

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 28, 2009**

ISIS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Charter)

Delaware

(State or Other Jurisdiction of Incorporation)

000-19125

(Commission File No.)

33-0336973

(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:

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- 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 28, 2009, Alnylam Pharmaceuticals, Inc. ("Alnylam") and Isis Pharmaceuticals, Inc. ("Isis") formed a new collaboration focused on the development of single-stranded RNAi (ssRNAi) technology. As part of the collaboration, Isis has co-exclusively licensed its ssRNAi technology to Alnylam in exchange for upfront payments, research and development milestone payments, and royalties. The alliance provides Alnylam with access to Isis' intellectual property and expertise regarding the development of ssRNAi antisense drugs, while both companies will have the opportunity to discover and develop drugs employing the new technology. In addition to the new collaboration, Isis and Alnylam also agreed to extend their broad cross-licensing arrangement regarding double-stranded RNAi that was established in 2004.

Isis filed press releases describing this transaction, a copy of which 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 April 29, 2009.

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 28, 2009

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



ISIS AND ALNYLAM FORM NEW COLLABORATION TO DEVELOP SINGLE-STRANDED RNAi TECHNOLOGY

- *Single-Stranded RNAi Represents a Novel Strategy of Harnessing the RNAi Pathway for Gene Silencing*
- *Isis Co-Exclusively Licenses Intellectual Property and Technology to Alnylam*
- *Companies to Host Conference Call Webcast to Discuss Isis-Alnylam Collaboration on April 29, 2009 at 9:00 a.m. ET (6:00 a.m. PT)*

CAMBRIDGE, Mass. and CARLSBAD, Calif., April 29, 2009 — Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY) and Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today that they have formed a new collaboration focused on the development of single-stranded RNAi (ssRNAi) technology. As part of the collaboration, Isis has co-exclusively licensed its ssRNAi technology to Alnylam in exchange for upfront payments, research and development milestone payments, and royalties. The alliance provides Alnylam with access to Isis' intellectual property and expertise regarding the development of ssRNAi antisense drugs, while both companies will have the opportunity to discover and develop drugs employing the new technology. In addition to the new collaboration, Isis and Alnylam also agreed to extend their broad cross-licensing arrangement regarding double-stranded RNAi that was established in 2004.

As it is known to occur in nature, the RNAi pathway is mediated by short double-stranded RNA oligonucleotides called "small interfering RNAs" or "siRNAs." To date, efforts aimed at harnessing this pathway to silence disease-causing proteins have used double-stranded siRNAs. Using its expertise in oligonucleotide chemistry and design, Isis has discovered strategies for designing single-stranded oligonucleotides that act through the RNAi mechanism. With further development, these chemically modified, single-stranded, RNA-like oligonucleotides could have improved properties for systemic administration while harnessing certain advantages of the RNAi mechanism.

"At Isis, we have made significant breakthroughs showing that chemically modified single-stranded oligonucleotides can activate the RNAi pathway. It is now time to expand upon our efforts and broaden the applications of these inventions. We believe that Alnylam, the leading company in the field of RNAi therapeutics, is the perfect partner to work with in advancing this exciting effort," said Stanley Crooke, M.D., Ph.D., Chairman and Chief Executive Officer of Isis. "Since we began our collaborative efforts in 2004, Alnylam has been a great partner and has made excellent progress in its RNAi therapeutic programs. We are confident that working together in RNAi gives ssRNAi technology the best chance for success."

"We are committed to advancing RNAi therapeutics as a new class of innovative medicines for patients, and we continue to make significant progress in the advancement of double-stranded siRNA-based drugs. As we continue our primary focus on double-stranded siRNAs, we believe that ssRNAi technology and this new collaboration with Isis can strengthen our overall efforts," said John Maraganore, Ph.D., Chief Executive Officer of Alnylam. "We've recognized since Alnylam's beginning that Isis is the leader in all aspects of antisense technology. We've had a mutually beneficial collaboration based on their innovation and patents in the field of double-stranded RNAi drugs, and we've been impressed with their continued expansion of this innovation to single-strand RNAi approaches. While there's more to do, we are excited to combine our expertise with theirs in advancing this promising technology."

Under the terms of the licensing and collaboration agreement, Alnylam will potentially pay Isis up to \$31 million in license fees payable in four tranches that include \$11 million on signing, \$10 million in 18 months or earlier if *in vivo* efficacy in rodents is demonstrated sooner, \$5 million upon achievement of *in vivo* efficacy in non-human primates, and \$5 million upon initiation of the first clinical trial with an ssRNAi drug. Alnylam will fund research activities at a minimum of \$3 million each year for three years with research development activities conducted both at Isis and Alnylam. If Alnylam develops and commercializes drugs utilizing ssRNAi technology on its own or with a partner, Isis will receive milestones and royalties. Also, initially Isis is eligible to receive up to 50 percent of any sublicense payments due to Alnylam based on Alnylam partnering of ssRNAi products, which will decline over time as Alnylam's investment in the technology and drugs increases. In turn, Alnylam is eligible to receive up to 5 percent of any sublicense payments due to Isis based on Isis' partnering of ssRNAi products. Both Isis and Alnylam are eligible to receive royalties from each other on any ssRNAi products developed by the other company.

Conference Call Information

Alnylam and Isis will host a conference call on April 29, 2009 at 9:00 a.m. ET (6:00 a.m. PT) to discuss the ssRNAi licensing and collaboration agreement. The call may be accessed by dialing 866-202-3109 (domestic) or 617-213-8844 (international) five minutes prior to the start time, and providing the passcode 65336266. A replay of the call will be available from 12:00 p.m. ET (9:00 a.m. PT) April 29, 2009 until May 6, 2009. To access the replay, please dial 888-286-8010 (domestic) or 617-801-6888 (international), and provide the passcode 32011671. A live audio webcast of the call will be available on Isis' website at www.isispharm.com and on the "Investors" section of the Alnylam's website, www.alnylam.com. An archive of the webcast will be available on the both companies' websites approximately two hours after the event.

About Alnylam Pharmaceuticals

Alnylam is a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. The company is applying its therapeutic expertise in RNAi to address significant medical needs, many of which cannot effectively be addressed with small molecules or antibodies, the current major classes of drugs. Alnylam is leading the translation of RNAi as a new class of innovative medicines with peer-reviewed research efforts published in the world's top scientific journals including *Nature*, *Nature Medicine*,

and *Cell*. The company is leveraging these capabilities to build a broad pipeline of RNAi therapeutics; its most advanced program is in Phase II human clinical trials for the treatment of respiratory syncytial virus (RSV) infection and is partnered with Cubist and Kyowa Hakko. In addition, the company is

developing RNAi therapeutics for the treatment of a wide range of disease areas, including liver cancers, hypercholesterolemia, Huntington's disease, and TTR amyloidosis. The company's leadership position in fundamental patents, technology, and know-how relating to RNAi has enabled it to form major alliances with leading companies including Medtronic, Novartis, Biogen Idec, Roche, Takeda, Kyowa Hakko, and Cubist. To reflect its outlook for key scientific, clinical, and business initiatives, Alnylam established "*RNAi 2010*" in January 2008 which includes the company's plan to significantly expand the scope of delivery solutions for RNAi therapeutics, have four or more programs in clinical development, and to form four or more new major business collaborations, all by the end of 2010. Alnylam and Isis are joint owners of Regulus Therapeutics Inc., a company focused on the discovery, development, and commercialization of microRNA therapeutics. Founded in 2002, Alnylam maintains headquarters in Cambridge, Massachusetts. For more information, please visit www.alnylam.com.

About Isis Pharmaceuticals

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 19 drugs in development. Isis' drug development programs are focused on treating cardiovascular and metabolic diseases. Isis' partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. Isis and Alnylam Pharmaceuticals are joint owners of Regulus Therapeutics Inc., a company focused on the discovery, development and commercialization of microRNA therapeutics. Isis also has made significant innovations beyond human therapeutics resulting in products that other companies, including Abbott, are commercializing. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of over 1,600 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

Alnylam Forward-Looking Statements

Various statements in this release concerning Alnylam's future expectations, plans and prospects, including statements related to Alnylam's approach to discover and develop novel drugs using double-stranded siRNA-based drugs and ssRNAi technology, both of which may never lead to marketable products, constitute forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995.

Isis Forward Looking Statements

This press release includes forward-looking statements regarding the discovery, development and commercialization of ssRNAi-based technology and ssRNAi drugs and the potential success of the collaboration with Alnylam. 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. 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, 2008, which is on file with the SEC. Copies of these and other documents are available from the Company.
