

Isis Pharmaceuticals Expects to Earn Initial Payments of Nearly \$4 Million From Alnylam's Recent RNAi Collaboration

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Isis' Leading Intellectual Property Position in RNA-Based Drug Discovery and Development Has Generated Approximately \$75 Million

CARLSBAD, Calif., Sept. 12 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today that it expects to receive initial payments of nearly \$4 million from Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY) as a result of Alnylam's recently announced alliance with a major pharmaceutical company for the development of RNA interference (RNAi) therapeutics. Isis is entitled to a portion of the upfront payments and equity investment under Alnylam's recent collaboration. In addition, Isis has the potential to earn additional revenue in the form of milestone and royalty payments on drugs which utilize the Isis technology licensed to Alnylam. Alnylam's recent collaboration is subject to customary regulatory approvals, including antitrust review under the Hart-Scott-Rodino Antitrust Improvements Act.

"As a leader in RNA-based drug discovery and development, we have built one of the industry's largest patent estates focused on RNA. Leveraging our intellectual property position through licensing agreements, such as the agreement with Alnylam, allows us to realize significant value from our inventions in oligonucleotide chemistry and antisense mechanisms, including RNAi," said B. Lynne Parshall, Executive Vice President and Chief Financial Officer of Isis Pharmaceuticals.

"When we forged the alliance with Alnylam in 2004, we did so believing they were the leaders in RNAi and had the ability to advance the potential of RNAi for therapeutic applications. Our strategy at Isis is to actively create opportunities for the industry to access our patents, allowing us to generate revenue for the continued development of our drugs, while supporting our partners' efforts for the advancement of new drugs capable of treating a broad range of disease. Alnylam's recently announced major alliance is an example of this strategy at work, as it allows us to participate in all areas of RNA-based drug discovery, including RNAi," Ms. Parshall said.

In March 2004, Isis and Alnylam Pharmaceuticals established an alliance that combines Isis' intellectual property and development expertise with Alnylam's intellectual property and research expertise in RNAi therapeutics. The patents Isis licensed to Alnylam include the "Crooke" patents that describe fundamental mechanisms for RNase-dependent antisense activity and chemically modified oligonucleotides designed to exploit such mechanisms. The license also includes over 150 issued U.S. patents from Isis' extensive portfolio of chemistry patents for use in modifying double-stranded oligonucleotides. As part of the agreement, Isis licensed to Alnylam its patent estate relating to certain antisense mechanisms and oligonucleotide chemistries for double-stranded RNAi therapeutics in exchange for a technology access fee, participation in fees for Alnylam's partnering programs, as well as downstream milestone and royalty payments.

Isis has an extensive intellectual property estate of more than 1,500 issued patents that the Company owns or exclusively licenses covering RNA-based drug discovery. Isis' patent estate covers fundamental oligonucleotide chemistries; antisense drug discovery (multiple mechanisms); antisense therapeutics; manufacturing; formulations, and delivery of oligonucleotide therapeutics, as well as Isis' RNA technology for the identification of infectious organisms.

About RNA Interference (RNAi)

RNA interference, or RNAi, is a naturally occurring mechanism within cells for selectively silencing and regulating specific genes. Since many diseases are caused by the inappropriate activity of specific genes, the ability to silence genes selectively through RNAi could provide a new way to treat a wide range of human diseases. RNAi is induced by small, double-stranded RNA molecules. One method to activate RNAi is with chemically synthesized small interfering RNAs, or siRNAs, which are double-stranded RNAs that correspond to a specific disease-associated gene. The siRNA molecules are used by the natural RNAi machinery in cells to cause highly targeted gene silencing.

About Antisense

An antisense oligonucleotide hybridizes with a complementary target RNA to form a duplex. The formation of this duplex prevents the target RNA from functioning normally. Antisense drugs are short, chemically-modified RNA-like and DNA-like molecules that scientists design to complement a small, specific segment of messenger RNA. To date, there are at least 12 known antisense mechanisms, including RNase H, RNAi and alternative splicing. Each of these mechanisms has expanded the opportunities in which antisense drugs may be successful.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis Pharmaceuticals, Inc. 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 12 antisense drugs in development to treat metabolic, cardiovascular and inflammatory diseases, and cancer. In its Isis 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 more than 1,500 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release includes forward-looking statements regarding Isis Pharmaceuticals and the potential of the Company's intellectual property position and potential future payments to Isis related to the success of Alnylam's recent collaboration with a major pharmaceutical company. 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, 2004, and its quarterly report on Form 10-Q for the quarter ended June 30, 2005, which are on file with the SEC. Copies of these and other documents are available from the Company.

SOURCE Isis Pharmaceuticals, Inc.

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