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 13, 2008**

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 13, 2008, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the quarter and fiscal year ended December 31, 2007. 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.

(d) Exhibits.

99.1 Press Release dated March 13, 2008.

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 12, 2008

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 13, 2008.

ISIS REPORTS FINANCIAL RESULTS AND HIGHLIGHTS FOR FISCAL YEAR 2007

- **2007 Net Operating Loss 54% Lower than 2006**
- **Successful Execution of Partnership Strategy Provides Nearly $450 Million in Cash and Committed Cash**
- **2008 Projected Net Operating Loss Less than $15 Million**
- **2008 Projected Year-End Cash Greater than $450 Million**
- **Conference Call Webcast Thursday, March 13, 08:30 a.m. EDT at www.isispharm.com**

CARLSBAD, Calif., March 13, 2008 - Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced its 2007 financial results and business highlights. The Company finished a very successful year by meeting its 2007 pro forma net operating loss (NOL) guidance with an NOL of $29.0 million. The 2007 NOL was 54% lower than the Company's 2006 NOL. Due to its strong financial performance during 2007, Isis reduced its 2007 NOL guidance from the mid to high $60 million range down to the mid to high $20 million range. Isis' 2007 loss from operations of $38.9 million also decreased significantly (43%) from its 2006 loss from operations of $68.1 million, according to GAAP.

"2007 was a transformational year for Isis. The execution of our business strategy is tangibly visible in our 2007 results of operations and our year end balance sheet," said B. Lynne Parshall, COO and CFO of Isis. "Financial rewards from our existing partnership with Alnylam, as well as new partnerships with Bristol-Myers Squibb, Ortho-McNeil, Abbott and Genzyme have resulted in additional cash of nearly $450 million, of which approximately $270 million has been received to date. The breadth of Isis innovation has also enhanced our financial strength, including our recently announced funding transaction with Abbott for our Ibis subsidiary, which has the potential to provide up to $210 million of additional cash beyond the $20 million we have already received, and our Regulus microRNA joint venture, financed with $10 million by our partners at Alnylam. Our improved financial position supported the early purchase of Symphony GenIsis, saving us roughly $75 million over the lifetime of that transaction, and our debt refinancing has saved us significant interest expense."

"Our recent successful transactions have not only enhanced our 2007 financial performance, they should also support very strong performance in 2008. Based on our existing cash and committed cash, including the $175 million mipomersen licensing fee from Genzyme, but not including the up to $210 million we could receive from Abbott, we expect that our 2008 year end cash balance will be greater than $450 million and will last for at least five years. Furthermore, we are predicting a 2008 NOL of less than $15 million, excluding non-cash stock compensation, which reflects a reduction of over 50% from 2007," continued Ms. Parshall.

"Of course, the most important aspect of the implementation of our business strategy is its long-term impact. We have 18 drugs in our pipeline that we and our partners are advancing. With the efficiency of our antisense technology we expect to continue to expand this pipeline. Each of our partnered drugs will provide milestones and royalties as the drugs meet key development, regulatory and commercial milestones. This ongoing revenue stream should continue to support our strong financial performance as our pipeline matures," added Ms. Parshall.

"We also continue to make strong progress with our most important asset, mipomersen. Earlier in the year, we announced the initiation of the Phase 3 studies in patients with homozygous Familial Hypercholesterolemia. Today we are announcing that we are initiating the rest of the Phase 3 program for mipomersen including studies in patients with heterozygous Familial Hypercholesterolemia," said Ms. Parshall. "We also plan to report additional clinical safety data this year."

Results of Operations

The 43% decrease in the Company's loss from operations for 2007 compared to 2006 was primarily a result of a significant increase in revenue in 2007 from corporate partnerships offset, somewhat, by higher expenses associated with the expansion of its key programs and an increase in non-cash stock compensation reflecting the increase in Isis' stock price from 2006 to 2007. The reasons for the decrease in the Company's pro forma loss from operations were the same as those for the decrease in the Company's loss from operations according to GAAP other than the effect of non-cash compensation expense related to stock options.

As illustrated in the Selected Financial Information in this press release, pro forma operating expenses and pro forma loss from operations were adjusted from GAAP to exclude compensation expense related to stock options, which are non-cash, and costs associated with restructuring activities, which are not part of ongoing operations. 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 these pro forma results to better enable financial statement users to assess and compare 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, 2007 was $24.7 million and $69.6 million, respectively, compared to $11.9 million and $24.5 million for the same periods in 2006. Revenue was higher in the fourth quarter of 2007 compared to the same period of 2006 due to the addition of new revenue generating collaborations with Bristol-Myers Squibb (BMS) in May 2007 and Ortho-McNeil, Inc. (OMI) in September 2007. In addition to the revenue from these two strategic partnerships, the $26.5 million in sublicensing revenue that Isis earned in the third quarter of 2007 from Alnylam contributed to the significant year over year increase in revenue. Quarter-to-quarter fluctuations in revenue are common for Isis as its revenue is significantly affected by

the nature and timing of payments under agreements with its partners, including license fees and milestone-related payments, such as the $26.5 million Isis received from Alnylam in the third quarter.

Expenses

In 2007, as its drugs advanced into and through development, Isis expanded its clinical development programs, resulting in an increase in operating expenses of $5.0 million in 2007 compared to 2006. Additionally, Isis built the manufacturing, marketing and sales infrastructure required to successfully commercialize the Ibis T5000™ Biosensor System, resulting in an increase in operating expenses of $4.9 million in 2007 compared to 2006. On a pro forma basis, operating expenses for the quarter and year ended December 31, 2007 were $30.5 million and $98.7 million, respectively, compared to $27.2 million and $87.4 million for the same periods in 2006.

Isis' operating expenses for the quarter and year ended December 31, 2007 were $33.2 million and $108.6 million, respectively, compared to $28.7 million and $92.7 million for the same periods in 2006, according to GAAP. Isis includes in its operating results non-cash compensation expense related to stock options, which was $2.7 million and $9.9 million for the quarter and year ended December 31, 2007, respectively, compared to $1.6 million and $5.7 million for the same periods in 2006, primarily reflecting the significant increase in Isis' stock price from 2006 to 2007.

Ibis Biosciences, Inc.

Ibis' revenue for the quarter and year ended December 31, 2007 of $3.2 million and $11.3 million, respectively, increased significantly compared to $1.9 million and $9.7 million for the same periods in 2006. Ibis earned commercial revenue of $1.0 million and $3.5 million for the quarter and year ended December 31, 2007, respectively, compared to $405,000 and $556,000 for the same periods in 2006. Commercial revenue consisted of revenue from sales of Ibis T5000 Biosensor Systems and assay kits, as well as revenue from Ibis' assay services business. Because Ibis provides a full year of support for each Ibis T5000 Biosensor System following installation, Ibis is amortizing the revenue for instrument and assay kits over the period of this support obligation. Primarily as a result of the increased number of T5000 Biosensor System placements in 2007, commercial revenue in 2007 was substantially higher than in 2006. In addition, Ibis generated revenue from its government contracts and grants of $2.2 million and $7.8 million for the quarter and year ended December 31, 2007, respectively, compared to $1.5 million and $9.1 million for the same periods in 2006. As Ibis has matured from the research and development stage to the commercial stage, some of its large government contracts that

supported technology development have been successfully completed, leading to a transient decline in contract revenue for the year ended December 31, 2007. In general, new Ibis contracts support diverse applications of the Ibis T5000 Biosensor System, which benefits not only the government contracting agency, but also Ibis' non-government commercial customers. In addition to its ongoing government contracts, Ibis has recently been granted contracts worth up to $2.8 million. Isis expects that government contracts will continue to provide a solid revenue base going forward.

Excluding non-cash compensation expense related to stock options, operating expenses for Ibis were $6.3 million and $20.5 million for the quarter and year ended December 31, 2007, respectively, compared to $4.9 million and $15.6 million for the same periods in 2006. The increase in operating expenses primarily reflects an increase in sales, marketing and manufacturing costs necessary to support the early commercialization phase of the Ibis T5000 Biosensor System. Ibis generated a loss from operations, excluding non-cash compensation expense related to stock options, of $3.2 million and $9.2 million for the quarter and year ended December 31, 2007, respectively, compared to $3.0 million and $6.0 million for the same periods in 2006.

Regulus Therapeutics LLC

In September 2007, Isis and Alnylam formed Regulus, a joint venture focused on the discovery, development, and commercialization of microRNA therapeutics. Under accounting rules, Isis is considered the primary beneficiary of Regulus and consolidates the financial results of Regulus. As a result, Isis' consolidated financial statements include the $10 million of cash contributed by Alnylam to fund Regulus. Isis' consolidated financial statements also include a line item called "Noncontrolling Interest in Regulus Therapeutics LLC." On Isis' Consolidated Balance Sheet, this line reflects Alnylam's minority ownership of Regulus' equity. As the joint venture progresses, this line item will be reduced by Alnylam's share of Regulus' net losses, which were $629,000 in 2007, until the balance becomes zero. The reductions to the Noncontrolling Interest in Regulus will be reflected in Isis' Consolidated Statement of Operations using a similar line item and will provide a positive adjustment to Isis' net income (loss) equal to Alnylam's share of Regulus' losses.

Early Retirement of Debt

In January 2007, Isis issued $162.5 million of 2 $^{5}/_{8}$% convertible subordinated notes due 2027. Using a portion of the net proceeds from the issuance of these 2 $^{5}/_{8}$% notes, Isis repurchased its 5 $^{1}/_{2}$% convertible subordinated notes due 2009. The significantly lower interest rate of the 2 $^{5}/_{8}$% notes reduces the Company's cash interest payments by approximately $2.6 million per year. In addition, the extended maturity date of the 2 $^{5}/_{8}$% notes further strengthens Isis' financial position. Isis recognized a loss of $3.2 million in 2007 as a result of the early repayment of the 5 $^{1}/_{2}$% notes of which $1.2 million was a non-cash write-off of unamortized debt issuance costs.

Net Loss

Isis' strong financial performance was also reflected in the substantial decrease in its net loss from 2006 to 2007. Isis' net loss for the quarter and year ended December 31, 2007 was $7.0 million and $11.0 million, respectively, compared to $14.1 million and $45.9 million for the same periods in 2006. Isis recognized a benefit of $23.2 million and $23.0 million for the year ended December 31, 2007 and 2006, respectively, in the loss attributed to noncontrolling interest in Symphony GenIsis, Inc., related to its collaboration with Symphony GenIsis. Isis' net loss for 2007 was lower than 2006 because of a decrease in the Company's loss from operations, higher interest income, lower interest expense and an increase in net gain on investments, offset by the loss on early retirement of debt.

Net Loss Applicable to Common Stock

Isis' improved financial position supported the early purchase in September 2007 of Symphony GenIsis, saving the Company roughly $75 million over the lifetime of the transaction. Isis purchased the equity of Symphony GenIsis at the pre-negotiated price of $120 million, which Isis paid for with $80.4 million in cash and approximately 3.4 million shares of Isis stock. The $125.3 million on Isis' Statement of Operations in a line item called Excess Purchase Price over Carrying Value of Noncontrolling Interest in Symphony GenIsis, Inc. represents a deemed dividend to the previous owners of Symphony GenIsis, a portion of which was non-cash. A portion of the $125.3 million reflects the significant increase in Isis' stock price used to calculate the value of the shares issued to Symphony Capital. This deemed dividend only impacts Isis' net loss applicable to common stock and its net loss per share calculations and does not affect Isis' net loss.

Isis' net loss applicable to common stock for the quarter ended December 31, 2007 was $7.0 million or $0.08 per share and for the year ended December 31, 2007 it was $136.3 million or $1.63 per share, of which $1.50 per share was attributable to the purchase of Symphony GenIsis, compared to $14.1 million or $0.18 per share and $45.9 million or $0.62 per share for the same periods in 2006.

Balance Sheet

In 2007 and early 2008, Isis completed several transactions that significantly strengthened its financial position. In 2007, Isis issued $162.5 million of 2 5/8% convertible subordinated notes and used the proceeds of this issuance to retire its outstanding, more expensive convertible debt. In addition, Isis added two major pharmaceutical partners with its collaborations with BMS and OMI. In the third quarter of 2007, Isis received the $26.5 million sublicensing fee from Alnylam's transaction with Roche. Since the 2007 balance sheet date, Isis has entered into major strategic alliances with Genzyme and Abbott. These transactions represent the value that Isis is realizing from its extensive product pipeline and the successes of its partnering strategy, and provide Isis with the financial strength to continue to successfully execute its goals.

As of December 31, 2007, Isis had cash, cash equivalents and short-term investments of $193.7 million, which included $10.1 million of cash and cash equivalents held by Regulus. At December 31, 2006, Isis had cash, cash equivalents and short-term investments of $193.3 million. Isis used $63.3 million of cash for operations in 2007, which was comparable to 2006. Even with the $80.4 million cash payment that Isis made in the third quarter of 2007 for the acquisition of Symphony GenIsis, Isis' cash position at December 31, 2007 was virtually unchanged from the end of 2006 due to significant cash inflows including the:

- $30 million net cash received from the issuance of the 2 5/8% notes after repayment of the 5 1/2% notes,
- $15 million upfront licensing fee received from BMS,
- $26.5 million sublicensing fee received from Alnylam,
- $10 million invested in Regulus,
- $50 million upfront licensing fee and milestone payment received from OMI,
- $18 million of research and development funding from the Company's partnerships, and
- $10.3 million from stock options exercised in 2007.

Not included in the Company's cash balance at December 31, 2007 are the cash payments totaling $170 million that Isis has received in early 2008 from its strategic partnerships with Genzyme and Abbott. In addition, upon the completion of the license agreement for mipomersen, Genzyme will pay Isis an additional $175 million. Isis also has the potential to receive up to $210 million from Abbott in exchange for the remainder of Ibis' stock.

As of December 31, 2007, Isis had consolidated working capital of $145.1 million compared to $181.1 million at December 31, 2006. In connection with its collaborations with BMS and OMI, Isis received large upfront payments, initially classified as liabilities, that it is amortizing into revenue over the collaboration terms, three and two years, respectively. A significant amount of the unamortized portion of these liabilities is included in current liabilities at December 31, 2007 and as a result Isis' working capital at the end of 2007 is less than it was at the end of 2006.

Business Highlights

"Our 2007 success was more than simply financial. We made significant progress in every element of our business, resulting in substantial benefit in 2007. Additionally, our progress has poised us to continue to benefit significantly as key assets move forward in our partner's hands supporting our very strong 2008 projected financial performance. Mipomersen, our flagship drug, continued to display very positive activity in multiple patient populations studied both as a single agent and in combination with other lipid lowering agents, and a safety profile that we believe will make mipomersen a very attractive drug in patients with high cholesterol who are at high risk of cardiovascular disease. We conducted a successful auction process that resulted in the license of mipomersen on very lucrative terms to Genzyme, including a very favorable profit sharing arrangement that allows us to participate in the long term commercial success of mipomersen. We advanced all of the drugs in our pipeline, and we licensed two of our metabolic drugs to Ortho-McNeil and a new cardiovascular research program on PCSK9 to Bristol-Myers Squibb, all high value transactions. The funds from these collaborations will enable us to advance valuable new drugs into development. We believe that the value across all of our drug discovery programs has greatly increased because of mipomersen's continued clinical success, and this has enabled us to license our drugs on very attractive terms to high quality partners," said Ms. Parshall.

"We commercialized the Ibis technology and secured a valuable strategic relationship with Abbott on excellent financial terms. This relationship provides Ibis with the necessary capital and expertise to continue to move toward clinical diagnostics. Abbott has the option to purchase the remaining shares of Ibis through mid 2009. Abbott's favorable valuation of Ibis and the Ibis technology at $215 million reflects the significant value of our technology and innovation. If Abbott purchases Ibis, Isis and our shareholders will continue to participate in Ibis' commercial success through the earn out provision. We look forward to the benefit Ibis will receive from an experienced partner in diagnostics focused on Ibis' commercial success," added Ms. Parshall.

"We continue to place carefully selected antisense drugs in the hands of dedicated and highly focused partners for the treatment of diseases that are outside our core therapeutic areas. Altair Therapeutics and Excaliard Pharmaceuticals are two of our most recent examples of this business strategy, which enables us to benefit in the form of licensing and milestone payments and equity ownership in these venture-financed companies while also expanding the therapeutic reach of our antisense technology," added Ms. Parshall. "In addition, we leverage our investments in our core technologies and maintain our leadership position by providing access to our extensive patent estate and expertise enabling partners to develop new therapeutic approaches. As part of this strategy we received $26.5 million from Alnylam, in association with its Roche deal and added a new technology partner, Archemix, for discovery and development of aptamer drugs. We are also using our technology to expand into new biological areas such as microRNA with the formation of our joint venture Regulus Therapeutics, which will benefit from our extensive expertise, chemistry and technology as the company exploits new biological mechanisms for disease treatments. The caliber of the management team, Scientific Advisory Board and Board of Directors we have put together for Regulus is a reflection of the high level of excitement about this new area of biology and Regulus' leadership position in the field. All of these achievements provide the financial strength and momentum that make it likely that 2008 will be another year of excellent progress."

"The continued exploitation of Isis' unique and effective business strategy should produce another strong year in 2008. Building on our 2007 and early 2008 successes, we have the opportunity to aggressively advance our drugs in development, with significant data milestones planned for our two most advanced drugs, mipomersen and ISIS 113715, and expand our pipeline with two to four new drugs. Our partnering successes over the last year have created substantial interest in Isis and our technology, which we plan to exploit with new strategic relationships. In short, we believe 2007 is just the beginning of value creation from Isis' antisense platform and look forward to an exciting upcoming year," concluded Ms. Parshall.

Drug Development Highlights

Isis' cardiovascular franchise matured appreciably during the last year, with mipomersen at the forefront. The clinical success of mipomersen has added significant value to the entire drug development pipeline.

- Mipomersen (formerly ISIS 301012) continues to demonstrate an excellent safety and efficacy profile supported by strong Phase 2 clinical results in all patient populations tested. As a result, Isis has initiated registration studies of mipomersen in Familial Hypercholesterolemia patients.
- Isis established a strategic alliance with BMS for the discovery and development of antisense drugs targeting PCSK9, an important regulator of the LDL-receptor.
- Isis initiated IND-enabling studies of ISIS 353512, an antisense drug that targets C-reactive protein, in partnership with the Korea Institute of Technology.

Isis' metabolic disease franchise continued to expand with the addition of new diabetes drugs into development, and new research efforts toward attractive targets for the treatment of obesity.

- Isis continued Phase 2 studies of ISIS 113715 for the treatment of type 2 diabetes in patients on stable sulfonylurea treatment. In humans and preclinical studies, ISIS 113715 demonstrated reductions in blood glucose without causing low blood sugar, called hypoglycemia, weight gain or nausea.
- Isis initiated Phase 1 studies of ISIS 325568, an antisense drug partnered with OMI, that targets the glucagon receptor, GCGR.
- Isis identified a development candidate, ISIS 377131, an antisense drug also partnered with OMI that targets the glucocorticoid receptor, GCCR.
- Isis added ISIS 388626 to its development pipeline. ISIS 388626 targets SGLT2, a protein that is responsible for glucose re-absorption in the kidney.

Cancer continues to be a disease in which antisense drugs could make a profound difference in treatment

options. Isis' partners are developing antisense drugs discovered by Isis to treat cancer.

- OncoGenex reported encouraging Phase 2 data for OGX-011, an antisense drug that targets clusterin, in several studies in patients with advanced prostate or lung cancers. The most recent study showed that OGX-011 was well-tolerated in combination with certain chemotherapy agents and showed ongoing survival durations that were more favorable than with the chemotherapy agents alone, based on historical controls.
- OncoGenex initiated Phase 1 clinical studies of OGX-427, an antisense drug that targets Hsp-27, a cell survival protein that is overly abundant in cancer cells.
- Lilly advanced its Phase 1 studies of LY2275796, which targets eIF-4E, a protein involved in tumor progression and in the Journal of Clinical Investigation, Isis and Lilly published preclinical study results that support the therapeutic potential of LY2275796.

Isis is exploring new applications and disease indications for antisense drugs to treat neurodegenerative diseases and other diseases for which antisense drugs are uniquely suited.

- Isis was granted orphan drug status for ISIS 333611, an antisense drug in IND-enabling studies that targets SOD1 for the treatment of an inherited, aggressive form of ALS, which is also known as Lou Gehrig's disease. IND-enabling preclinical studies are being funded by the ALS Association and the Muscular Dystrophy Association.
- Isis initiated a program to discover and develop antisense drugs to treat Huntington's Disease in collaboration with CHDI, which is providing Isis with nearly $10 million in funding for the program.
- Antisense Therapeutics Ltd. (ATL) licensed ATL1102 to Teva Pharmaceutical Industries. ATL1102 is an antisense drug discovered by Isis and licensed to ATL and is currently in Phase 2 studies for the treatment of multiple sclerosis.
- iCo initiated Phase 1 studies of iCo-007, an antisense drug discovered by Isis for the treatment of various eye diseases. Isis received a $1.25 million milestone payment in equity for the initiation of this study.

Partnership Highlights

Isis has added three major new pharmaceutical partners for drugs in its cardiovascular and metabolic franchises, underscoring the confidence of the industry in the promise of antisense drugs for treatment of chronic conditions such as these.

- Isis licensed mipomersen to Genzyme as part of a strategic alliance that includes a $150 million equity investment, an upfront licensing fee of $175 million, over $1.5 billion in milestone payments, and a share of profits on mipomersen and follow-on drug(s) ranging from 30-50% of all commercial sales. As part of the alliance, Genzyme became a preferred development partner for Isis for programs in CNS and certain rare diseases.
- Isis licensed two type 2 diabetes drugs that target GCGR and GCCR to Johnson & Johnson's OMI for a $45 million upfront licensing fee and could receive more than $230 million in milestone payments, and Isis established a research collaboration with OMI to identify additional antisense drugs to treat metabolic diseases. Isis received the first development milestone payment of $5 million under this collaboration.
- Isis licensed its lipid-lowering PCSK9 program to BMS for a $15 million upfront licensing fee and up to $168 million in milestone payments.

Isis expanded clinical opportunities for its drugs by licensing several antisense drugs that are outside of the Company's key therapeutic focus areas to companies with disease-area expertise devoted to optimizing the future development of these drugs.

- Isis licensed ISIS 369645, an inhaled antisense drug, to Altair for the treatment of respiratory diseases.
- Isis entered into a collaboration with Excaliard to discover and develop antisense drugs for the local treatment of fibrotic diseases, including scarring.
- Isis licensed alicaforsen, an antisense drug targeting ICAM-1 for ulcerative colitis, to Atlantic Healthcare.

Isis demonstrated the value of its technology innovation and dominant intellectual property through partnerships with industry leaders in a variety of related areas.

- Isis received $26.5 million under its collaboration with Alnylam, associated with Alnylam's transaction with Roche.
- Isis licensed technology to Archemix for aptamer drug applications in exchange for milestones and royalties on aptamer drugs developed by Archemix that incorporate Isis' proprietary chemistries or manufacturing methods; Isis received the first milestone payment from Archemix for the advancement of Archemix' aptamer drug into Phase 2a studies.

Other Highlights

Isis has improved its financial position significantly in 2007, strengthening its balance sheet and reducing its net operating loss.

- Isis refinanced its convertible debt, which extended the maturity of the debt, strengthened the Company's balance sheet, and reduced its cash interest payments by approximately $2.6 million annually due to the lower coupon rate.
- Isis purchased Symphony GenIsis relatively early in the term of that financing arrangement saving approximately $75 million in the predetermined purchase price, regaining full ownership of mipomersen, which Isis licensed to Genzyme, and the GCGR and GCCR drugs, which Isis licensed to OMI.
- As a result of Isis' partnering strategy, the Company was able to reduce its pro forma net operating loss guidance by $40 million over the course of 2007.

Isis strengthened its leadership team with the addition of:

- Jeffrey M. Jonas, M.D. to lead Clinical Development, Preclinical Development, Regulatory Affairs, and Quality Assurance and Compliance. Dr. Jonas was formerly Chief Medical Officer and Executive Vice President at Forest Laboratories, Inc.

Regulus Highlights

Isis and Alnylam founded Regulus Therapeutics LLC and hired senior management to lead the joint venture company in discovering and developing antisense drugs targeting microRNAs.

- Kleanthis G. Xanthopoulos, Ph.D., was appointed as President and Chief Executive Officer of Regulus. Dr. Xanthopoulos is the co-founder and former President and Chief Executive Officer of Anadys Pharmaceuticals, Inc.
- Peter S. Linsley, Ph.D., was appointed as Chief Scientific Officer of Regulus. Dr. Linsley was Executive Director of Cancer Biology at Merck Research Laboratories, and was previously Vice President of Research of Rosetta Inpharmatics.

Ibis Highlights

Isis' Ibis subsidiary gained a strategic partner, Abbott, who will enable Ibis to aggressively prepare to enter larger commercial markets including hospital-acquired infection control and clinical diagnostics. Ibis also successfully completed its first full year of commercializing the Ibis T5000 Biosensor System.

- Abbott invested $20 million in Ibis and now owns 10.25% equity in Ibis at a post money valuation of $215 million with the option to invest an additional $20 million in Ibis for a total equity holding of 18.6%.
    - Abbott acquired the option to purchase the remaining shares of Ibis for a total purchase price of $215 to $230 million.
    - If Abbott exercises its option to acquire Ibis, Isis will receive an earn out tied to the achievement of certain cumulative sales.
- Ibis placed eight instruments, including placements with research hospitals.
- Ibis finished constructing its commercial assay kit manufacturing facility.
- Ibis has received over $12 million in contracts and grants during 2007 to advance the detection and identification of infectious organisms for a broad range of applications, including biodefense.

2008 Goals

Financial

The successful execution of Isis' business strategy and the advancement of many of Isis' drugs in development have greatly enhanced the Company's financial strength. This momentum is predicted to continue in 2008.

- Isis expects to maintain a strong balance sheet ending the year with over $450 million in cash, which is expected to last for at least five years.
- Isis expects to achieve a NOL of less than $15 million, excluding non-cash stock compensation.

Drug Development

With a substantial pipeline of 18 drugs discovered by Isis and being developed by Isis and Isis' partners, the Company anticipates many clinical events for 2008; some are highlighted below:

- Isis' cardiovascular franchise will continue to provide clinical evidence to support the activity and safety profiles of second-generation antisense drugs. Isis completed two key goals early, including the licensing of mipomersen, the lead drug in this franchise, to Genzyme and the initiation of Phase 3 studies of mipomersen

in patients with Familial Hypercholesterolemia.

    - Over the upcoming months, Isis expects to effect a seamless transition of mipomersen development to Genzyme.
    - Isis and Genzyme expect to report new safety data for mipomersen.
    - Isis expects to initiate Phase 1 clinical studies of ISIS 353512 that targets CRP for the treatment of coronary artery disease.
    - Isis and BMS expect to advance into development a drug targeting PCSK9 for the treatment of cardiovascular disease.
- Isis' metabolic franchise, which consists of four novel and complementary drugs to treat type 2 diabetes, will continue to grow, with clinical data expected from the most advanced of the four drugs, ISIS 113715, and Isis will continue to explore the therapeutic opportunities for antisense drugs to treat obesity.
    - Isis expects to report Phase 2 study data in Type 2 diabetics treated with ISIS 113715 and sulfonylureas.
    - Isis expects to complete the Phase 1 study of ISIS 325568, an antisense drug licensed to OMI that targets GCGR to treat diabetes. Isis expects OMI will choose to initiate Phase 2 studies of ISIS 325568 in patients with type 2 diabetes.
- Isis' partners developing antisense drugs to treat cancer continue to support the unique therapeutic potential of antisense drugs. Already this year, OncoGenex reported Phase 2 results for OGX-011 in prostate cancer.
    - OncoGenex expects to report additional Phase 2 results for OGX-011 in patients with cancer.
    - OGX-011 will be further evaluated in prostate cancer with the initiation of a Phase 3 study in patients with prostate cancer.
    - OncoGenex expects to initiate Phase 2 clinical studies of OGX-427 that targets Hsp27 for cancer treatment.
    - Lilly expects to begin Phase 2 clinical studies of LY2181308 that targets survivin for cancer treatment.
- The broad therapeutic potential of antisense drugs enables Isis to discover drugs that are outside of Isis' core focus areas. Isis' partners are instrumental in driving the clinical development of these drugs.
    - ATL1102, which targets VLA-4 to treat multiple sclerosis, is currently in Phase 2 studies with results expected to be reported this year.
- In addition to the highlighted drugs above, Isis and Isis' drug development partners intend to initiate clinical studies on two new antisense drugs.
- Isis also intends to advance two to four new drugs into development within the next year.

Ibis

Ibis is committed to advancing the Ibis T5000 Biosensor System into larger commercial markets, including hospital-acquired infection control and clinical diagnostics. Early in 2008, Ibis achieved a key goal to establish a strategic partner in the diagnostics arena and to secure funding to support continued progress in commercial development.

- Ibis intends to continue expanding its customer base and to place at least eight additional Ibis T5000 Biosensor Systems.
- Ibis will focus on completing the next steps in its Abbott transaction.

Regulus

2008 will mark a year of substantial growth for Regulus as the company initiates focused drug discovery programs that will take advantage of the therapeutic opportunities that microRNAs offer. In 2007 and early 2008, Regulus recruited a strong senior management team to drive this growth.

- Regulus will initiate additional drug discovery programs.

Corporate Development

Isis plans to continue the momentum and successes of 2007 and early 2008 throughout the rest of the year. This includes the continued growth of the Company's core antisense technology, the addition of new and novel drugs into development as well as maintaining and adding to a broad range of partnerships.

- Isis will support its current partnerships to ensure success.
- Isis will continue to advance its pipeline and to build its revenue stream by adding new partnerships and/or satellite company relationships.

Conference Call

At 08:30 a.m. Eastern Time today, March 13, Isis will conduct a live webcast conference call to discuss this earnings release and related activities. Interested parties may access the webcast at www.isispharm.com, or listen to the call by dialing 877-718-5107. A webcast replay will be available for a limited time at the same address.

About Isis Pharmaceuticals, Inc.

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 18 drugs in development. Isis' drug development programs are focused on treating cardiovascular and metabolic diseases. Isis' partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. Ibis Biosciences, Inc., Isis' majority-owned subsidiary, is developing and commercializing the Ibis T5000™ Biosensor System, a revolutionary system to identify infectious organisms. Isis is a joint owner of Regulus Therapeutics LLC, a joint venture focused on the discovery, development and commercialization of microRNA therapeutics. As an innovator in RNA-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 as well as its Ibis Biosciences subsidiary and its Regulus joint venture, 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. 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, 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, 2006, and its quarterly report on Form 10-Q for the quarter ended September 30, 2007, which are on file with the SEC. Copies of these and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries.

ISIS PHARMACEUTICALS, INC.
SELECTED FINANCIAL INFORMATION

Condensed Consolidated Statements of Operations
(In Thousands, Except Per Share Data)

	Three months ended, December 31,		Years ended, December 31,	
	2007	2006	2007	2006
	(unaudited)		(unaudited)	
Revenue:				
Research and development revenue under collaborative agreements	$ 16,191	$ 3,832	$ 33,596	$ 15,091
Licensing and royalty revenue	8,536	8,114	36,025	9,441
Total revenue	24,727	11,946	69,621	24,532
Expenses:				
Research and development	28,012	24,240	92,641	80,567
Selling, general and administrative	5,159	4,521	15,928	12,619
Restructuring activities	—	(79)	—	(536)
Total operating expenses	33,171	28,682	108,569	92,650
Loss from operations	(8,444)	(16,736)	(38,948)	(68,118)
Other income (expense):				
Investment income	2,386	2,124	11,443	5,960
Interest expense	(1,441)	(2,213)	(7,573)	(9,029)
Gain on investments, net	—	—	3,510	2,263
Loss on early retirement of debt	—	—	(3,212)	—

Loss attributed to noncontrolling interest in Symphony GenIsis, Inc.	—	2,679	23,157	23,021
Loss attributed to noncontrolling interest in Regulus Therapeutics LLC	542	—	629	—
Net loss	(6,957)	(14,146)	(10,994)	(45,903)
Excess purchase price over carrying value of noncontrolling interest in Symphony GenIsis, Inc.	—	—	(125,311)	—
Net loss applicable to common stock	$ (6,957)	$ (14,146)	$ (136,305)	$ (45,903)
Basic and diluted net loss per share	$ (0.08)	$ (0.18)	$ (1.63)	$ (0.62)
Shares used in computing basic and diluted net loss per share	86,970	78,385	83,739	74,308

Isis Pharmaceuticals, Inc.
Reconciliation of GAAP to Pro Forma Basis:
Condensed Consolidated Operating Expenses and Loss From Operations
(In Thousands)

	Three months ended, December 31,		Years ended, December 31,	
	2007	2006	2007	2006
	(unaudited)		(unaudited)	
As reported operating expenses according to GAAP	$ 33,171	$ 28,682	$ 108,569	$ 92,650
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(2,702)	(1,557)	(9,910)	(5,747)
Excluding restructuring activities	—	79	—	536
Pro forma operating expenses	$ 30,469	$ 27,204	$ 98,659	$ 87,439
As reported loss from operations according to GAAP	$ (8,443)	$ (16,736)	$ (38,948)	$ (68,118)
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(2,702)	(1,557)	(9,910)	(5,747)
Excluding restructuring activities	—	79	—	536
Pro forma loss from operations	$ (5,741)	$ (15,258)	$ (29,038)	$ (62,907)

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

	Three months ended, December 31,		Years ended, December 31,	
	2007	2006	2007	2006
	(unaudited)		(unaudited)	
Revenue:				
Commercial revenue (1)	$ 1,022	$ 405	$ 3,512	$ 556
Research and development revenue under collaborative agreements	2,150	1,521	7,765	9,117
Total revenue	3,172	1,926	11,277	9,673
Expenses:				
Cost of commercial revenue (2)	701	362	2,705	427
Research and development	4,456	3,700	14,458	13,247
Selling, general and administrative	1,568	1,150	4,919	2,939
Total operating expenses	6,725	5,212	22,082	16,613
Loss from operations	$ (3,553)	$ (3,286)	$ (10,805)	$ (6,940)

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

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

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

	Three months ended, December 31,		Years ended, December 31,	
	2007	2006	2007	2006
	(unaudited)		(unaudited)	
As reported operating expenses according to GAAP	$ 6,725	$ 5,212	$ 22,082	$ 16,613
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(400)	(277)	(1,612)	(983)
Pro forma operating expenses	$ 6,325	$ 4,935	$ 20,470	$ 15,630
As reported loss from operations according to GAAP	$ (3,553)	$ (3,286)	$ (10,805)	$ (6,940)
Excluding compensation expense related to stock options pursuant to SFAS 123(R)	(400)	(277)	(1,612)	(983)
Pro forma loss from operations	$ (3,153)	$ (3,009)	$ (9,193)	$ (5,957)

Isis Pharmaceuticals, Inc.
Condensed Consolidated Balance Sheets
(In Thousands)

	December 31, 2007	December 31, 2006
	(unaudited)	
Assets:		
Cash, cash equivalents and short-term investments	$ 193,719	$ 193,333
Other current assets	13,598	12,870
Property, plant and equipment, net	7,131	7,157
Other assets	44,410	42,547
Total assets	$ 258,858	$ 255,907
Liabilities, noncontrolling interest and stockholders' equity:		
Current liabilities	$ 62,205	$ 25,139
5 1/2% convertible subordinated notes	—	125,000
2 5/8% convertible subordinated notes	162,500	—
Long-term obligations, net of current portion	23,910	7,866
Noncontrolling interest in Symphony GenIsis, Inc.	—	29,339
Noncontrolling interest in Regulus Therapeutics LLC	9,371	—
Stockholders' equity	872	68,563
Total liabilities, noncontrolling interest and stockholders' equity equity	$ 258,858	$ 255,907

###