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): **April 7, 2006**

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 1.01. Entry into a Material Definitive Agreement.

On April 7, 2006, Isis Pharmaceuticals, Inc. ("Isis"), entered a series of related agreements in connection with a transaction with Symphony Capital Partners, L.P. and a group of co-investors to provide $75 million to fund the development of Isis' cholesterol-lowering drug, ISIS 301012, and two novel drugs from Isis' metabolic disease program. The financing will support ISIS 301012 through the completion of registration-supporting clinical studies in patients with familial hypercholesterolemia and the completion of Phase 2b clinical trials in patients with high cholesterol. The financing will also support development of two novel diabetes drugs through initial proof of concept in human clinical trials. In addition to providing the financial support to move these drugs forward aggressively, the transaction allows Isis to continue to control and manage the development of ISIS 301012 and two other potentially valuable drugs through key development milestones.

Symphony Capital has formed Symphony GenIsis, Inc., capitalized with $75 million, to provide funding for the development of these three drugs in collaboration with Isis. Isis licensed to Symphony GenIsis the intellectual property for its apoB-100, glucagon receptor (GCGR) and glucocorticoid receptor (GCCR) programs. Isis has received an exclusive purchase option from Symphony GenIsis' investors that will allow Isis to reacquire the intellectual property by purchasing all of Symphony GenIsis' equity at a predetermined price that reflects a compounded annual rate of return that averages 32% and is 27% at the end of the anticipated four-year collaborative development period. The option exercise may be paid in cash or a combination of cash and Isis common stock (up to 33% of the purchase price), at Isis' discretion.

In exchange for the purchase option, Isis granted to Symphony Capital a five-year warrant to purchase 4.25 million shares of common stock at an exercise price of $8.93 per share, a 25% premium over Isis' prior 60 day average trading price, which was $7.14. To compensate Symphony Capital for structuring the transaction and the payment of certain of its expenses, Isis paid a structuring fee of $3.75 million. Isis intends to consolidate the financial results of Symphony GenIsis into its financial statements.

On April 7, 2006 Isis filed a a press release describing this transaction. A copy of this press release is attached as Exhibit 99.1 to this Current Report.

Item 2.01. Completion of Acquisition or Disposition of Assets.

The information set forth in Item 1.01 is incorporated herein by this reference.

Item 3.02. Unregistered Sales of Equity Securities.

The information set forth in Item 1.01 is incorporated herein by this reference.

The warrant was issued only to an accredited investor, as such term is defined in Rule 501 of Regulation D promulgated under the Securities Act of 1933, as amended (the "Securities Act"). The warrant has not been registered under the Securities Act or any state securities laws. Isis relied on the exemption from the registration requirements of the Securities Act set forth in Section 4(2) thereof and the rules and regulations promulgated thereunder. Isis has agreed to file a registration statement for the resale of the shares of common stock underlying the warrant. Neither this current report on Form 8-K nor any of the exhibits attached hereto is an offer to sell or the solicitation of an offer to buy shares of common stock or other securities of Isis.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

99.1 Press Release dated April 7, 2006.

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: April 7, 2006

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

INDEX TO EXHIBITS

99.1 Press Release dated April 7, 2006.

Exhibit 99.1

Contact: Navjot Rai
Corporate Communications
760-603-2331

ISIS PHARMACEUTICALS AND SYMPHONY GENISIS ENTER INTO $75 MILLION PRODUCT DEVELOPMENT COLLABORATION

- *Accelerates and Maintains Control of Development of ISIS 301012*
- *Funds Two New Diabetes Drugs Through Clinical Proof of Concept*
- *Permits Later Stage Corporate Partnering At Attractive Economics*

Company Holds Conference Call at 8:30 a.m. E.T. on Monday, April 10 to Discuss Transaction

CARLSBAD, Calif. – April 7, 2006 - Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today that it has completed a transaction with Symphony Capital Partners, L.P. and a group of co-investors to provide $75 million to fund the development of Isis' cholesterol-lowering drug, ISIS 301012, and two novel drugs from Isis' metabolic disease program. The financing will support ISIS 301012 through the completion of registration-supporting clinical studies in patients with familial hypercholesterolemia and the completion of Phase 2b clinical trials in patients with high cholesterol. The financing will also support development of two novel diabetes drugs through initial proof of concept in human clinical trials. In addition to providing the financial support to move these drugs forward aggressively, the transaction allows Isis to continue to control and manage the development of ISIS 301012 and two other potentially valuable drugs through key development milestones.

Symphony Capital has formed Symphony GenIsis, Inc., capitalized with $75 million, to provide funding for the development of these three drugs in collaboration with Isis. Isis has granted a license to the intellectual property for the three programs to Symphony GenIsis, but retains the exclusive right to reacquire the intellectual property at any time by acquiring all of Symphony GenIsis' equity.

"This transaction with Symphony Capital accelerates and expands our development pipeline and enhances our future economic opportunities in these drugs, while minimizing dilution and financial risk. Symphony Capital will provide the funds necessary to progress ISIS 301012 and two drugs from our exciting diabetes programs through several value inflection points," said B. Lynne Parshall, Executive Vice President and CFO of Isis Pharmaceuticals. "The transaction represents an attractive alternative to partnering these very promising compounds. In contrast to working with a pharmaceutical company, we retain control of development of these drugs and exclusive rights to them. We believe the funding will enable us to create substantial value in these drugs, which should be reflected in our stock price as development progresses. The opportunity to reacquire all rights to these drugs in the future without residual royalty obligations, after using the funding to increase their value, is very attractive. Based on the value we hope to create in these assets, we believe this financing is less dilutive than any alternatives available to us, including corporate partnering, and maximizes value for our shareholders."

"In the process of structuring and completing this transaction, we have had the opportunity to work closely with Symphony and their collaborators at RRD International, a highly respected and experienced

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drug development group, and we are looking forward to working closely with them to further enhance the value of these assets," Ms. Parshall continued. "We have been remarkably productive over the last two years in populating our pipeline and that of our partners with novel second-generation antisense drugs. Moving attractive drugs forward to key value inflection points is critical to our success, and requires significant financial investment. This transaction represents another example of our strategy to finance our efforts to broaden and strengthen our pipeline while minimizing dilution and risk to our shareholders."

"This transaction supports the development of our most important asset, ISIS 301012, and at the same time broadens our exciting diabetes pipeline. When this collaboration is complete, we expect to have data demonstrating that ISIS 301012 is a novel, safe, and effective drug to treat patients who have familial hypercholesterolemia and plan to register the drug initially for that indication," said Stanley T. Crooke, M.D., Ph.D., President and Chief Executive Officer at Isis Pharmaceuticals. "We also expect to have completed a broad Phase 2 program in the general high cholesterol patient population, which will prepare us to initiate Phase 3 trials and to understand the breadth of the potential profile for this drug both as a stand alone drug and as a combination therapy. Already we have seen the potential for significant triglyceride lowering and reduction of the most atherogenic LDL particles. We continue to be pleased with the safety profile the drug is exhibiting. ISIS 301012 is an important asset to Isis and this transaction will provide us with the resources to aggressively move this drug forward to a key value inflection point."

"In addition, this transaction allows us to move two promising earlier stage diabetes drugs into development. These compounds inhibit glucagon receptor and glucocorticoid receptor in the liver and fat tissues, tissues to which antisense oligonucleotides preferentially distribute. With these newly added funds, we expect to move both of these drugs rapidly through proof of concept in man," Dr. Crooke added. "Consistent with our strategy, we have designed initial clinical trials that should provide us with significant information about the therapeutic utility of these drugs. These two projects enhance our strong metabolics pipeline, particularly when added to ISIS 113715, our initial second-generation drug to treat type 2 diabetes. We are completing initial Phase 2 studies with ISIS 113715 and hope to present results at the American Diabetes Association meeting in June."

SUMMARY TERMS OF THE TRANSACTION

Isis licensed to Symphony GenIsis the intellectual property for its apoB-100, glucagon receptor (GCGR) and glucocorticoid receptor (GCCR) programs. Isis has received an exclusive purchase option from Symphony GenIsis' investors that will allow Isis to reacquire the intellectual property by purchasing all of Symphony GenIsis' equity at a predetermined price that reflects a compounded annual rate of return that averages 32% and is 27% at the end of the anticipated four-year collaborative development period. The option exercise may be paid in cash or a combination of cash and Isis common stock (up to 33% of the purchase price), at Isis' discretion.

In exchange for the purchase option, Isis granted to Symphony Capital a five-year warrant to purchase 4.25 million shares of common stock at an exercise price of $8.93 per share, a 25% premium over Isis' prior 60 day average trading price, which was $7.14. To compensate Symphony Capital for structuring the transaction and the payment of certain of its expenses, Isis paid a structuring fee of $3.75 million. Isis intends to consolidate the financial results of Symphony GenIsis into its financial statements.

ABOUT SYMPHONY GENISIS, INC.

Symphony GenIsis has been capitalized with $75 million from Symphony Capital and a select group of co-investors, and will be used exclusively for the development of ISIS 301012 and drugs from the GCGR and GCCR projects. Symphony GenIsis will be governed by a Board of Directors consisting of Isis, Symphony Capital and independent Board members. The Isis designee will be Dr. Stanley T. Crooke, President and CEO of Isis. The initial Symphony Capital designees will be Neil J. Sandler and

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Mark Kessel, Managing Directors of Symphony Capital. Symphony GenIsis has selected as its first independent Board member Dr. John Kastelein of the University of Amsterdam, a leading academic clinician in the cardiovascular community. Dr. Kastelein, a professor of medicine and chairman of the department of Vascular Medicine at the University of Amsterdam, is an expert in lipid and protein metabolism, founded the Lipid Research Clinic at the University of Amsterdam, and set up a foundation to identify patients with familial hypercholesterolemia. Symphony GenIsis has retained RRD International, LLC, whose senior executives will serve as Symphony GenIsis' management and will collaborate with Isis to conduct the clinical trials.

ABOUT ISIS 301012
ISIS 301012, a second-generation antisense drug, inhibits apoB-100, a protein critical to the synthesis and transport of the "bad" cholesterol involved in heart disease — low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein (VLDL). Lowering cholesterol and triglyceride levels is a key component in the prevention and management of cardiovascular disease.

In September 2005, Isis initiated the Phase 2 development program of ISIS 301012. Isis is conducting Phase 2 trials of ISIS 301012 in patients with high cholesterol, including a single-agent trial of ISIS 301012 designed to optimize dose and frequency of dosing, and to further evaluate the safety and efficacy of ISIS 301012 in patients with high cholesterol, a Phase 2 trial of ISIS 301012 in combination with statin therapy in patients with high cholesterol, and Phase 2 studies of ISIS 301012 in patients with familial hypercholesterolemia, a genetic disorder that causes extremely high cholesterol levels and results in the early onset of heart disease.

In Phase 1 trials, ISIS 301012 produced rapid, dose-dependent and prolonged reductions of its target, apoB-100, with concomitant reductions in LDL-C, VLDL, total cholesterol and triglycerides in normal subjects with elevated cholesterol. In a drug-drug interaction study, ISIS 301012 did not interact with simvastatin or ezetimibe, currently available lipid lowering drugs with which ISIS 301012 may be dosed in combination. Additionally, the drug has been well tolerated.

ABOUT THE GCGR PROGRAM
Glucagon receptor (GCGR) is the cellular receptor for glucagon, one of the counter-regulatory hormones that oppose the action of insulin and help maintain normal blood glucose levels. GCGR is mainly expressed in the liver, where it is responsible for initiating the signal that stimulates glucose production. In type 2 diabetes, unopposed action of glucagon can lead to excessive glucose production by the liver, resulting in increased blood glucose levels. Reducing the expression of GCGR using antisense inhibitors can thereby reduce excessive hepatic glucose production, which represents a novel approach to diabetes therapy. GCGR has been very difficult to target with small molecule drugs. Antisense oligonucleotides (ASOs) distribute preferentially to the liver and fat cells, making them ideal for this therapeutic approach.

Preclinical studies with Isis' ASOs targeting GCGR produced excellent glucose control and reduced levels of blood triglycerides without producing hypoglycemia. In addition, GCGR ASOs increased the levels of circulating active glucagon-like peptide 1 (GLP-1), which resulted in preservation of pancreatic function and an improvement in insulin secretion. Data from preclinical studies indicate that the drug could also have disease modifying potential in humans. Based upon these findings, Isis has added ISIS 325568, a generation 2.2 antisense oligonucleotide targeting GCGR, to its development pipeline.

ABOUT THE GCCR PROGRAM
The glucocorticoid receptor (GCCR) is an intracellular protein that serves as the receptor for the steroid hormones of the glucocorticoid (GC) family. Excessive GC action causes a spectrum of clinical features such as obesity, insulin resistance and glucose intolerance. GCs promote breakdown of protein and fat from storage and ultimately result in increased hepatic glucose production. GCs work by binding to

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GCCR; as a result, reducing GCCR levels should attenuate GC action and have a positive effect on glucose control. While many groups have attempted to develop a GCCR inhibitor for the treatment of metabolic disorders, the side effects that would result from systemic GCCR inhibition, principally in the brain, have hindered progress. Because second-generation ASOs exhibit potent activity in the liver and fat tissues, and not in the brain or adrenals, this potential safety concern is overcome. Thus, antisense technology is ideally suited for liver and fat specific GCCR inhibitor development.

Isis has studied its second-generation ASOs targeting GCCR in multiple animal models. These studies have shown that the ASOs have a very broad therapeutic profile that includes significant glucose lowering effects and a robust lowering of blood cholesterol and triglyceride levels. In addition, because ASOs do not affect GCCR in the brain or other tissues such as the adrenal glands, these animal studies have shown that the ASOs provide significant therapeutic benefit without causing systemic steroid-like side effects. Thus, an antisense inhibitor to GCCR has the potential to treat a multitude of abnormalities that are seen in diabetic patients and may therefore provide therapeutic benefit that extends far beyond glucose control. These data support the value of GCCR inhibition in the liver as a therapeutic strategy to treat type 2 diabetes. Isis is in the process of optimizing its human lead compound to inhibit GCCR and plans to initiate development of this drug in the near-term.

CONFERENCE CALL INFORMATION
Isis will conduct a live webcast conference call to discuss this press release on Monday, April 10 at 8:30 am Eastern time. To participate over the Internet go to http://www.videonewswire.com/event.asp?id=33093 or http://www.isispharm.com. A replay of the webcast will be available at these addresses for a limited time.

ABOUT SYMPHONY CAPITAL PARTNERS, L.P.
Symphony Capital is a New York-based private equity firm that invests in development stage biopharmaceutical programs. Symphony has the most experienced team in R&D project-specific financings and has $315 million in private equity capital dedicated to invest exclusively in the type of collaboration undertaken with Isis. Symphony Capital Partners is the lead investor in Symphony GenIsis. Additional information about Symphony is available at www.symphonycapital.com.

ABOUT RRD INTERNATIONAL, LLC

RRD International, LLC (RRD) is an innovative product development company dedicated to supporting the global regulatory, preclinical and clinical needs of biotechnology, pharmaceutical and medical device companies. RRD provides comprehensive strategic planning and operational support from program inception to product approval including the design, management and execution of clinical trials. RRD's team of highly experienced drug and device developers has a substantial record of favorable FDA interactions and outcomes. Through its customized and flexible business approach, RRD offers a unique risk-sharing model, enabling its goals and interests to be aligned with a partner company's success. Additional information about RRD is available at www.rrdintl.com.

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 14 antisense drugs in development to treat cardiovascular, metabolic, inflammatory and ocular diseases, and cancer. In its Ibis division, Isis is developing and commercializing the TIGER biosensor system, a revolutionary system to identify infectious organisms. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of approximately 1,500 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release includes forward-looking statements regarding the development, therapeutic potential and safety of ISIS 301012, and the antisense drugs targeted to GCCR and GCGR, and the potential success of the collaboration with Symphony GenIsis, Inc. Any statement describing Isis' goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such products. Isis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2005, which is on file with the U.S. Securities and Exchange Commission (SEC) and available from the Company.

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