UNITED STATES
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): **March 8, 2007**

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.)

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:

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 March 8, 2007, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter and fiscal year ended December 31, 2006. 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, including stock compensation related to the variable accounting of 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.

(d) Exhibits.

99.1	Press Release dated March 8, 2007.

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: March 7, 2007

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

INDEX TO EXHIBITS

99.1	Press Release dated March 8, 2007.

ISIS PHARMACEUTICALS REPORTS FINANCIAL RESULTS AND HIGHLIGHTS FOR FISCAL YEAR 2006

Isis Significantly Strengthens Balance Sheet and Advances Pipeline

· **Conference Call Webcast Thursday, March 8, 11:00 am EST at www.isispharm.com**

Carlsbad, Calif., March 8, 2007 - - Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced its financial results for the year ended December 31, 2006. The Company's loss from operations for 2006 was $68.1 million compared to $57.2 million in 2005, according to GAAP. The Company's increase in loss from operations in 2006 compared to the same period in 2005 was principally a result of lower revenue in 2006 compared to 2005 offset in part by cost savings resulting from the Company's focus on its key programs.

Isis' pro forma loss from operations was $62.9 million for 2006, compared to $50.8 million for 2005, and was slightly higher than the Company's guidance of a pro forma loss from operations in the high $50 million range as a result of lower than expected revenue as described in more detail below under "Revenue." The Company's pro forma operating expenses were in line with its guidance. The reasons for the Company's increase in its pro forma loss from operations in 2006 compared to the same period in 2005 were the same as those for the increase in the Company's loss from operations according to GAAP.

As illustrated in the Selected Financial Information in this press release, Isis' pro forma operating expenses and loss from operations were adjusted from GAAP to exclude non-cash compensation related to stock options, including stock compensation related to the variable accounting of stock options, and costs associated with restructuring activities. Isis has regularly reported non-GAAP measures for operating expenses and loss from operations as pro forma results. These measures are provided as supplementary information and are not a substitute for financial measures calculated in accordance with GAAP. Isis reports pro forma results excluding certain items primarily related to stock option expense/benefit, which are non-cash, and restructuring activities, which are not part of ongoing operations. Isis reports these pro forma results to better enable financial statement users to assess its historical performance and project its future operating results and cash flows. Further, the presentation of Isis' pro forma results is consistent with how Isis' management internally evaluates the performance of its operations.

Revenue

Total revenue for the quarter and year ended December 31, 2006 was $11.9 million and $24.5 million, respectively, compared to $14.6 million and $40.1 million for the same periods in 2005. The decrease in revenue for 2006 compared to 2005 was primarily due to a decrease in revenue associated with Isis' collaboration with Eli Lilly and Company. This ongoing collaboration was extended in August 2005 to focus on a select number of targets. Isis' revenue fluctuates based on the nature and timing of payments under agreements with the Company's partners, including license fees, milestone-related

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payments and other payments, including those for drugs the Company manufactures for its partners. For example, Isis earned revenue in 2006 of $750,000 and revenue of $3.7 million in 2005 from Alnylam Pharmaceuticals, Inc. when Alnylam sublicensed Isis' technology to pharmaceutical partners for the development of RNA interference therapeutics. In addition, in the fourth quarter of 2005 and 2006, in accordance with agreed upon timing, Isis earned $7.0 million and $8.0 million, respectively, of revenue from Drug Royalty USA, Inc. as partial payment for the acquisition of a part of Isis' royalty rights in Macugen®.

Ibis Biosciences, Inc., formerly a division of Isis and now a wholly owned subsidiary, met a significant milestone in commercializing the Ibis T5000™ Biosensor System by achieving its first commercial sales and revenue in the second half of 2006. Ibis continues to earn most of its revenue from government contracts. Ibis' government contract revenue fluctuates as described below under "Ibis Biosciences, Inc."

Expenses

Operating expenses on a pro forma basis for the quarter and year ended December 31, 2006 were $27.2 million and $87.4 million, respectively, compared to $23.6 million and $90.9 million for the same periods in 2005. These results represent a decrease of approximately 4% in the Company's pro forma operating expenses for 2006 compared to 2005 and were in line with the Company's guidance of pro forma operating expenses of approximately $88 million. Isis' operating expenses, according to GAAP, also decreased in 2006 compared to 2005 and were $28.7 million and $92.7 million for the three and twelve months ended December 31, 2006, respectively, compared to $23.2 million and $97.3 million for the same periods in 2005. The cost savings achieved through the Company's increased focus led to a decrease of $4.6 million in the Company's operating expenses, which included compensation related to stock options for 2006 of $5.7 million and a benefit related to the variable accounting of stock options of $544,000 in 2005. Excluding these two non-cash items related to stock options, the Company's operating expenses were $10.8 million, or 11%, lower in 2006 than in 2005, primarily due to decreases in expenditures in 2006 following the Company's 2005 restructuring.

Beginning in the first quarter of 2006, Isis included in its operating results non-cash compensation expense related to stock options as required by Statement of Financial Accounting Standards No. 123R, *Share-Based Payment* (SFAS 123R), which, for 2006, was $5.7 million. Prior to 2006, the Company's operating expenses included non-cash compensation benefit or expense as a result of variable accounting for stock options, which, for 2005, was a benefit of $544,000. The adjustment to pro forma operating expenses for 2006 and 2005 also included a benefit of $536,000 and expense of $7.0 million, respectively, associated with restructuring activities.

Ibis Biosciences, Inc.

During 2006, Ibis achieved important milestones in implementing its commercial plan, including receiving its first commercial order for two Ibis T5000 Biosensor Systems, one of which was delivered in late 2006 and the second of which Ibis expects to deliver early in 2007. Additionally, in 2006, Ibis received a contract worth up to $1.9 million to analyze samples in its assay services laboratory. As a result of these achievements, Ibis earned 2006 commercial revenue of $556,000. Because Ibis provides a full year of support for each Ibis T5000 Biosensor System following installation, Ibis is amortizing the revenue

for each instrument sold over the period of this support obligation. Ibis generated revenue from its government contracts and grants of $1.5 million and $9.1 million for the three months and year ended December 31, 2006, respectively, compared to $3.1 million and $11.8 million for the same periods in 2005. Ibis' revenue from government contracts fluctuates based on when the contracts are

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awarded, the period of performance for the contracts, the funding amount of the contracts, the labor rates applicable to the activities under the contract, and the timing and type of these activities. For example, in 2006, two large government contracts that were active in 2005 ended and were replaced with several new, but smaller contracts, resulting in reduced revenue in 2006 compared to 2005. Additionally, the average labor rate that Ibis charged its government partners in 2006 was lower than in 2005, which also contributed to Ibis' reduced revenue in 2006 compared to 2005. During the fourth quarter of 2006, Ibis announced that it had successfully completed the first phase of its Challenge Grant from the National Institute of Allergy and Infectious Diseases, a part of the National Institutes of Health, and had been granted funding for subsequent phases that provide for the installation of an Ibis T5000 Biosensor System at Johns Hopkins University Medical Center. Ibis expects that this additional funding, combined with extensions of other existing contracts and new contracts will be the basis for Ibis' revenue from government contracts in 2007.

Excluding non-cash compensation expense related to stock options, operating expenses for Ibis were $4.9 million and $15.6 million for the three months and year ended December 31, 2006, respectively, compared to $3.8 million and $14.0 million for the same periods in 2005. The increase in operating expenses primarily reflects an increase in sales, marketing and manufacturing costs necessary to support commercialization of the Ibis T5000 Biosensor System, partially offset by a decrease in costs associated with equipment purchased under government contracts. Ibis generated a loss from operations of $3.3 million and $6.9 million for the three months and year ended December 31, 2006, respectively, compared to $625,000 and $2.2 million for the same periods in 2005.

Isis expects that Ibis' 2007 revenue will be in the range of $16 million to $22 million consistent with the guidance that Isis provided in November 2006. The Company believes that predicting the timing and amount of Ibis' revenue from sales of products and services more precisely than this during Ibis' first full year of commercial operation is inherently difficult due to a lack of historical experience. Isis expects that Ibis' 2007 operating expenses and loss from operations, both excluding compensation expense from stock options, will also be consistent with Isis' November 2006 guidance of $19 million to $23 million for operating expenses, including costs of revenue, and $5 million to $1 million for loss from operations, assuming projected new placements during 2007 of between eight and fifteen Ibis T5000 Biosensor Systems.

Net Loss

Isis' net loss applicable to common stock for the quarter and year ended December 31, 2006 was $14.1 million and $45.9 million, respectively, compared with a net loss applicable to common stock of $7.9 million and $72.4 million, for the same periods in 2005. Isis recognized a benefit of $2.7 million and $23.0 million for the three months and year ended December 31, 2006, respectively, in the Loss Attributable to Noncontrolling Interest in Symphony GenIsis, Inc., resulting from Isis' collaboration with Symphony GenIsis. This benefit was a significant reason for the improvement in Isis' net loss applicable to common stock in 2006 compared to 2005. The decrease in the net loss applicable to common stock was also impacted by a net gain on investments and a decrease in interest expense, offset by an increase in Isis' loss from operations. The net gain on investments in 2006 was due to a gain of $2.7 million realized on the sale of a portion of the equity securities of Alnylam that Isis owns offset by a non-cash loss on investment of $465,000 related to the impairment of the Company's equity investment in Antisense Therapeutics Ltd. The decrease in interest expense was primarily due to the effect of a lower debt balance during 2006 compared to 2005 resulting from the conversion of the $100 million Lilly loan in the third quarter of 2005. The increase in the net loss applicable to common stock

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for the fourth quarter of 2006 compared to the fourth quarter of 2005 was primarily the result of a higher loss from operations for the fourth quarter of 2006 compared to the same period in 2005.

Net Loss per Share

Isis' net loss per share for the three months and year ended December 31, 2006 was $0.18 and $0.62 per share, respectively, compared to a net loss per share for the same periods in 2005 of $0.11 and $1.15 per share. During 2005, Isis issued 12 million shares of common stock in a private placement that raised net proceeds of approximately $48 million, and it issued 2.5 million shares to Lilly in connection with the conversion of the Company's $100 million Lilly loan. In 2006, Isis issued approximately 8.0 million shares of common stock to Azimuth Opportunity Ltd. under an equity financing that raised proceeds of $75 million and approximately 2.0 million shares in connection with the exercise of stock options and warrants. These additional shares, combined with the substantial decrease in net loss applicable to common stock, resulted in the significant decrease in net loss per share for 2006 compared to 2005. The net loss per share for the fourth quarter of 2006 compared to the fourth quarter of 2005 increased principally as a result of an increase in net loss applicable to common stock offset by the increased number of shares in 2006 compared to 2005.

Balance Sheet

In 2006 and early 2007, Isis completed three important transactions that continued its successful efforts to strengthen its balance sheet. First, in April 2006, Isis entered into a $75 million collaboration with Symphony GenIsis, Inc. to fund development of ISIS 301012 and two new diabetes drugs. Additionally, during the second half of 2006, Isis drew down the entire $75 million under its equity line with Azimuth Opportunity Ltd. by issuing approximately 8.0 million shares of its common stock. Most recently, in January 2007, Isis issued $162.5 million of 2 5/8% Convertible Subordinated Notes due 2027 ("New Notes"). Concurrent with this financing, Isis repurchased approximately $44.1 million of the total amount outstanding of its 5 ½% Convertible Subordinated Notes due 2009 ("Existing Notes") and intends to use a portion of the remaining net proceeds from this offering to repurchase the remaining Existing Notes. The significantly reduced interest rate of the New Notes compared to the Existing Notes reduces the Company's annual cash interest payments by approximately $2.6 million. In addition, the extended maturity date of the New Notes compared to the Existing Notes further strengthens Isis' balance sheet. The Symphony GenIsis collaboration, the Azimuth Opportunity transaction and the issuance of the New Notes provide Isis with the financial strength to continue to successfully execute its goals.

Isis ended the year with cash, cash equivalents and short-term investments of $193.3 million, which included $54.8 million of cash and cash equivalents held by Symphony GenIsis, and had consolidated working capital of $181.1 million. The cash, cash equivalents and short-term investments balance at December 31, 2006 does not include the $157.0 million net proceeds from the New Notes. At December 31, 2005, Isis had cash, cash equivalents and short-term

investments of $94.4 million and working capital of $82.1 million. This significant increase in cash, cash equivalents and short-term investments primarily reflects the cash received from the Azimuth transaction and the consolidation of the cash and cash equivalents held by Symphony GenIsis. Also contributing to the increase was $10.9 million that Isis received from stock option exercises, $4.4 million that Isis received from the sale of a portion of its Alnylam equity securities in 2006, and amounts received from contracts, offset by cash used in operations. We used $62.6 million of cash for operations in 2006, which represents a decrease of $5.6 million, or 8%, compared to $68.2 million in 2005.

“In 2006, Isis expanded and significantly advanced its internal drug pipeline in cardiovascular and metabolic diseases, while forging deeper relationships with development partners for advancement of Isis-discovered drugs in cancer, inflammatory and other indications,” said B. Lynne Parshall, Executive Vice President and CFO of Isis. “We reported impressive lipid-lowering activity with our Phase 2 apoB-100 drug, ISIS 301012, along with a strong safety profile. In our diabetes program, we initiated IND-enabling toxicology studies for ISIS 325568, our antisense drug targeting the glucagon receptor, and we have selected our development candidate targeting the glucocortocoid receptor, ISIS 377131. Additionally, our partners OncoGenex and Lilly each advanced two Isis anti-cancer drugs in development. These are examples of development activities for our 17-drug pipeline enabled by our continuing pioneering work in RNA-based drug discovery.

“Today we are adding another partner to our pipeline list: Atlantic Healthcare Limited has licensed alicaforsen, our ICAM-1 antisense drug, and will continue its further development. Atlantic Healthcare is a U.K.-based company which was founded in 2006 by experienced gastrointestinal drug developers, and we’re pleased to have alicaforsen moving forward in the hands of its dedicated team. This agreement is consistent with our strategy of outlicensing drugs for diseases outside of our cardiovascular and metabolic areas of focus. As with many of our partnerships with emerging companies, Isis will receive an upfront payment from Atlantic Healthcare in the form of equity, valued at approximately $2 million, and will earn milestones and royalties as the drug progresses in development. This agreement places Atlantic Healthcare among our satellite companies, along with Alnylam, OncoGenex, and others,” continued Ms. Parshall.

“In addition to our discovery and development accomplishments, Ibis has also enjoyed considerable success in 2006 with its instrument partnership with Bruker and receipt of its first commercial orders. Also, we recently took another step toward our goal of making Ibis more independent by incorporating Ibis as a wholly owned subsidiary called Ibis Biosciences, Inc. We look forward to Ibis’ continued maturation as an emerging commercial-stage medical technology company with a truly industry-changing product franchise,” added Ms. Parshall.

“We continued to strengthen our balance sheet, raising $150 million during the year through our deals with Symphony and Azimuth. Further, earlier this year we took important steps to refinance our outstanding 5 ½% convertible debt with new 2 5/8% notes, which will save us several million in interest payments over the next two years. Ending the year with almost $200 million in cash puts us in a strong position for negotiations with prospective partners, as well as providing us with the means to successfully execute our 2007 corporate goals. Based on reasonable assumptions for new sources of revenue and cash, we believe we have sufficient resources to meet our anticipated funding requirements through at least the middle of 2010.

“We project a net operating loss, excluding non-cash compensation expense from stock options, in the mid to high $60 million range for 2007, reflecting increased costs principally in two areas: the clinical development of our most important asset, ISIS 301012; and building the manufacturing, marketing and sales infrastructure required to successfully commercialize the Ibis T5000 Biosensor System,” Ms. Parshall concluded.

BUSINESS HIGHLIGHTS AND UPCOMING ACTIVITY

Cardiovascular Program

The flagship drug in the Company’s cardiovascular program is ISIS 301012, which inhibits production of apoB-100 to reduce low-density lipoproteins (LDL-cholesterol) and other atherogenic lipids and triglycerides. ISIS 301012 is being developed to help the significant and growing number of patients who are unable to achieve recommended LDL levels on available lipid lowering therapies such as statins. Phase 2 development of ISIS 301012 is continuing in multiple studies.

- In November 2006 at the American Heart Association meeting, Isis reported Phase 2 results from two dose-escalation studies: a monotherapy study and a combination study with statins. Patients experienced potent, linear, dose-dependent reductions in all atherogenic lipids and triglycerides, and the effects were comparable when ISIS 301012 was administered as a single agent or when it was added to ongoing statin therapy. ISIS 301012 was well tolerated in the studies. Isis plans to present data from additional, higher-dose cohorts for the two studies at the American College of Cardiology Annual Scientific Session in New Orleans (ACC) at the end of March 2007, and it plans a webcast to discuss the new data and the ISIS 301012 program with the investment community on Tuesday, March 27.
- In 2006, Isis secured $75 million of financing from Symphony Capital to fund development of ISIS 301012 through Phase 2b development in polygenic high cholesterol patients as well as to develop to proof-of-concept clinical trials two new metabolic disease drugs. Consistent with its strategy, these funds enable the Company to fund and control the development of ISIS 301012 to key value inflection points prior to partnering.

Metabolic Program

Isis made progress with its metabolic program in 2006, and with funding from Symphony Capital, the Company now has three metabolic drugs in development.

- Isis reported positive Phase 2 results for ISIS 113715, which inhibits production of PTP-1B. In the single-agent, dose-escalation study in treatment-naïve patients with type 2 diabetes, Isis reported at the American Diabetes Association 2006 Scientific Sessions that ISIS 113715 reduced glucose levels, and also lowered cholesterol. In this small, short-term study Isis did not see a statistically significant improvement in glycosylated hemoglobin, or HbA1c, which is a measure of long-term glucose control. The single-agent treatment was well tolerated in all dose cohorts. Isis is continuing development of ISIS 113715 in a combination study treating patients with type 2 diabetes whose disease is not adequately controlled with sulfonylureas, a class of commonly used oral antidiabetics.
- Isis also advanced the first of two new diabetes drugs funded by Symphony Capital, ISIS 325568, into toxicology and pharmacokinetic studies in animals to support the initiation of human clinical studies. ISIS 325568 targets the receptor for glucagon (GCGR), which is a hormone that opposes the action of

insulin and stimulates the liver to produce glucose. Reducing the expression of GCGR using antisense inhibitors, and thereby reducing excessive liver glucose production, should lower blood sugar and help control type 2 diabetes.

- Isis recently advanced the second new diabetes drug funded by Symphony Capital, ISIS 377131, targeting the glucocorticoid receptor (GCCR), into its development pipeline. Glucocorticoids promote breakdown of protein and fat from storage and ultimately result in increased liver glucose production. Reducing GCCR levels should reduce glucocorticoid action and have a beneficial effect on glucose control, blood lipid levels and body fat.

Partner Development Pipeline

Isis' drug development strategy includes the partnering of early-stage drugs for indications outside the therapeutic areas Isis is pursuing in its internal pipeline. The Company's partnered pipeline continued to grow and mature in 2006, enabling Isis to advance more drugs into clinical development, adding to the cumulative experience with antisense drugs, and providing present and future revenue to the Company through milestones, royalties and in the case of satellite companies, equity participation in the partner companies.

Cancer

- OncoGenex Technologies Inc. showed encouraging Phase 1 activity in patients with non-small cell lung cancer for OGX-011, an antisense inhibitor of clusterin now in several Phase 2 trials. Isis is co-developing this drug with OncoGenex, which has a second Isis antisense drug in development, OGX-427 targeting Hsp27, that it expects to begin testing in Phase 1 clinical trials in 2007.
- Lilly highlighted two Isis anti-cancer drugs in its pipeline: LY2181308, targeting survivin, is poised to enter a broad Phase 2 program in 2007; and LY2275796, targeting eIF-4E, continues in Phase 1.

Inflammatory

- Antisense Therapeutics Ltd. advanced ATL1102 targeting VLA-4 into Phase 2 for multiple sclerosis, and added ATL1103, targeting growth hormone receptor for growth and sight disorders, to its development pipeline.
- Atlantic Healthcare has licensed alicaforsen for further development initially focusing on ulcerative colitis and pouchitis. Atlantic Healthcare is a new development partner for Isis.

Neurodegenerative

- Collaborators at UCSD and Isis published promising preclinical data based on intrathecal administration of ISIS 333611, which targets SOD1 to slow the progress of amyotrophic lateral sclerosis, also known as Lou Gehrig's disease.

Ocular

- iCo Therapeutics Inc. filed an IND for an Isis drug targeting c-Raf kinase for treatment of diabetic macular edema, diabetic retinopathy, and other eye diseases, for which Isis earned a milestone payment.

Infectious

- Isis licensed ISIS 5320, an HIV inhibitor, to ImQuest Pharmaceuticals, Inc.
- Merck & Co. Inc. advanced a hepatitis C virus drug discovered in collaboration with Isis into clinical development, for which Isis received a $1 million milestone payment.

Intellectual Property, Licensing and Partnered Research Activity

With over 1,500 issued patents, Isis continues to protect its inventions as a pioneer in RNA-based drug discovery. In 2006, the Company had several notable achievements related to its technology platform.

Awarded Key Patents

- Isis was issued a U.S. patent protecting the Company's antisense drugs with modified sugars, including Isis' proprietary second-generation chemistry, generation 2.2 chemistry, and numerous other sugar-modified antisense compounds until 2023.
- Isis was awarded a fundamental U.S. patent covering a method for bacterial identification that is the first issued patent protecting the core Ibis business.
- Isis was awarded a key U.S. patent that broadly covers certain chemical modifications of oligonucleotides used to introduce "drug-like" properties in antisense oligonucleotides, including small interfering RNAs (siRNAs).

- The European Patent Office upheld on appeal a key Isis patent covering antisense drugs with gapmer structures including Isis' second-generation structures.

Added Four New Satellite Companies

- Isis licensed its aminoglycoside antibiotics program to Achaogen, Inc.
- Isis licensed a non-antisense oligonucleotide compound, ISIS 5320, to ImQuest Pharmaceuticals, Inc. to be developed as an anti-HIV topical microbicide.
- Isis and Rosetta Genomics Ltd. entered into a research collaboration to discover and develop antisense drugs that regulate microRNAs.
- Isis licensed alicaforsen to Atlantic Healthcare for further development.

Generated More Than $10 Million From Licensing Activities

- Isis received a $1 million milestone payment from Merck for the initiation of clinical trials of a compound that was discovered during a research collaboration between the companies.
- Alnylam paid Isis $750,000 related to Alnylam's sublicense of Isis' technology to a pharmaceutical company.
- Isis received $8 million from Drug Royalty USA, Inc. related to Macugen.
- Isis received a milestone payment from iCo Therapeutics based on its filing of an IND for iCo-007.
- Isis and Pfizer Inc. extended their research agreement, adding to the scope of target validation activities.

Ibis Biosciences, Inc.

2006 marked the transition of Ibis Biosciences from research and development to commercial stage. Reflecting this maturation, Isis recently reorganized the division to be a wholly owned subsidiary called Ibis Biosciences, Inc.

- Ibis announced a strategic alliance with Bruker Daltonics, Inc., a subsidiary of Bruker BioSciences — Bruker will provide Ibis T5000 instrument manufacturing along with global installation and support services.
- Ibis earned revenue from its first commercial orders for Ibis T5000 systems and assay services.

Financing and Other Corporate Activity

- In 2006, Isis received $75 million from its collaboration with Symphony Capital to fund continued development of ISIS 301012 and two preclinical metabolic program drugs targeting GCGR and GCCR.
- During the second half of 2006, Isis raised $75 million by selling approximately 8.0 million shares of its common stock at an average price of $9.41 per share under its equity line of credit with Azimuth Opportunity Ltd.
- In early 2007, Isis issued lower-coupon (2 5/8%), longer-maturity (due 2027) convertible notes, the proceeds of which are intended to repurchase the Company's 5 1/2% convertible notes due 2009. The Company expects to save approximately $2.6 million per year in interest payments as a result of this transaction, and the extended maturity date further strengthens Isis' balance sheet.
- On February 1, Jeffrey M. Jonas, M.D., joined Isis as Executive Vice President. Dr. Jonas leads Clinical Development, Preclinical Development, Regulatory Affairs, and Quality Assurance and Compliance at Isis. He brings valuable regulatory and later-stage drug development experience to the Isis team, and he is broadly responsible for the entire pipeline, both partnered and internal.

2007 MILESTONES

Cardiovascular Program

- Report results of ISIS 301012 (apoB-100) three month monotherapy Phase 2 study *(1st quarter)*
- Report results of ISIS 301012 five week statin add-on Phase 2 study *(1st quarter)*
- Report results of ISIS 301012 three month statin add-on Phase 2 study *(2nd half)*
- Initiate longer-duration Phase 2 study in polygenic high cholesterol patients *(2nd half)*
- Report results of ISIS 301012 Familial Hypercholesterolemia (FH) Phase 2 Studies *(2nd half)*
- Initiate registration study for FH *(2nd half)*
- Advance ISIS 353512, targeting C-reactive protein (CRP), into IND-enabling toxicology studies

Metabolic Program

- Advance ISIS 113715 (PTP-1B) Phase 2 sulfonylurea add-on study
- Initiate ISIS 325568 (GCGR) Phase 1 study *(2nd half)*
- Advance ISIS 377131 (GCCR) into IND-enabling toxicology studies

Partnered Programs

Isis intends to support its partners' activities in advancing Isis antisense drugs in development.

OncoGenex (cancer)

- Report results from OGX-011 (clusterin) Phase 2 studies
- Initiate Phase 1 study for OGX-427 (Hsp27)

Lilly (cancer)

- Initiate Phase 2 program for LY2181308 (survivin)
- Advance LY2275796 (eIF-4E) in Phase 1

iCo Therapeutics (ocular)

- Initiate Phase 1 study for iCo-007 (c-Raf kinase) in diabetic macular edema

Antisense Therapeutics (inflammatory)

- Advance Phase 2 study of ATL1102 (VLA-4)
- Advance ATL1103 (GHr) into IND-enabling toxicology studies

Atlantic Healthcare (inflammatory)

- Continue clinical development of alicaforsen

Ibis Biosciences, Inc.

- Transfer instrument manufacturing to Bruker Daltonics
- Place at least eight new instruments

Conference Call

At 11:00 a.m. Eastern Time today, March 8, Isis will conduct a live webcast conference call to discuss this earnings release and related activities. To participate over the Internet, go to www.isispharm.com. A replay will be available for a limited time at the same address.

About Isis Pharmaceuticals

Isis 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 17 drugs in development. Isis' drug development programs are focused on treating cardiovascular and metabolic diseases. Isis' partners are focused on cancer and inflammatory and other diseases. Ibis Biosciences, Inc., Isis' wholly owned subsidiary, is developing and commercializing the Ibis T5000 Biosensor System, a revolutionary system to identify infectious organisms. As an innovator in RNA-

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based drug discovery and development, Isis is the owner or exclusive licensee of over 1,500 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release includes forward-looking statements regarding Isis Pharmaceuticals' business, the financial position and outlook for Isis and Ibis Biosciences, and the therapeutic and commercial potential of the Company's technologies and products in development. Any statement describing Isis' goals, expectations, financial or other projections, 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 or projections. 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 detail in Isis' annual report on Form 10-K for the year ended December 31, 2005, and its quarterly report on Form 10-Q for the quarter ended September 30, 2006, which are on file with the SEC. Copies of these and other documents are available from the Company.

The information contained in this press release reflects preliminary financial results, as Isis' 2006 audit has not yet been completed. Under section 404 of the Sarbanes-Oxley Act of 2002, new integrated audit requirements will not be met until Isis has completed all of the steps necessary to file its 2006 audited financial statements with the SEC.

Isis Pharmaceuticals, Ibis Biosciences and Ibis T5000 are registered trademarks or trademarks of Isis Pharmaceuticals, Inc.

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

	Three months ended, December 31,		Years ended, December 31,	
	2006	2005	2006	2005
	(unaudited)		(unaudited)	
Revenue:				
Research and development revenue under collaborative agreements	$ 3,832	$ 3,916	$ 15,091	$ 28,610
Licensing revenue	8,114	10,725	9,441	11,523
Total revenue	11,946	14,641	24,532	40,133
Expenses:				
Research and development	24,240	20,944	80,567	82,467
Selling, general and administrative	4,521	2,661	12,619	8,432
Compensation (benefit) related to variable accounting of stock options	—	69	—	(544)
Restructuring activities	(79)	(425)	(536)	6,960
Total operating expenses	28,682	23,249	92,650	97,315
Loss from operations	(16,736)	(8,608)	(68,118)	(57,182)
Investment income	2,124	3,000	5,960	5,094
Interest expense	(2,213)	(2,304)	(9,029)	(20,313)
Gain on investments	—	—	2,263	—
Net loss before noncontrolling interest in Symphony GenIsis, Inc.	(16,825)	(7,912)	(68,924)	(72,401)
Loss attributed to noncontrolling interest in Symphony GenIsis, Inc.	2,679	—	23,021	—

Net loss applicable to common stock	$ (14,146)	$ (7,912)	$ (45,903)	$ (72,401)
Basic and diluted net loss per share	$ (0.18)	$ (0.11)	$ (0.62)	$ (1.15)
Shares used in computing basic and diluted net loss per share	78,385	72,202	74,308	62,877

Ibis Biosciences, Inc.
Statements of Operations
(In Thousands)

	Three months ended December 31,		Years ended December 31,	
	2006	2005	2006	2005
	(unaudited)		(unaudited)	
Revenue				
Commercial revenue (1)	$ 405	$ —	$ 556	$ —
Research and development revenue under collaborative agreements	1,521	3,142	9,117	11,793
Total revenue	1,926	3,142	9,673	11,793
Operating expenses:				
Cost of commercial revenue (2)	362	—	427	—
Research and development	3,700	3,459	13,247	12,931
Selling, general and administrative	1,150	308	2,939	1,090
Total operating expenses	5,212	3,767	16,613	14,021
Loss from operations	$ (3,286)	$ (625)	$ (6,940)	$ (2,228)

(1) Ibis' commercial revenue has been classified as research and development revenue under collaborative agreements on Isis' consolidated statement of operations.

(2) Ibis' cost of commercial revenue has been classified as research and development expenses on Isis' consolidated statement of operations.

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

	Three months ended, December 31,		Years ended, December 31,	
	2006	2005	2006	2005
	(unaudited)		(unaudited)	
As reported operating expenses according to GAAP	$ 28,682	$ 23,248	$ 92,650	$ 97,315
Excluding compensation (expense)/benefit related to stock options	—	(69)	—	544
Excluding compensation expense related to stock options pursuant to SFAS 123R	(1,557)	—	(5,747)	—
Excluding restructuring activities	79	425	536	(6,960)
Proforma operating expenses	$ 27,204	$ 23,604	$ 87,439	$ 90,899
As reported loss from operations according to GAAP	$ (16,737)	$ (8,607)	$ (68,118)	$ (57,182)
Excluding compensation (expense)/benefit related to stock options	—	(69)	—	544
Excluding compensation expense related to stock options pursuant to SFAS 123R	(1,557)	—	(5,747)	—
Excluding restructuring activities	79	425	536	(6,960)
Proforma loss from operations	$ (15,259)	$ (8,963)	$ (62,907)	$ (50,766)

Condensed Consolidated Balance Sheets
(In Thousands)

	December 2006 (Unaudited)	December 31, 2005
Assets:		
Current assets	$ 206,203	$ 105,858
Property, plant and equipment, net	7,157	9,130
Other assets	42,547	51,385
Total assets	$ 255,907	$ 166,373
Liabilities and stockholders' equity		

Current liabilities	$ 25,139	$ 23,793
5.5% convertible subordinated notes	125,000	125,000
Long-term obligations, net of current portion	7,866	14,915
Noncontrolling interest in Symphony GenIsis, Inc.	29,339	—
Stockholders' equity	68,563	2,665
Total liabilities and stockholders' equity	$ 255,907	$ 166,373

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