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): **January 10, 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 2.05. Costs Associated With Exit or Disposal Activities.

On January 10, 2005, Isis Pharmaceuticals, Inc. (the "Company") issued a press release announcing that it has 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. 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 January 10, 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: January 10, 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 January 10, 2005.

Exhibit 99.1

Contact: Kristina Peterson
Navjot Rai
Investor Relations & Corporate Communications
760-603-2331

ISIS PHARMACEUTICALS PROVIDES GUIDANCE ON NEW CORPORATE STRUCTURE AND RESEARCH AND DEVELOPMENT PROGRAMS FOR 2005

Company Focuses on Advancing Key Second-Generation Antisense Drug Candidates and Implements Significant Cost Savings Plan

CARLSBAD, Calif., January 10, 2005 — Isis Pharmaceuticals, Inc. (Nasdaq: ISIS), today announced that it has 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. As a result of this strategic reorganization, the Company will reduce its workforce by approximately 40% with commensurate expense savings. These measures will significantly reduce the Company's cash usage.

"Through our investment in antisense we have advanced the technology to a point where we and our partners now have extensive clinical and preclinical development pipelines that are full of product opportunities. As a result of this productivity, we have far more drug assets than we can afford to develop on our own and, therefore, we believe we can better achieve our strategic goals with a smaller organization," said Stanley T. Crooke, M.D., Ph.D., and Chief Executive Officer of Isis. "As we move forward, our central tasks will be the successful development and commercialization of alicaforsen enema for ulcerative colitis and the advancement of our robust pipeline of second-generation antisense drugs. We intend to build on our strong corporate partnering history and license these drugs at key value inflection points, thus enabling us to participate in the commercial upside of numerous drugs."

"With this reorganization, we have taken significant steps to implement cost containment measures that are consistent with accomplishing our goals," added B. Lynne Parshall, Executive Vice President and Chief Financial Officer of Isis. "While we are still in the process of finalizing our plan for this year and will provide additional financial guidance in our fourth quarter financial results announcement, our goal for our 2005 net operating loss, excluding restructuring charges and non-cash compensation expense from stock options, is a 40% or greater reduction from 2004."

"As part of this restructuring effort, we will focus our resources on our most important research and development activities to advance our pipeline. As a result, we are strategically reexamining our assets and will incur non-cash write downs of tangible and intangible assets, such as equipment and patents, in areas that are non essential to our current focus. We anticipate that these write downs will occur primarily in the fourth quarter of 2004 with an initial estimate of $30 - $40 million. Further restructuring charges including those associated with termination costs will be incurred in the first quarter of 2005. Before the restructuring charges, we are on track to meet our net operating loss target for 2004, which is in the mid-$80 million range, excluding non-cash compensation expense," Ms. Parshall stated.

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Goals of the reorganization include:

- Attain strong commercial partner for alicaforsen enema for the treatment of ulcerative colitis, a near-term product opportunity
- Aggressively advance clinical development of the following key second-generation antisense drugs to clinical proof-of-value:

    - ISIS 301012 for the treatment of high cholesterol (oral and subcutaneous forms) is currently completing Phase 1 studies. In 2004, Isis reported preliminary data from a Phase 1 trial of ISIS 301012, a second-generation antisense inhibitor of apoB-100. ISIS 301012 produced dose-dependent, rapid and prolonged reductions of its target, in low density lipoprotein (LDL), in very low density lipoprotein (VLDL) and in total cholesterol levels in volunteers with borderline elevated cholesterol. ApoB-100 is the molecular carrier of LDL and VLDL cholesterol, the "bad" cholesterol involved in heart disease.

      The Company has also demonstrated that an oral formulation of ISIS 301012 reduces cholesterol in animals. Isis plans to begin human clinical trials of oral ISIS 301012 in 2005.

    - ISIS 113715 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, or excessively low blood sugar, which is an adverse effect observed with many currently available treatments for type 2 diabetes. A primary characteristic of type 2 diabetes is inefficient use of insulin to metabolize glucose. Correcting this defect is important in managing the disease. ISIS 113715 is a second-generation drug that targets protein tyrosine phosphatase (PTP-1B), an enzyme that interferes with insulin's ability to regulate glucose or blood sugar levels. PTP-1B is an attractive disease-associated target historically considered "undruggable" by the pharmaceutical industry.

- Capture value from Isis' deep portfolio of second-generation antisense product opportunities
- Expand partners' development pipelines and continue to advance currently partnered drugs:
    - OGX-011 - targeting clusterin to treat cancer
    - OGX-225 – targeting IGFBP-2 and IGFBP-5 to treat cancer
    - ATL-1102 - targeting VLA-4 to treat multiple sclerosis
    - ATL-1101 – targeting IGF-1R to treat psoriasis
    - LY2181308 - targeting survivin to treat cancer
    - LY2275796 - targeting eIF-4E to treat cancer
- Continue to advance the technology and maintain the Company's leadership role in RNA-based drug discovery and development
- Continue to license Isis' intellectual property
- Capitalize on TIGER biosensor commercial product opportunities

“With our large and growing clinical and preclinical development pipelines, we believe we can better achieve our strategic goals with a more focused drug portfolio. Therefore, we have decided to terminate the development of two lower priority drugs, ISIS 14803, a first-generation drug for the treatment of hepatitis C, and ISIS 104838 for the treatment of rheumatoid arthritis. We believe the prioritization of our drug portfolio combined with the other measures we are taking position the Company for success in 2005 and the years to come,” Dr. Crooke continued.

“We also plan to continue to derive value from our other assets, namely our TIGER biosensor and our patents. Our TIGER program is unaffected by this restructuring and is a growing asset that requires modest investment from Isis. With regard to our patent estate, we have already generated nearly $70 million from successful licensing activities, and those proceeds help support our clinical development programs. As we move forward with our research efforts, we intend to continue to expand the breadth of the utility of antisense and extend our leading patent position, while developing multiple antisense drugs for ourselves and with our partners,” Dr. Crooke added.

“We are saddened that as a result of this reorganization people must leave the Company. We are providing continuing support and career transition assistance to the employees affected by this reorganization that reflect our respect and appreciation for the contributions they have made to the Company’s growth,” Dr. Crooke concluded.

Isis will conduct a live webcast conference call to review this press release today, Monday, January 10, at 9:00 AM Eastern Time. To participate over the Internet go to www.isispharm.com. A replay of the webcast will be available at this address.

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 11 antisense products in development to treat metabolic, cardiovascular, inflammatory diseases, and cancer. Through its Ibis Therapeutics(R) program, Isis is developing a biosensor to identify infectious organisms, and is discovering small molecule drugs that bind to RNA. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of more than 1,400 issued patents worldwide. Additional information about Isis is available at http://www.isispharm.com.

This press release includes forward-looking statements regarding the financial position of Isis Pharmaceuticals, Inc., the projected success of this reorganization and the therapeutic and commercial potential of drugs and technologies developed by the Company. Any statement describing our goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis’ clinical goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of developing technology, in discovering and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such products. 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. Copies of these and other documents are available from the company.

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