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): **June 24, 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 1.01. Entry into a Material Definitive Agreement.

On June 24, 2008, Genzyme Corporation ("Genzyme") and Isis Pharmaceuticals, Inc. ("Isis") entered into a license and co-development agreement for mipomersen (the "License Agreement"). The License Agreement provides Genzyme with exclusive worldwide rights to mipomersen, a lipid-lowering drug targeting apolipoprotein B-100 that was discovered and developed by Isis and that is in phase 3 clinical development for patients with homozygous familial hypercholesterolemia ("FH"). The License Agreement was negotiated pursuant to a strategic alliance that Genzyme and Isis entered into on January 7, 2008.

Under the License Agreement, Isis will receive a $175 million license fee for mipomersen. In February, Isis received a $150 million payment from Genzyme to purchase 5 million shares of Isis common stock at $30 per share under the terms of the strategic alliance.

Under the License Agreement, over the next 30 days, the companies will transition the mipomersen IND and all regulatory authority to Genzyme. As the sponsor of mipomersen, Genzyme will take the lead on discussions with regulatory agencies and filings. In response to guidance received from the FDA, the companies have modified the initial development plan for mipomersen, subject to further discussions with the agency.

The key changes to the plan include:

- The addition of clinical studies of mipomersen in apheresis-eligible patients.
- Consolidation of the planned filings for heterozygous FH patients and other high-risk, high cholesterol patients into a single registration in the U.S.
- Acceleration of the planned outcome study so that it can be used to support the above mentioned consolidated U.S. filing.

As a result of the changes in the development plan and consistent with the premise of the transaction in which the companies are sharing the value of mipomersen, the following changes to the original financial terms of the strategic alliance have been made:

- Isis will contribute up to the first $125 million in development funding, reflecting an additional contribution of up to $50 million. Thereafter Isis and Genzyme will share development costs equally. The initial Isis development funding commitment and the shared funding will end when the program is profitable. In exchange for this additional contribution, Isis has the opportunity to receive certain milestone payments early.

- $75 million of the $150 million milestone associated with the heterozygous FH indication (the portion related to U.S. registration) may be accelerated, to be paid $25 million at annual product revenue of $250 million and $50 million at annual product revenue of $500 million. The $75 million milestone for European approval of the heterozygous FH indication remains the same.

All other financial terms of the transaction remain unchanged. In addition to the up-front payments from Genzyme ($175 million license fee and the $150 million February 2008 stock purchase), Isis is eligible to receive up to $825 million in development and regulatory milestone payments plus up to $750 million in commercial milestone payments.

The development and regulatory milestones payments are broken out as follows:

· Total milestones related to homozygous FH		US$ 50 million
· Total milestones related to heterozygous FH		US$150 million
· $75 million for U.S. approval (may be accelerated based on earlier achievement of sales targets)		
· $75 million for E.U. approval		
· Total milestones related to approvals of a first Non-FH indication		US$375 million
· Total milestones related to approvals of a follow-on product		US$250 million
	TOTAL	US$825 million

The commercial milestones payments are broken out as follows:

· Upon US$3 billion in annual sales for two consecutive years:		US$250 million
· Upon US$4 billion in annual sales for two consecutive years:		US$250 million
· Upon US$5 billion in annual sales for two consecutive years:		US$250 million
	TOTAL	US$750 million

Isis and Genzyme will allocate responsibility for funding development expenses as described above. Genzyme will be responsible for funding sales and marketing expenses until revenues are sufficient to cover them.

Genzyme and Isis will share mipomersen profits, beginning with a 70/30 Genzyme/Isis split. This split will adjust on a sliding scale, reaching 50/50 when annual revenues reach $2 billion. As part of the strategic relationship, Genzyme will also have preferred access to future Isis drugs for central nervous system and certain rare diseases.

THIS REPORT INCLUDES FORWARD-LOOKING STATEMENTS REGARDING ISIS' COLLABORATION WITH GENZYME CORPORATION, ITS FINANCIAL AND BUSINESS DEVELOPMENT ACTIVITIES, AND THE DEVELOPMENT, ACTIVITY, THERAPEUTIC POTENTIAL AND SAFETY OF MIPOMERSEN IN TREATING PATIENTS WITH HIGH CHOLESTEROL. ANY STATEMENT DESCRIBING ISIS' GOALS, EXPECTATIONS, FINANCIAL OR OTHER PROJECTIONS, INTENTIONS OR BELIEFS IS A FORWARD-LOOKING STATEMENT AND SHOULD BE CONSIDERED AN AT-RISK STATEMENT, INCLUDING THOSE STATEMENTS THAT ARE DESCRIBED AS ISIS' GOALS OR PROJECTIONS. SUCH STATEMENTS ARE SUBJECT TO CERTAIN RISKS AND UNCERTAINTIES, PARTICULARLY THOSE INHERENT IN THE PROCESS OF DISCOVERING, DEVELOPING AND COMMERCIALIZING DRUGS THAT ARE SAFE AND EFFECTIVE FOR USE AS HUMAN THERAPEUTICS, IN DEVELOPING AND COMMERCIALIZING SYSTEMS TO IDENTIFY INFECTIOUS ORGANISMS THAT ARE EFFECTIVE AND COMMERCIALLY ATTRACTIVE, AND IN THE ENDEAVOR OF BUILDING A BUSINESS AROUND SUCH PRODUCTS. ISIS' FORWARD-LOOKING STATEMENTS ALSO INVOLVE ASSUMPTIONS THAT, IF THEY NEVER MATERIALIZE OR PROVE CORRECT, COULD CAUSE ITS RESULTS TO DIFFER MATERIALLY FROM THOSE EXPRESSED OR IMPLIED BY SUCH FORWARD-LOOKING STATEMENTS. ALTHOUGH ISIS' FORWARD-LOOKING STATEMENTS REFLECT THE GOOD

FAITH JUDGMENT OF ITS MANAGEMENT, THESE STATEMENTS ARE BASED ONLY ON FACTS AND FACTORS CURRENTLY KNOWN BY ISIS. AS A RESULT, YOU ARE CAUTIONED NOT TO RELY ON THESE FORWARD-LOOKING STATEMENTS. THESE AND OTHER RISKS CONCERNING ISIS' PROGRAMS ARE DESCRIBED IN ADDITIONAL DETAIL IN ISIS' ANNUAL REPORT ON FORM 10-K FOR THE YEAR ENDED DECEMBER 31, 2007, AND ITS QUARTERLY REPORT ON FORM 10-Q FOR THE QUARTER ENDED MARCH 31, 2008, WHICH ARE ON FILE WITH THE SEC. COPIES OF THESE AND OTHER DOCUMENTS ARE AVAILABLE FROM ISIS.

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: June 24, 2008

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