- 4E (eIF-4E), a protein involved in tumor progression, angiogenesis and metastases. Isis earned a $750,000 payment from Lilly for the license.

- Lilly plans to initiate Phase 1 trials of LY2181308, the first antisense anti-cancer drug licensed from Isis under the companies' antisense drug discovery collaboration, later this year. LY2181308 targets survivin, a molecule that allows the survival of cells that would normally undergo programmed cell death.

The companies are optimistic that additional antisense drug candidates incorporating Isis' advanced chemistries will emerge from the alliance in cancer, and in metabolic and inflammatory diseases.

In addition to its drug discovery partnership with Lilly, Isis is participating in two other collaborations that are focused on identifying new second-generation antisense anti-cancer drugs.

Isis' Robust Pipeline of Second-Generation Drugs Continues to Move Forward and Expand

Third quarter highlights include:

- In August 2004, Isis reported preliminary data from a Phase 1 trial of ISIS 301012, a second-generation antisense inhibitor of apoB-100, at the 9th Drug Discovery Technology World Congress in Boston. ISIS 301012 produced dose-dependent, rapid and prolonged reductions of its target, apoB-100, in low density lipoprotein (LDL), very low density lipoprotein (VLDL) and total cholesterol levels in normal volunteers with borderline elevated cholesterol. ApoB-100 is the molecular carrier of LDL and VLDL cholesterol, the "bad" cholesterol involved in heart disease.

- In September 2004, Isis continued to expand its pipeline of second-generation antisense drugs by adding a new anti-cancer drug, ISIS 345794. ISIS 345794 targets STAT-3, a protein that regulates cell division and growth, and prevents cell death. Preclinical studies of ISIS 345794 showed that antisense inhibition significantly delayed tumor growth and

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increased the rate of cancer cell death in multiple cell and animal models of cancer. Data on ISIS 345794 was presented at the Advances in Cancer Therapies 2004 meeting in London, England. Isis intends to rapidly move ISIS 345794 into clinical development, and anticipates initiating clinical trials in patients with cancer in 2005.

TIGER Program Awarded New Contracts

In October 2004, Isis' Ibis program was granted three new government contracts valued at up to $10 million for the continued development of its TIGER biosensor technology.

A key highlight of these new contracts is funding from the NIAID (National Institute of Allergy and Infectious Disease), part of the National Institutes of Health, to develop a TIGER application aimed at ensuring vaccine safety. Currently, there are few tests available that can specifically address safety issues unique to cell substrates used in vaccine manufacturing, such as the identification of unknown or novel microbes that have the potential to contaminate vaccine cell lines and substrates. Successful development of an application to simultaneously identify a broad array of infectious agents in vaccine cell substrates would create a new commercial prospect for the biosensor. Together with prior awards, Ibis has received contracts for up to $65 million in funding from several government entities, including DARPA, the CDC, the NIH, the FBI, NIST and USAMRIID.

Patent Portfolio Continues to Provide New Opportunities

In October 2004, Isis announced that it had expanded its strong intellectual property position in RNA-based drug discovery by licensing core intellectual property regarding therapeutic uses of microRNA (miRNA) from the Max Planck Society. miRNAs play a central role in the regulation of gene expression in mammalian cells, and abnormalities in their function may play a role in human diseases. Isis' main miRNA research effort is based in its Singapore lab, which is focused on discovering new miRNA drugs.

Upcoming Pipeline Events

Isis and its partners plan to report data from several 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 data from a Phase 2 study of ISIS 14803 (target: HCV) in combination with current therapy in patients with HCV infection who have failed current therapy

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

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 Antisense Therapeutics Limited)
- Phase 1 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)

ABOUT ISIS PHARMACEUTICALS, INC.

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 12 antisense products in development to treat metabolic, cardiovascular, inflammatory, and viral diseases, and cancer. Through its Ibis Therapeutics(R) 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 1,400 issued patents worldwide. Additional information about Isis is available at 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, and quarterly report on Form 10-Q for the quarter ended June 30, 2004, which are on file with the U.S. Securities and Exchange Commission. Copies of these and other documents are available from the company.

Affinitak™ is a trademark of Eli Lilly and Company.

Gemzar® is registered trademark of Eli Lilly and Company.

Ibis Therapeutics® is a registered trademark of Isis Pharmaceuticals, Inc.

FINANCIAL TABLES

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

	Three months ended, September 30,		Nine months ended, September 30,	
	2004	2003	2004	2003
	(unaudited)		(unaudited)	
Revenue:				
Research and development revenue under collaborative agreements	$ 9,055	$ 11,263	$ 24,270	$ 39,944
Licensing revenue	38	31	6,969	347
Total revenue	9,093	11,294	31,239	40,291
Expenses:				
Research and development	29,566	27,410	90,549	87,849
General and administrative	2,373	2,147	7,394	7,201
Compensation related to stock options	(466)	804	(649)	936
Restructuring activities	—	—	—	1,803
Total operating expenses	31,473	30,361	97,294	97,789
Loss from operations	(22,380)	(19,067)	(66,055)	(57,498)
Investment and other income	561	1,177	2,536	3,980
Interest expense	(5,832)	(4,313)	(16,387)	(13,665)
Loss on investments	(5,057)	—	(5,057)	(2,438)
Net loss	(32,708)	(22,203)	(84,963)	(69,621)
Accretion of dividends on preferred stock	—	(175)	(361)	(518)
Net loss applicable to common stock	$ (32,708)	$ (22,378)	$ (85,324)	$ (70,139)
Basic and diluted net loss per share	$ (0.57)	$ (0.40)	$ (1.51)	$ (1.27)

Shares used in computing basic and diluted net loss per share	57,267	55,540	56,415	55,418

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

	Three months ended, September 30,		Nine months ended, September 30,	
	2004	2003	2004	2003
	(unaudited)		(unaudited)	
As reported operating expenses according to GAAP	$ 31,473	$ 30,361	$ 97,294	$ 97,789
Excluding compensation related to stock options	(466)	804	(649)	936
Excluding restructuring activities	—	—	—	1,803
Proforma operating expenses	$ 31,939	$ 29,557	$ 97,943	$ 95,050
As reported loss from operations according to GAAP	$ (22,380)	$ (19,067)	$ (66,055)	$ (57,498)
Excluding compensation related to stock options	(466)	804	(649)	936
Excluding restructuring activities	—	—	—	1,803
Proforma loss from operations	$ (22,846)	$ (18,263)	$ (66,704)	$ (54,759)

Condensed Consolidated Balance Sheets
(In Thousands)

	September 30, 2004	December 31, 2003
	(Unaudited)	
Assets:		
Current assets	$ 159,355	$ 239,561
Property, plant and equipment, net	30,857	34,790
Other assets	65,059	60,591
Total assets	$ 255,271	$ 334,942
Liabilities and stockholders' equity:		
Current liabilities	$ 42,897	$ 45,557
5.5% convertible subordinated notes	125,000	125,000
Long-term obligations, net of current portion	104,369	88,397
Long-term deferred revenue, net of current portion	644	8,810
Stockholders' equity (deficit)	(17,639)	67,178
Total liabilities and stockholders' equity (deficit)	$ 255,271	$ 334,942

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