



Isis Pharmaceuticals Forms Strategic Alliance With Alnylam Pharmaceuticals in RNAi Therapeutics

Isis and Alnylam Bring Together Leading RNAi Patent Estates and Expertise to Develop RNAi Therapeutics

CARLSBAD, Calif., March 11 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS), the leading company focused on novel therapeutics targeting RNA, announced today that it has entered into a strategic alliance with Alnylam Pharmaceuticals, Inc., the leading RNAi therapeutics company to develop and commercialize RNAi therapeutics. The alliance combines Isis' intellectual property and development expertise with Alnylam's intellectual property and research expertise in RNAi therapeutics. The alliance provides Isis with an opportunity to realize significant value from its pioneering work in antisense mechanisms and oligonucleotide chemistry and strengthens Alnylam's RNAi therapeutics discovery and commercialization efforts.

"We are confident that Alnylam will continue to be the center of excellence in RNAi and that together we will make great progress in developing promising RNAi therapeutics," said Dr. Stanley Crooke, Chairman and CEO of Isis Pharmaceuticals. "This alliance with Alnylam is an example of our strategy to participate in all areas of RNA-based drug discovery directly and through collaborations with outstanding companies focused in specific areas such as RNAi, a potent antisense mechanism with significant therapeutic potential."

Under the terms of the agreement, Isis licensed to Alnylam its patent estate relating to antisense mechanisms and oligonucleotide chemistry for double stranded RNAi therapeutics in exchange for a \$5 million technology access fee, participation in fees for Alnylam's partnering programs, as well as downstream milestone and royalty payments. Access to this technology will be exclusive to Isis and Alnylam. In addition, Alnylam and Isis will share the proceeds of any licenses Alnylam grants under its previously announced InterfeRx™ program that include sublicenses to Isis' patents.

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. These exclusive licenses granted by Isis, when combined with Alnylam's fundamental intellectual property estate in RNAi, further strengthen Alnylam's industry-leading intellectual property portfolio for double stranded RNAi therapeutics.

The terms of the strategic alliance also include a \$10 million minority equity investment by Isis in Alnylam. In addition, Isis will provide Alnylam with access to its state-of-the-art downstream capabilities for development and commercialization of RNAi therapeutics, including process development, bioanalytic methods, quality control, and manufacturing. Isis will retain certain rights to a limited number of targets for double-stranded RNAi drugs. Should Isis develop an RNAi-based drug that relies on Alnylam's technologies, Isis will pay Alnylam milestones and royalties.

"A key element of the collaboration is to provide Alnylam with immediate access to Isis' manufacturing facilities and expertise in oligonucleotide-based drug development," said Lynne Parshall, Isis' Executive Vice President and CFO. "This will enable Alnylam to accelerate its drug discovery and development program and defer investment in these costly facilities. Thus, this strategic alliance further enhances Alnylam's leading position in this important new drug discovery platform."

Invitation to Webcast Conference Call

On Friday, March 12 at 9:00 am Eastern time, Isis will conduct a live webcast conference call to discuss this alliance with Alnylam. To participate over the Internet go to <http://www.isispharm.com> or <http://www.firstcallevents.com/service/ajwz402078339gf12.html>. A replay of the webcast will be available at these addresses for up to 30 days.

Alnylam is a biopharmaceutical company seeking to develop and commercialize novel therapeutics based on RNA interference, or RNAi. RNAi is a recently discovered mechanism that occurs naturally within cells and selectively silences the activity of specific genes. Because many diseases are caused by the inappropriate activity of specific genes, the ability to silence such genes selectively through RNAi could provide a means to treat a wide range of human diseases.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs. The company has successfully commercialized the world's first antisense product, and has 11 antisense products in development. In the company's GeneTrove™ program, Isis uses antisense technology as a tool to determine the function of genes and uses

that information to direct the company's internal drug discovery research and that of its corporate partners. Through its Ibis Therapeutics® program, Isis is developing a novel diagnostic tool to identify infectious organisms and is focused on the discovery of small molecule drugs that bind to RNA. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of more than 1,300 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release contains forward-looking statements concerning the discovery and development of RNAi-based technology and drugs and the potential success of the collaboration with Alnylam. Any statement describing a goal, expectation, intention or belief of the company 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 financing such activities. Actual results could differ materially from those projected in this press release. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' research and development programs are described in additional detail on its Form 10-Q for the period ended September 30, 2003, and its Form 10-K for the year ended December 31, 2002, which are on file with the U.S. Securities and Exchange Commission, copies of which are available from the company.