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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): **November 8, 2005**

### **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.)

**1896 Rutherford Road**

**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:

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
  - Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
  - Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
  - Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))
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#### **Item 2.02. Results of Operations and Financial Condition.**

On November 8, 2005, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter ended September 30, 2005. 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 non-cash compensation related to stock options and costs associated with restructuring activities. 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 November 8, 2005.

#### **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.

Dated: November 8, 2005

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

INDEX TO EXHIBITS

99.1 Press Release dated November 8, 2005.

Contact: Elizabeth Hougen, Vice President, Finance  
 Claudine Prowse, Ph.D., Director, Investor Relations  
 Isis Pharmaceuticals, 760-603-2331  
<http://www.isispharm.com>

**ISIS PHARMACEUTICALS REPORTS FINANCIAL RESULTS AND HIGHLIGHTS  
 FOR THE THIRD QUARTER 2005**

*Company Strengthens Financial Position While Advancing Pipeline and TIGER Biosensor System*

**CARLSBAD, CA, November 8, 2005** — Isis Pharmaceuticals, Inc. (Nasdaq: ISIS), today announced its financial results for the third quarter of 2005. The Company's proforma loss from operations decreased significantly to \$12.5 million and \$41.8 million for the three and nine months ended September 30, 2005, respectively, compared to a proforma loss from operations of \$22.8 million and \$66.7 million for the same periods in 2004. The Company's loss from operations for the three and nine months ended September 30, 2005 was \$12.1 million and \$48.6 million, respectively, compared to \$22.4 million and \$66.1 million for the same periods in 2004, according to GAAP. The significant decrease in the Company's proforma loss from operations in 2005 was principally a result of cost savings achieved through its reorganization earlier this year, which focused its resources on key programs. The Company expects, consistent with previous guidance, that its 2005 proforma loss from operations will be in the low \$50 million range. The adjustment from GAAP to pro forma loss from operations is discussed under "Expenses" below and illustrated in the Selected Financial Information included in this press release.

**Revenue**

Total revenue for the three and nine months ended September 30, 2005 was \$7.5 million and \$25.5 million, respectively, compared to \$9.1 million and \$31.2 million for the same periods in 2004. Isis' revenue fluctuates from period to period based on the nature and timing of license fees, milestone-related payments and other payments under agreements with its partners. The decrease in revenue for the first nine months of 2005 compared to the same period in 2004 was primarily a result of more revenue from one-time license fees and milestone payments in the first nine months of 2004 than in the corresponding period in 2005. In the first nine months of 2005, Isis has earned \$2 million in upfront fees and milestone payments in connection with its ocular disease collaboration with Pfizer. In addition, in 2005 compared to 2004, Isis purchased less equipment under government contracts, which also contributed to the Company's decrease in revenue year to year. The cost of equipment purchased under government contracts is billable to the government. A more detailed explanation follows below under "Isis' Ibis Division".

**Expenses**

Operating expenses on a proforma basis for the three and nine months ended September 30, 2005 decreased significantly to \$19.9 million and \$67.3 million, respectively, compared to \$31.9 million and \$97.9 million for the same periods in 2004. These results represent a decrease of more than 30% in the Company's expenses for the first nine months of 2005. The decrease in operating expenses on a proforma basis for the three and nine months ended September 30, 2005 compared to the same periods in 2004 reflects the impact of the Company's cost containment measures implemented during the first quarter of 2005. Isis' operating expenses, according to GAAP, also reflect this significant decrease and were \$19.6 million and \$74.1 million for the three and nine months ended September 30, 2005, respectively, compared to \$31.5 million and \$97.3 million for the same periods in 2004.

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As illustrated in the Selected Financial Information in this press release, Isis' proforma operating expenses and loss from operations were adjusted from GAAP to exclude non-cash compensation related to stock options and costs associated with restructuring activities. This adjustment consisted of a non-cash compensation benefit of \$613,000 for the nine months ended September 30, 2005, compared to a non-cash compensation benefit of \$649,000 for the same period in 2004. Variable accounting for stock options can result in significant increases and decreases in non-cash compensation expense related to stock options as a result of the variability in the Company's stock price. The adjustment for the first nine months of 2005 also included \$7.4 million of costs associated with restructuring activities, primarily employee termination costs, building consolidation costs and costs related to the closure of Isis' Singapore laboratory.

**Net Loss**

The Company's net loss applicable to common stock for the three and nine months ended September 30, 2005 decreased to \$15.2 million or \$0.24 per share, and \$64.5 million or \$1.08 per share, respectively, compared with a net loss applicable to common stock of \$32.7 million or \$0.57 per share, and \$85.3 million or \$1.51 per share, for the same periods in 2004. The decrease in net loss applicable to common stock was primarily the result of the decrease in the Company's loss from operations. In addition, in 2004, the Company recorded a one-time non-cash loss on investments of \$5.1 million principally related to the impairment of the Company's equity investment in Alnylam Pharmaceuticals, Inc. Alnylam's stock is currently trading significantly above its 2004 levels, which Isis believes reflects Alnylam's leading position in the field of RNAi. Offsetting, in part, the decrease in net loss applicable to common stock was an increase in interest expense due to the effect of a higher debt balance in 2005 compared to 2004 and a decrease in investment income due to the Company's lower average cash and short-term investments balance in 2005 compared to 2004.

**Isis' Ibis Division**

To develop TIGER technology and applications, Isis' Ibis division receives contracts and grants from government agencies. Ibis generated revenue from these contracts of \$3.4 million and \$8.7 million for the three and nine months ended September 30, 2005, respectively, compared to revenue of \$2.2 million and \$8.9 million for the same periods in 2004. Operating expenses for Ibis were \$3.5 million and \$10.3 million for the three and nine months ended September 30, 2005 compared to \$3.0 million and \$11.2 million for the same periods in 2004. During the first nine months of 2004, Ibis acquired equipment to build multiple TIGER systems for deployment to its government partners. This resulted in \$3.1 million in revenue and associated expense in the first nine months of 2004 compared to \$959,000 in revenue and associated expense for the same period in 2005. Ibis deployed its first TIGER system in August 2005, and plans to deploy additional systems to its government partners this year. Ibis' revenue, adjusted to exclude the equipment purchases, was \$7.7 million and \$5.8 million for the first nine months of 2005 and 2004, respectively. The increase in Ibis' adjusted revenue from the first nine months of 2004 to the same period in 2005 is a direct result of revenue from new government contracts awarded to Ibis in 2005. During the three and nine months ended September 30, 2005, Ibis generated a loss from operations of \$97,000 and \$1.6 million, respectively, compared to \$803,000 and \$2.3 million for the same periods in 2004. The decrease in the loss from operations from the first nine months of 2005 compared to the same period in 2004 was primarily related to a change in the mix

of expenses being funded by the government that increased funding for internal labor (and decreased funding for equipment purchases). Resulting in an increase in the utilization of internal labor under contracts and leaving less Ibis internal labor expense unfunded.

## **Balance Sheet**

During the third quarter of 2005, Isis took several important steps to strengthen its balance sheet. First, in August 2005, Isis received \$48.2 million in net proceeds from a private placement of 12 million shares of its common stock. The proceeds from the private placement will be used to meet the Company's operating needs. Isis further strengthened its balance sheet by converting the interest-free \$100.0 million loan that Eli Lilly and Company provided to Isis to fund their research collaboration into 2.5 million

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shares of common stock. The impact to the balance sheet was reflected in the Company's financial results as a reduction in long-term debt and an increase in stockholders' equity. In addition, in the second and third quarters of 2005, Isis successfully sold three of its buildings as it consolidated facilities. In these transactions, Isis received \$7.9 million of net proceeds and repaid \$5.8 million of debt. Isis further strengthened its financial position by selling a portion of its Alnylam stock resulting in net proceeds of approximately \$2.6 million.

Isis ended the quarter with cash, cash equivalents and short-term investments of \$101.7 million and working capital of \$90.3 million. At December 31, 2004, Isis had cash, cash equivalents and short-term investments of \$103.9 million and working capital of \$82.2 million. Cash, cash equivalents and short-term investments decreased primarily as a result of cash used in operations offset by the proceeds received from the private offering. Quarter-to-quarter operating cash usage decreased from \$23.2 million in the second quarter to \$15.0 million in the third quarter reflecting the full impact of Isis' cost reduction measures. The cost containment measures the Company implemented during the first quarter of 2005 should continue to maintain this decreased cash use throughout the remainder of 2005.

"This quarter we successfully implemented various pieces of our financial strategy in balancing equity and corporate partnering to create the optimal mix of funding to support the execution of our goals," said B. Lynne Parshall, Isis' Executive Vice President and CFO. "First, we fortified the Company's cash position with the private placement, which added \$48.2 million to our balance sheet. This financing provides us with the capital necessary to negotiate potential drug discovery and development collaborations and licensing arrangements from a position of financial strength. In addition, we further strengthened our balance sheet with the conversion of our \$100 million loan from Lilly, which is now reflected in our third quarter financials. Finally, we successfully sold three of our buildings, sold a portion of our Alnylam stock, and continue to realize a significant reduction in our cash burn as a result of the corporate restructuring we implemented earlier this year."

"We also continued to benefit from our satellite company strategy that allows us to leverage our intellectual property portfolio. The \$7 million payment from Drug Royalty USA, Inc. as partial payment for the monetization of Isis' royalty rights in Macugen®, and the approximate \$4 million payment from Alnylam associated with its newly announced collaboration with Novartis illustrate that this strategy is continuing to provide us financial value," Ms. Parshall added.

"Thanks to the continued funding from our government partners, we continue to develop TIGER without significant cost to our shareholders. Importantly, with the addition of \$12.5 million in new government grants and contracts this year, we are accelerating our applications development in ways we believe will be important not only to government customers but also to non-government commercial customers. The successful deployment of our first TIGER system to one of our government partners in August demonstrates that we are meeting important milestones in our commercialization plan for TIGER. These advances, combined with the steady progress in the clinical development of our antisense pipeline demonstrate that Isis has an extremely rich portfolio of assets to exploit," Ms. Parshall said.

### **2005 Third Quarter Highlights and Recent Accomplishments**

#### **Isis Executes Financial Strategy and Strengthens Cash Position**

*Historically, Isis has funded the Company through a combination of licensing, corporate partnerships and equity to invest in its' robust pipeline, the TIGER biosensor system, and intellectual property estate. The Company announced several achievements demonstrating the successful execution of this financial strategy in the third quarter of 2005:*

- Significantly increased cash position by raising \$51 million (\$48.2 million in net proceeds) in a private placement of 12 million shares of Isis' common stock at a price of \$4.25 per share.

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- Reduced long-term debt and increased stockholders' equity by converting the \$100 million interest-free loan provided by Lilly into 2.5 million shares of Isis common stock.
- Increased cash position and reduced debt by completing the sale of three of its real properties, receiving net proceeds of approximately \$7.9 million and reducing \$5.8 million of debt.
- Further increased cash by capitalizing on the value of its extensive patent estate, receiving \$7 million from Drug Royalty USA, Inc. (DRC) as partial payment for a portion of Isis' royalty rights in Macugen.
- Earned additional revenue by benefiting from its satellite company strategy and intellectual property licensing, receiving nearly \$4 million under Alnylam's recent collaboration with Novartis for the development of RNAi therapeutics.
- Earned additional revenue from corporate partnerships, receiving \$2 million in upfront fees and milestones over the first nine months of 2005 in connection with its ophthalmology collaboration with Pfizer.

#### **Isis and Partners Advance Development of Second-generation Antisense Drugs**

**ISIS 301012**

- Initiated Phase 2 development program of ISIS 301012 for the lowering of high cholesterol. ISIS 301012 has potential to be used as an add-on therapy to lower cholesterol in patients who cannot reach their therapeutic target or as an alternative for patients who are not tolerating currently available therapies. In the third quarter, Isis:
  - Initiated a Phase 2 study to optimize dose and frequency of dosing of ISIS 301012 and to further evaluate the safety and efficacy of ISIS 301012, in patients with high cholesterol.
  - Initiated a Phase 2 combination study to evaluate the safety and efficacy of ISIS 301012 in combination with simvastatin, in patients with high cholesterol.
- Presented data from a Phase 1 study in which ISIS 301012 produced rapid reductions of its target, apoB-100, with concomitant reductions in LDL-C. In less than one month following dosing, normal volunteers with mildly elevated cholesterol, who were treated with an average of 350mg/week of ISIS 301012 for one month, achieved a median reduction of 60% in apoB-100 and a median reduction of 54% in LDL-C.

**OGX-011**

- OncoGenex initiated four Phase 2 studies of OGX-011 for the treatment of prostate, non-small cell lung and breast cancers.

**ATL1101**

- Antisense Therapeutics, Inc. reported results from its “proof of concept” study of ATL1101 in patients with psoriasis. ATL1101 demonstrated activity in the psoriasis patients and was well tolerated.

**iCo: ISIS 13650**

- Isis continued to expand the reach of antisense technology and fostering new partner relationships by licensing ISIS 13650 to iCo. The company will initially develop ISIS 13650 for the treatment of various eye diseases caused by the formation of new blood vessels such as age-related macular degeneration (AMD) and diabetic retinopathy.

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**Lilly: Signal Transducer and Activator of Transcription 3(STAT-3)**

- Extended the four-year drug discovery collaboration with Lilly to continue to collaborate on mutually agreed targets for approximately 24 months. As part of the extended collaboration, a second-generation antisense inhibitor targeting STAT-3 was added to the pipeline of Lilly’s two other second-generation antisense oncology drugs in development.

**Isis’ Ibis Division Executes Commercialization Plans for TIGER Biosensor System**

***Ibis division meets major business milestones and continues applications development with government funding.***

- Meets major milestone in achieving commercialization plan by shipping its first TIGER biosensor system to the United States Army Medical Research Institute for Infectious Disease, who will use it for biowarfare defense.
- Received additional government contracts and grants for approximately \$11.0 million from several government agencies to support the initial operations of the TIGER biosensor system and continue advancing the development of applications for infectious disease diagnostics, hospital-associated infection control, biowarfare defense, and microbial forensics. The grants also included funding to support further enhancement of the Microbial Rosetta Stone (MRS) database.

Isis will conduct a live webcast conference call to discuss this earnings release on Tuesday, November 8 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 a limited time.

**ABOUT ISIS PHARMACEUTICALS, INC.**

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel drugs for its product pipeline and for its partners. The Company has successfully commercialized the world’s first antisense drug and has 12 antisense drugs in development to treat metabolic, cardiovascular, ocular and inflammatory diseases, and cancer. In its Ibis division, Isis is developing and commercializing the TIGER biosensor system, a revolutionary system to identify infectious organisms. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of approximately 1,500 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 Isis Pharmaceuticals’ business, the financial position of Isis, and the therapeutic and commercial potential of the Company’s technologies and products in development. Any statement describing Isis’ 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’ goals. 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, in developing and commercializing systems to identify infectious organisms that are effective and commercially attractive, and in the endeavor of building a business around such products. Isis’ forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis’ forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis’ programs are described in additional

Macugen® is a registered trademark of Eyetech Pharmaceuticals, Inc.

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**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,	
	2005	2004	2005	2004
	(unaudited)		(unaudited)	
<b>Revenue:</b>				
Research and development revenue under collaborative agreements	\$ 7,122	\$ 9,055	\$ 24,695	\$ 24,270
Licensing and royalty revenue	336	38	797	6,969
<b>Total revenue</b>	<b>7,458</b>	<b>9,093</b>	<b>25,492</b>	<b>31,239</b>
<b>Expenses:</b>				
Research and development	18,212	29,566	61,523	90,549
General and administrative	1,724	2,373	5,771	7,394
Compensation expense/(benefit) related to stock options	15	(466)	(613)	(649)
Restructuring activities	(349)	—	7,385	—
<b>Total operating expenses</b>	<b>19,602</b>	<b>31,473</b>	<b>74,066</b>	<b>97,294</b>
<b>Loss from operations</b>	<b>(12,144)</b>	<b>(22,380)</b>	<b>(48,574)</b>	<b>(66,055)</b>
Investment and other income	1,241	561	2,095	2,536
Interest expense	(4,269)	(5,832)	(18,009)	(16,387)
Loss on investments	—	(5,057)	—	(5,057)
<b>Net loss</b>	<b>(15,172)</b>	<b>(32,708)</b>	<b>(64,488)</b>	<b>(84,963)</b>
Accretion of dividends on preferred stock	—	—	—	(361)
<b>Net loss applicable to common stock</b>	<b>\$ (15,172)</b>	<b>\$ (32,708)</b>	<b>\$ (64,488)</b>	<b>\$ (85,324)</b>
<b>Basic and diluted net loss per share</b>	<b>\$ (0.24)</b>	<b>\$ (0.57)</b>	<b>\$ (1.08)</b>	<b>\$ (1.51)</b>
Shares used in computing basic and diluted net loss per share	64,086	57,267	59,734	56,415

**Ibis Division Statements of Operations**

	Three months ended, September 30,		Nine months ended, September 30,	
	2005	2004	2005	2004
	(unaudited)		(unaudited)	
Revenue	\$ 3,429	\$ 2,189	\$ 8,651	\$ 8,949
Operating expenses	3,526	2,992	10,254	11,221
<b>Loss from operations</b>	<b>(97)</b>	<b>(803)</b>	<b>(1,603)</b>	<b>(2,272)</b>

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

	Three months ended, September 30,		Nine months ended, September 30,	
	2005	2004	2005	2004
	(unaudited)		(unaudited)	
<b>As reported operating expenses according to GAAP</b>	<b>\$ 19,602</b>	<b>\$ 31,473</b>	<b>\$ 74,066</b>	<b>\$ 97,294</b>
Excluding compensation (expense)/benefit related to stock options	(15)	466	613	649
Excluding restructuring activities	349	—	(7,385)	—
<b>Proforma operating expenses</b>	<b>\$ 19,936</b>	<b>\$ 31,939</b>	<b>\$ 67,294</b>	<b>\$ 97,943</b>

<b>As reported loss from operations according to GAAP</b>	\$	(12,144)	\$	(22,380)	\$	(48,574)	\$	(66,055)
Excluding compensation (expense)/benefit related to stock options		(15)		466		613		649
Excluding restructuring activities		349		—		(7,385)		—
<b>Proforma loss from operations</b>	\$	<u>(12,478)</u>	\$	<u>(22,846)</u>	\$	<u>(41,802)</u>	\$	<u>(66,704)</u>

**Condensed Balance Sheets  
(In Thousands)**

	<u>September 30, 2005</u>	<u>December 31, 2004</u>
	<u>(Unaudited)</u>	
<b>Assets:</b>		
Current assets	\$ 114,242	\$ 125,609
Property, plant and equipment, net	10,181	28,454
Other assets	52,959	54,362
<b>Total assets</b>	<b>\$ 177,382</b>	<b>\$ 208,425</b>
<b>Liabilities and stockholders' equity (deficit):</b>		
Current liabilities	\$ 23,905	\$ 43,416
5.5% convertible subordinated notes	125,000	125,000
Long-term obligations, net of current portion	16,845	111,611
Long-term deferred revenue, net of current portion	92	531
Common stock warrants	7,500	—
Stockholders' equity (deficit)	4,040	(72,133)
<b>Total liabilities and stockholders' equity (deficit)</b>	<b>\$ 177,382</b>	<b>\$ 208,425</b>

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