SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K/A

(Amendment No.1)

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 1, 2005**

ISIS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Charter)

Delaware
(State or Other Jurisdiction of Incorporation)

000-19125	**33-0336973**
(Commission File No.)	(IRS Employer Identification No.)

2292 Faraday Avenue
Carlsbad, CA 92008
(Address of Principal Executive Offices and Zip Code)

Registrant's telephone number, including area code: **(760) 931-9200**

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

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

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

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

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

Item 2.02. Results of Operations and Financial Condition.

On March 1, 2005, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing the Company's financial results for the year ended December 31, 2004. In addition to disclosing results that are determined in accordance with Generally Accepted Accounting Principles (GAAP), the Company also discloses pro forma or non-GAAP results of operations, which are adjusted from GAAP to exclude certain expenses or benefits associated with non-cash compensation related to stock options and restructuring charges. 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.

Item 2.05. Costs Associated With Exit or Disposal Activities.

On January 10, 2005, the Company issued a press release and filed a Form 8-K announcing that it had reorganized and refocused the Company's resources to advance its most promising second-generation antisense drug candidates and to continue its development of antisense technology (the "Restructuring").

On March 1, 2005 the Company issued a press release announcing the Company's financial results for the year ended December 31, 2004. The press release contained additional information regarding the Restructuring. This press release is attached to this Current Report as Exhibit 99.1 and is incorporated herein by reference.

Item 9.01. Financial Statements and Exhibits.

(c) Exhibits.

99.1 Press Release dated March 1, 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.

ISIS PHARMACEUTICALS, INC.

Dated: March 1, 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 March 1, 2005.

Exhibit 99.1

Contact: Elizabeth Hougen, Vice President, Finance
Kristina Peterson, Executive Director, Corporate Communications
(760) 603-2331

ISIS PHARMACEUTICALS REPORTS FINANCIAL RESULTS AND HIGHLIGHTS FOR 2004

Company Previews 2005 Plans

Carlsbad, CA, March 1, 2005 - Isis Pharmaceuticals, Inc. (Nasdaq: ISIS), today announced its unaudited financial results for the year ended December 31, 2004. In line with its guidance, the Company's proforma loss from operations was $85.4 million for 2004, which is adjusted from generally accepted accounting principles (GAAP) to exclude non-cash compensation benefit of $6,000 and non-cash costs associated with restructuring activities of $32.4 million, compared to $76.3 million for 2003, which excluded $913,000 in non-cash compensation charges and restructuring charges of $1.8 million. The Company's loss from operations for 2004 was $117.9 million compared to $79.0 million in 2003, according to GAAP. The Company's increase in loss from operations in 2004 principally was a result of non-cash costs associated with restructuring activities of $32.4 million related to the Company's recent strategic decision to reorganize and refocus its resources to advance its most promising second-generation drugs and to continue its development of antisense technology. The cost containment measures the Company has implemented should significantly decrease its cash use.

Revenue

Total revenue for the quarter and year ended December 31, 2004 was $11.4 million and $42.6 million, respectively, compared to $9.7 million and $50.0 million for the same periods in 2003. The decrease in revenue on an annual basis primarily reflects the completion of Isis' Phase 3 clinical trial of Affinitak™ with an associated reduction in revenue, offset in part by increased revenue from the Company's alliances and licenses, particularly with: government agencies relating to its TIGER biosensor program; Alnylam Pharmaceuticals, Inc. (RNAi); Eyetech Pharmaceuticals, Inc. (milestone payments associated with Macugen®; pegaptanib sodium injection); and Eli Lilly and Company (research relationship and milestone payments). Isis' revenue may fluctuate from period to period based on the nature and timing of license fees and milestones earned, and other deliverables under agreements with its partners. For example, the Company's fourth quarter 2004 revenue increased over the same period in 2003 primarily as a result of the $3.0 million milestone from Eyetech associated with the marketing clearance of Macugen for the treatment of wet age-related macular degeneration (AMD) by the U.S. Food and Drug Administration (FDA).

Expenses

Isis' operating expenses were $63.2 million and $160.5 million for the quarter and year ended December 31, 2004, respectively, compared to $31.2 million and $129.0 million for the same periods in 2003, according to GAAP.

The Company's 2004 operating expenses included $32.4 million in non-cash costs associated with restructuring activities consisting principally of write downs of tangible and intangible assets, such as equipment and patents, for areas that are non-essential to the Company's current focus. Further restructuring charges including those associated with employee termination costs and the closure of Isis' Singapore laboratory will be incurred in the first quarter of 2005. The 2003 annual operating expenses included a restructuring charge of $1.8 million.

- more -

Total operating expenses for the year ended December 31, 2004 included a non-cash compensation benefit of approximately $6,000 related to variable accounting for stock options, compared to a non-cash compensation expense of $913,000 for 2003. 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.

As illustrated in the Selected Financial Information in this press release, operating expenses on a proforma basis for the quarter and year ended December 31, 2004 were $30.1 million and $128.1 million, respectively, compared to $31.2 million and $126.3 million for the same periods in 2003. Operating expenses on a proforma basis were adjusted from GAAP to exclude non-cash compensation related to stock options and costs associated with restructuring activities for both years. The decrease in fourth quarter operating expenses on a proforma basis compared to the same period in 2003 included reduced spending by the Company's Ibis division. In the fourth quarter of 2003, Isis purchased a substantial amount of equipment to support various government contracts. In the fourth quarter 2004, the Company had a significantly lower volume of such equipment purchases.

The decrease in fourth quarter 2004 operating expenses on a proforma basis compared to the same period in 2003 was also due to the completion of the Company's development activities for alicaforsen for Crohn's disease, ISIS 14803 for hepatitis C and ISIS 104838 for rheumatoid arthritis. These reductions were partially offset by increased spending in 2004 compared to 2003, to support the completion of a large Phase 2 clinical program for alicaforsen enema in patients with ulcerative colitis. Positive Phase 2 trial data suggest alicaforsen enema has the potential to be an important new drug in the marketplace, and represents a relatively near-term product opportunity for the Company. Additionally, reductions were partially offset by increased spending to support the Company's highest priority second-generation drug candidates, ISIS 301012 and ISIS 113715. Further, increased annual spending for these two drugs was the primary reason for the increased year-to-date expenditures in 2004 compared to 2003. Cumulative data from numerous clinical trials show that second-generation antisense drugs inhibit their intended targets, resulting in the desired pharmacological effects, such as cholesterol lowering with ISIS 301012 or the killing of prostate cancer cells with OGX-011.

Net Loss

The Company's net loss applicable to common stock for the quarter and year ended December 31, 2004 was $57.5 million, or $1.00 per share, and $142.9 million, or $2.52 per share, respectively, compared with a net loss applicable to common stock of $25.6 million, or $0.46 per share, and $95.7 million, or $1.73 per share, for the same periods in 2003. The increase in the net loss applicable to common stock was the result of the increase in loss from operations, as well as a decrease in investment income due to the Company's lower average cash balance in 2004 compared to 2003, an increase in interest expense primarily due to the effect of a higher debt balance during 2004 compared to 2003, and a non-cash loss on investments of $5.1 million principally related to

the impairment of the Company's equity investment in Alnylam, compared to a non-cash loss on investments of $2.4 million in 2003 related to the impairment of investments in Antisense Therapeutics Limited (ATL) and Hybridon.

The 2004 loss on investments reflects a decrease in the market value of Alnylam's stock in 2004, which Isis believes was primarily a result of financial market conditions related to biotechnology companies. The Isis-Alnylam alliance, established in 2004 to develop RNAi drugs, provides Isis with an opportunity to realize substantial value from its pioneering work in antisense mechanisms and oligonucleotide chemistry and is an example of Isis' strategy to participate in all areas of RNA-based drug discovery.

Isis' Ibis Division

Isis believes it is appropriate to discuss the financial results of its Ibis division as a separate operating segment from the consolidated results of the Company. This decision is based on:

1. The technological and organizational advancements that the Ibis division made during 2004 to advance the Company's TIGER biosensor program,
2. The future commercialization plans for TIGER technology, and
3. The significant contribution that the division made to Isis' 2004 revenue.

The Ibis division has invented TIGER (**T**riangulation **I**dentification for **G**enetic **E**valuation of **R**isks), a platform technology that has the potential to revolutionize the identification of infectious diseases. The Ibis division was founded to take advantage of the Company's expertise in RNA and utilize that knowledge and innovation to create a fundamentally different approach for the identification of bacterial and viral organisms. Isis scientists have applied proprietary technologies to develop a biological sensor to identify a broad range of infectious organisms contained in a sample, including those that are newly-emerging, genetically altered and unculturable. The Company has successfully demonstrated proof-of-principle of the TIGER biosensor through the identification of a variety of bacteria and viruses in both environmental and human clinical samples. During 2004, the Ibis team advanced the development of its TIGER technology to include application development for epidemiological surveillance and biological products screening. In addition, Isis scientists continue to expand the TIGER microbial agent database to support broader applications. These applications represent the first of many the Company plans to develop to enhance the TIGER system's commercial value and opportunity in the government, research, medical and diagnostic markets.

The advancement of TIGER technology application development has brought Isis closer to realizing the commercial potential of this unique and proprietary technology. To continue this progress, Isis recently hired Michael Treble to head its Ibis division. Mr. Treble's knowledge and expertise in product development and in commercializing technologies and diagnostics will complement the expertise and innovation of David J. Ecker, Ph.D., the scientific leader of TIGER technology development initiatives.

The Ibis division has generated revenue from grants and contracts from U.S. government agencies, including the Defense Advanced Research Projects Agency (DARPA), the Centers for Disease Control and Prevention (CDC), the Federal Bureau of Investigation (FBI), the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), and the National Institute of Standards and Technology (NIST). During 2004, the Company announced it had received grants and contracts for up to $29.5 million in multi-year funding from various governmental agencies to further the development of its TIGER technology. The Ibis division generated revenue of $2.0 million and $10.9 million for the quarter and year ended December 31, 2004, respectively, including revenue related to equipment purchased on behalf of the respective government agencies. Operating expenses for Ibis were $3.0 million and $14.2 million for the quarter and year ended December 31, 2004, respectively. These expenses included principally scientific labor in support of the numerous government contracts and grants, equipment purchased in support of these contracts and grants, lab supplies and specialized bioinformatic consulting. In general, when Ibis purchases equipment, it records expenses associated with the purchase and corresponding revenue. Ibis' revenue and operating expenses may fluctuate on a quarter to quarter basis due primarily to the timing of equipment purchased in support of its government contracts and grants. During the quarter and year ended December 31, 2004, the Ibis operating segment generated net operating losses of $995,000 and $3.3 million, respectively.

Balance Sheet

Isis ended the year with cash, cash equivalents and short-term investments of $103.9 million and working capital of $82.2 million. At December 31, 2003, Isis had cash, cash equivalents and short-term investments of $215.5 million and working capital of $194.0 million. Cash, cash equivalents and short-term investments decreased primarily as a result of cash used in operations, Isis' equity investment in Alnylam and the retirement of partner debt.

"The cost containment measures we recently implemented are consistent with accomplishing our goals for this year. We project our 2005 net operating loss, excluding costs associated with restructuring activities and non-cash compensation expense from stock options, to be in the low $50 million range. Based on our current operating plan with reasonable assumptions for new sources of revenue and cash, we believe our resources will be sufficient to meet our anticipated requirements through at least mid 2007," said B. Lynne Parshall, Executive Vice President and Chief Financial Officer of Isis. "As a result of this reorganization we are streamlining our efforts and moving our most exciting second-generation drugs forward in development to value inflection points where we are most likely to obtain the best terms from licensing partners. This in turn, will allow us to put additional product opportunities into our pipeline, grow the number of antisense drugs in development and decrease our development expenses, while continuing to participate substantially in the financial upside of multiple drugs. This goal is achievable because of the efficiency of antisense and our leadership position in the technology."

"We have also made significant progress in extracting value from our TIGER biosensor technology and our intellectual property estate, both of which generated substantial revenue in 2004. TIGER has great potential not only in government sectors, but in the non-government commercial markets as well. We are pleased with the technology's development progress and look forward to presenting our commercial business plan for this division in the next few months, continued Ms. Parshall. "Isis' patent portfolio and RNA-based drug discovery expertise continue to fuel our ability to enter into revenue-generating licensing transactions and drug discovery and development partnerships. Examples of our latest successes include our agreement with Eyetech for Macugen and our partnerships with satellite companies, including Alnylam, OncoGenex, ATL, and most recently Sarissa. We intend to continue to realize value from our patent estate, which represents the strength of our scientific innovation and the broad utility of our inventions within the pharmaceutical and diagnostic industries."

Isis' 2005-2006 Clinical Development Programs and Goals

Isis' main corporate objective is to put numerous antisense drugs on the market. To accomplish this, the Company designs its development programs to rapidly demonstrate the clinical profile and strong commercial potential of each of its drugs.

2005-2006 goals for ISIS 301012 clinical development programs for lowering high cholesterol (subcutaneous injection and oral formulations)

1. Understand the optimal dose and schedule for the drug as a single agent
2. Prepare to initiate combination studies with Lipitor®, and other drugs
3. Define the oral bioavailability of ISIS 301012 and demonstrate reduction of apoB-100, its target, and cholesterol in man
4. Advance ISIS 301012 into additional clinical trials to evaluate longer-term dosing

2005 – 2006 clinical plans for ISIS 301012

- Complete and report results from an ongoing Phase 1 single agent study in normal volunteers with borderline elevated cholesterol
- Initiate a Phase 2 trial to evaluate dose and dose schedule in patients with high cholesterol
- Initiate a Phase 2 study in patients with high cholesterol who are also taking statins
- Initiate a Phase 1 trial of the oral formulation in normal volunteers

2005 - 2006 goals for ISIS 113715 clinical development program for type 2 diabetes

1. Demonstrate safety of the drug as a single agent in patients with type 2 diabetes to support longer-term dosing
2. Define the optimal dose and schedule to support future clinical trials
3. Advance ISIS 113715 into additional clinical trials to evaluate longer-term dosing
4. Explore the drug in patients who are also taking oral anti-diabetic therapies

2005 – 2006 clinical plans for ISIS 113715

- Complete and report results from an ongoing Phase 2 single agent trial in patients with type 2 diabetes
- Initiate dosing in patients with type 2 diabetes who are also taking oral anti-diabetic therapy

2005-2006 goals for alicaforsen enema development program for ulcerative colitis

1. Meet with the FDA to discuss Phase 3 development plans for the drug
2. Identify a marketing partner with late stage development and commercial expertise, and work with that partner to develop and implement a successful Phase 3 development program

2005 – 2006 Isis pipeline goals

- Advance two new drug candidates from the Company's cardiovascular, metabolic or inflammatory disease research programs into development

2005 - 2006 Partner Development Programs and Goals

Isis' objective is to participate with its partners in advancing their products through the clinical development process and towards commercialization.

Eli Lilly and Company

- Support Lilly's ongoing anti-cancer antisense research and development programs through the progression of a Phase 1 trial of LY2181308 (survivin) in patients with cancer and the continued preclinical development of LY2275796 (eIF-4E) for cancer. Further, add new antisense drug candidates to Lilly's oncology franchise, and continue to discover and progress additional compounds for licensing consideration by Lilly.

OncoGenex Technologies, Inc.

- Support OncoGenex's expansion of OGX-011 development into additional cancer therapeutic areas through the completion of a second Phase 1 trial evaluating OGX-011 in combination with Taxotere® in solid tumors, and the initiation of Phase 2 clinical trials in patients with lung, breast and prostate cancers.

Antisense Therapeutics Limited

- Support ATL's ongoing development efforts to determine the potential of ATL1102 as an effective treatment for multiple sclerosis (MS) through the completion of an ongoing Phase 2a trial.
- Support ATL's program to explore activity of ATL1101 in patients with mild to moderate psoriasis through the completion of an ongoing proof-of-concept Phase 1 trial.

2004 Company Highlights

Advanced Isis' Drugs in Development with Focus on Second-Generation Drugs

Second-Generation Drugs – ISIS 301012, ISIS 113715, ISIS 345794 and ISIS 104838

- ISIS 301012 for the treatment of high cholesterol is currently completing Phase 1 studies. Preliminary data from a Phase 1 trial showed that ISIS 301012 produced dose-dependent, rapid and prolonged reductions of its target, ApoB-100, in low density lipoprotein (LDL), in very low density lipoprotein (VLDL) and in total cholesterol levels in volunteers with borderline elevated cholesterol. Isis has also demonstrated that an oral formulation of ISIS 301012 reduces cholesterol in animals.

- ISIS 113715, an inhibitor of PTP-1b, for the treatment of type 2 diabetes is in Phase 2 clinical trials. In a Phase 1 study, ISIS 113715 increased insulin sensitivity in normal volunteers. Further, subjects treated with ISIS 113715 did not experience hypoglycemia (excessively low blood sugar), which is an adverse effect observed with many currently available treatments for type 2 diabetes.

- ISIS 345794 was added to the Company's development pipeline. The compound is in preclinical development for cancer. Antisense inhibition of the drug target STAT-3 (Signal Transducer and Activator of Transcription 3), significantly delayed tumor growth and increased the rate of cancer cell death in multiple cell and animal models of cancer, according to data presented at the Advances in Cancer Therapies 2004 meeting in London, England. STAT-3 is a protein that regulates cell division and growth and prevents cell death.

- ISIS 104838 produced positive disease responses in patients with rheumatoid arthritis, according to results of two Phase 2 studies. While the Company was encouraged by the performance of this drug, in light of the strong competition in this market and the significant investment required to bring the first oral anti-TNF product to market, Isis elected to discontinue development of this drug.

First-Generation Drugs –Alicaforsen Enema, Alicaforsen IV, Affinitak and ISIS 14803

- Alicaforsen enema was well-tolerated and improved signs and symptoms of disease in ulcerative colitis patients, according to results of three Phase 2 clinical trials. In the Phase 2 studies, alicaforsen enema outperformed both placebo and the enema standard-of-care. Isis plans to find a strong commercial partner for alicaforsen enema, while planning a Phase 3 program for the drug.

- Alicaforsen when administered intravenously (IV) did not demonstrate statistically significant induction of clinical remissions in patients with Crohn's disease compared to placebo in two Phase 3 clinical trials. As a result of these trials, Isis will not invest further in the development of alicaforsen for Crohn's disease.

- Affinitak in combination with Gemzar® (gemcitabine HCl) and cisplatin did not demonstrate statistically significant improvement in median survival in patients with non-small cell lung cancer (NSCLC). This Phase 3 clinical trial was sponsored and conducted by Lilly. Isis will not invest further in the development of Affinitak.

- ISIS 14803 is a first-generation antisense drug to treat hepatitis C that Isis will not continue to develop.

Isis' Partnered Second-Generation Development Pipeline Continues to Expand

Eli Lilly and Company

- LY2181308, the first drug from the Isis-Lilly drug discovery alliance to advance to the clinic, entered Phase 1 clinical trials in patients with cancer. For the accomplishment of this milestone, Isis earned a $1.5 million payment from Lilly. The drug targets survivin, a molecule that allows the survival of cells that would normally undergo programmed cell death.

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

OncoGenex Technologies, Inc.

- OGX-011 was well-tolerated, achieved excellent drug concentration in its target tissue, the prostate, and produced up to a 91 percent dose-dependent reduction of its target, clusterin, according to results of a Phase 1 study. This drug is currently completing a second Phase 1 clinical trial. Clusterin is a cell survival protein that, when overproduced, prevents cancer cell death and counters the effectiveness of standard anti-tumor treatments.

Antisense Therapeutics Limited

- ATL1102 entered into a Phase 2a clinical trial in patients with multiple sclerosis (MS). Results of a dose-escalating Phase 1 study of the second-generation antisense drug showed that 6 mg/kg/week of ATL1102 appeared well-tolerated. ATL1102 is an antisense inhibitor of an immune system protein called VLA-4 (alpha-4 integrin chain; CD49d), which is known to play a part in both the onset and progression of MS.

- ATL1101 entered a proof-of-concept study in patients with mild to moderate psoriasis. The drug is designed to block the synthesis of the IGF-1 receptor, a protein involved in the regulation of cell overgrowth in psoriasis.

Business Developments

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

- Jointly developed a new high performance solid support for the manufacture of oligonucleotides with Nitto Denko Corporation of Osaka, Japan. The new solid support has the potential to decrease manufacturing costs of oligonucleotide-based drugs, such as antisense.

- Acquired Elan Corporation plc's minority interest in Orasense and HepaSense, joint ventures arising out of prior collaborations between Isis and Elan. Through the acquisition, Isis eliminated all future royalties to Elan related to the oral delivery platform developed within the Orasense collaboration and to ISIS 14803. As previously announced, Elan's participation in Orasense and HepaSense concluded in January 2003 and November 2002, respectively.

RNA-Based Drug Discovery Expertise, Patent Portfolio and IP Licenses Continue to Generate Revenue and Provide New Opportunities

Alnylam Pharmaceuticals, Inc.

- Formed a strategic alliance with Alnylam Pharmaceuticals, the leading RNAi therapeutics company, to accelerate the development and commercialization of RNAi therapeutics. Isis licensed to Alnylam its patent estate relating to antisense mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5 million technology access fee, participation in fees for Alnylam's partnering programs, and downstream milestone and royalty payments.

- Earned $500,000 from Alnylam related to Alnylam's alliance with Merck to develop and commercialize RNAi therapeutics for ocular diseases.

- Expanded its and Alnylam's strong intellectual property positions in RNA-based drug discovery by licensing core intellectual property regarding all therapeutic uses of microRNA (miRNA) from the Max Planck Society.

Eyetech Pharmaceuticals, Inc.

- Earned $4 million in milestone payments from Eyetech Pharmaceuticals in 2004 associated with Eyetech's filing of a new drug application for Macugen with the FDA and Eyetech's receipt of marketing clearance for the drug.

- Sold a portion of its royalty rights in Macugen to Drug Royalty USA, Inc. (DRC) in exchange for aggregate payments of $24 million over the next three years. Through 2009 DRC will receive royalties on the first $500 million of annual sales of Macugen. Isis and DRC will each receive 50 percent of royalties on annual sales between $500 million and $1 billion. Isis retains 90 percent of all royalties on annual sales in excess of $1 billion and 100 percent of all royalties after 2009.

Furthered TIGER Biosensor Program

- Received a two-year contract providing up to $19.5 million to further the development of the Company's TIGER biosensor to identify infectious agents in potential biological warfare attacks. DARPA is the source of this added funding, which Isis receives under a subcontract from San Diego-based Science Applications International Corporation (SAIC).

- Received three new government contracts valued at up to $10 million for the continued development of its TIGER biosensor technology.

A key highlight of these new contracts was funding from the NIAID to develop a TIGER application aimed at ensuring vaccine safety. Currently, there are few tests available that can specifically address safety issues unique to cell substrates used in vaccine manufacturing, such as the identification of unknown or novel microbes that have the potential to contaminate vaccine cell lines and substrates. Successful development of an application to simultaneously identify a broad array of infectious agents in vaccine cell substrates would create a new commercial prospect for the biosensor.

- Hired Michael Treble to head its Ibis program. Mr. Treble and David J. Ecker, Ph.D., scientific head of Ibis, will be responsible for spearheading the strategic direction and commercialization of the Company's TIGER biosensor technology.

Advanced Antisense Research Programs

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

- Announced data from preclinical studies evaluating an antisense drug that suppressed the production of the mutant protein Cu/Zn superoxide dismutase (SOD1), a molecule associated with an aggressive form of amyotrophic lateral sclerosis (ALS).

Additional Corporate Activities

- Elected Richard D. DiMarchi, Ph.D., to the Company's Board of Directors. Dr. DiMarchi is a Professor and the Jack and Linda Gill Distinguished Chair in Biomolecular Science at Indiana University, Bloomington, Indiana.

Isis will conduct a live webcast conference call to discuss this earnings release on XXX at 10:00 AM Eastern time. To participate over the Internet go to http://www.isispharm.com or http://phx.corporate-ir.net/phoenix.zhtml?p=irol-eventDetails&c=94554&eventID=1022184. A replay of the webcast will be available at these addresses for up to 30 days.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs for its pipeline and for its partners. The company has successfully commercialized the world's first antisense drug and has 10 antisense products in development to treat metabolic, cardiovascular and inflammatory diseases, and cancer. Through its Ibis division, Isis is developing a biosensor to identify infectious organisms. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of more than 1,500 issued patents worldwide. Additional information about Isis is available at http://www.isispharm.com.

This press release includes forward-looking statements regarding our business, the financial position of Isis Pharmaceuticals, and the therapeutic and commercial potential of our technologies and products in development. Any statement describing our goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' clinical goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, in developing and commercializing technology and systems used to identify infectious agents, and in the endeavor of building a business around such products and services. Actual results could differ materially from those discussed in this press release. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' research and development programs are described in additional detail in Isis' Annual Report on Form 10-K for the year ended December 31, 2003, and quarterly report on Form 10-Q for the quarter ended September 30, 2004**,** which are on file with the U.S. Securities and Exchange Commission (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' 2004 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 2004 audited financial statements with the SEC.

Affinitak™ is a trademark of Eli Lilly and Company.
Gemzar® is registered trademark of Eli Lilly and Company.
Ibis Therapeutics® is a registered trademark of Isis Pharmaceuticals, Inc.
Lipitor® is a registered trademark of Pfizer Inc.
Macugen® is a registered trademark of Eyetech Pharmaceuticals, Inc.
Taxotere® is a registered trademark of Aventis.

- Financial Data to Follow –

FINANCIAL TABLES

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,	
	2004	2003	2004	2003
	(unaudited)		(unaudited)	
Revenue:				
Research and development revenue under collaborative agreements	$ 8,347	$ 9,523	$ 32,617	$ 49,467
Licensing revenue	3,038	176	10,007	523
Total revenue	11.385	9,699	42,624	49,990
Expenses:				
Research and development	27,925	29,114	118,474	116,963
General and administrative	2,188	2,088	9,582	9,289
Compensation related to stock options	643	(23)	(6)	913
Restructuring activities	32,427	—	32,427	1,803
Total operating expenses	63,183	31,179	160,477	128,968
Loss from operations	(51,798)	(21,480)	(117,853)	(78,978)
Investment and other income	463	1,120	2,999	5,100
Interest expense	(6,205)	(5,015)	(22,592)	(18,680)
Loss on investments	—	—	(5,057)	(2,438)
Net loss	(57,540)	(25,375)	(142,503)	(94,996)
Accretion of dividends on preferred stock	—	(176)	(361)	(694)
Net loss applicable to common stock	$ (57,540)	$ (25,551)	$ (142,864)	$ (95,690)
Basic and diluted net loss per share	$ (1.00)	$ (0.46)	$ (2.52)	$ (1.73)
Shares used in computing basic and diluted net loss per share	57,319	55,555	56,642	55,463

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

	Three months ended, December 31,		Years ended, December 31,	
	2004	2003	2004	2003
	(unaudited)		(unaudited)	

As reported operating expenses according to GAAP	$ 63,183	$ 31,179	$ 160,477	$ 128,968
Excluding compensation related to stock options	(643)	23	6	(913)
Excluding restructuring activities	(32,427)	—	(32,427)	(1,803)
Proforma operating expenses	$ 30,113	$ 31,202	$ 128,056	$ 126,252
As reported loss from operations according to GAAP	$ (51,798)	$ (21,480)	$ (117,853)	$ (78,978)
Excluding compensation related to stock options	643	(23)	(6)	913
Excluding restructuring activities	32,427	—	32,427	1,803
Proforma loss from operations	$ (18,728)	$ (21,503)	$ (85,432)	$ (76,262)

Condensed Consolidated Balance Sheets
(In Thousands)

	December 2004 (Unaudited)	December 31, 2003
Assets:		
Current assets	$ 125,609	$ 239,561
Property, plant and equipment, net	28,454	34,790
Other assets	54,362	60,591
Total assets	$ 208,425	$ 334,942
Liabilities and stockholders' equity:		
Current liabilities	$ 43,416	$ 45,557
5.5% convertible subordinated notes	125,000	125,000
Long-term obligations, net of current portion	111,611	88,397
Long-term deferred revenue, net of current portion	531	8,810
Stockholders' equity (deficit)	(72,133)	67,178
Total liabilities and stockholders' equity (deficit)	$ 208,425	$ 334,942

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