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): **November 5, 2012 (October 30, 2012)**

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.)

2855 Gazelle Court
Carlsbad, CA 92010
(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 November 5, 2012, Isis Pharmaceuticals, Inc. ("Isis") announced that Isis and GlaxoSmithKline agreed to amend the clinical development plan and financial terms relating to ISIS-TTR$_{Rx}$ to reflect the accelerated development plan for ISIS-TTR$_{Rx}$.

Isis filed a press release describing this transaction. A copy of this press release is attached as Exhibit 99.1 to this Current Report and incorporated herein by reference.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

99.1	Press Release dated November 5, 2012.

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: November 5, 2012 By: /s/ B. Lynne Parshall

B. LYNNE PARSHALL
Chief Operating Officer,
Chief Financial Officer and Director

INDEX TO EXHIBITS

99.1 Press Release dated November 5, 2012.

Exhibit 99.1

ISIS ANNOUNCES EXPEDITED DEVELOPMENT OF ISIS-TTR$_{RX}$ AND AMENDMENT TO THE COLLABORATION WITH GSK TO SUPPORT PHASE 2/3 STUDY

CARLSBAD, Calif., November 5, 2012 — Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today that Isis and GlaxoSmithKline (NYSE: GSK) have agreed to amend the clinical development plan and financial terms relating to ISIS-TTR$_{Rx}$ to reflect the accelerated development plan for the drug. ISIS-TTR$_{Rx}$ is an antisense drug in development with GSK for the treatment of TTR amyloidosis, a severe and rare genetic disease characterized by progressive dysfunction of peripheral nerves and/or heart tissue. The revised development plan anticipates initiation of a Phase 2/3, registration-directed, clinical study later this year. ISIS-TTR$_{Rx}$ is one of several promising drugs in Isis' pipeline that Isis expects will begin registration-directed studies within the next several years.

"In our Phase 1 study, we demonstrated that ISIS-TTR$_{Rx}$ was generally well tolerated and produced dose-dependent significant reductions in TTR protein with several subjects reaching TTR protein levels that were below the limit of assay detection," said Brett Monia, Ph.D., senior vice president, antisense drug discovery at Isis. "We anticipate initiating the next clinical study this year, which will evaluate the effects of ISIS-TTR$_{Rx}$ on neurological dysfunction and on quality-of-life in patients with familial amyloid polyneuropathy."

Under the terms of the original collaboration agreement with GSK, which includes five programs in addition to the TTR program, Isis is eligible to receive on average up to $20 million in milestone payments per program, before Phase 2 proof-of-concept, plus a licensing fee, additional post-licensing milestone payments and double-digit royalties on sales from each product. Isis has already received $10 million in milestone payments from GSK related to the development of ISIS-TTR$_{Rx}$. Under the amended terms of the agreement Isis will receive a $2.5 million upfront payment and is eligible to earn a $7.5 million milestone payment upon the initiation of the ISIS-TTR$_{Rx}$ Phase 2/3 study. Isis is also eligible to earn an additional $50 million in pre-licensing milestone payments to support the ISIS-TTR$_{Rx}$ Phase 2/3 study. In addition, GSK has increased the regulatory and sales milestones payable to Isis should the product achieve registration and meet certain sales thresholds. Isis will also receive double-digit royalties on sales of ISIS-TTR$_{Rx}$.

"We have a robust pipeline of novel new drugs. Many of which, including ISIS-TTR$_{Rx}$, could advance into registration studies in the next 12 to 18 months. Together with GSK, we have been able to rapidly advance the TTR program from research to late-stage clinical development in just over two years," said B. Lynne Parshall, J.D., chief operating officer and chief financial officer at Isis. "Under the updated plan, Isis continues to manage the clinical development of ISIS-TTR$_{Rx}$ while benefiting from GSK's late-stage development and commercial expertise. We believe that ISIS-TTR$_{Rx}$ could be a best-in-class medicine for patients who have limited therapeutic options."

ABOUT ISIS-TTR$_{Rx}$

Transthyretin amyloidosis is a genetic disease in which the patient inherits a mutant gene that produces a misfolded form of transthyretin (TTR) protein, which progressively accumulates in tissues, impairing their function. In patients with transthyretin amyloidosis, both the mutant and normal forms of TTR can build up as fibrils in tissues, including heart, peripheral nerves, and the gastrointestinal tract. The presence of TTR aggregates interferes with the normal functions of these tissues, and as the TTR protein aggregates enlarge more tissue damage occurs and the disease worsens. There are two common types of transthyretin amyloidosis, familial amyloid polyneuropathy (FAP), which affects more than 10,000 patients worldwide, and familial amyloid cardiomyopathy (FAC), which affects more than 40,000 patients worldwide. Patients with FAP have TTR build up in peripheral nerve tissue leading to the loss of nerve function and wasting. Patients with FAC have TTR build up in the heart muscle and succumb to heart failure five to six years after symptom onset. ISIS-TTR$_{Rx}$ is an investigational drug that is designed to inhibit the production of all forms of TTR, and could offer an alternative approach to treat all types of transthyretin-related amyloidosis.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis is exploiting its leadership position in antisense technology to discover and develop novel drugs for its product pipeline and for its partners. Isis' broad pipeline consists of 25 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, and cancer. Isis' partner, Genzyme, plans to commercialize Isis' lead product, KYNAMRO™, following regulatory approval. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at www.isispharm.com.

ISIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Isis' collaboration with GlaxoSmithKline and the development, activity, therapeutic potential and safety of ISIS-TTR$_{Rx}$. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs, including the planned commercialization of KYNAMRO, is a forward-looking statement and should be considered an at-risk statement. 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 drugs. 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, 2011 and its most recent quarterly report on Form 10-Q, 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' Contacts:

D. Wade Walke, Ph.D.
Executive Director, Corporate Communications and Investor Relations
760-603-2741

Amy Blackley, Ph.D.
Associate Director, Corporate Communications
760-603-2772

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