



Isis and Alnylam Announce Issued U.S. Patent Broadly Covering Chemical Modifications of Oligonucleotide Therapeutics

November 27, 2006

New Patent Covers Oligonucleotide Compositions with Chemical Modifications to Improve Potency, Stability, and Selectivity

CARLSBAD, Calif. & CAMBRIDGE, Mass.--(BUSINESS WIRE)--Nov. 27, 2006--Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) and Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY) announced today that a key patent was issued by the United States Patent and Trademark Office (USPTO). The U.S. patent (U.S. Patent No. 7,138,517 or "517 patent") broadly covers certain chemical modifications of oligonucleotides used to introduce "drug-like" properties in antisense oligonucleotides, including small interfering RNAs (siRNAs), the molecules that mediate RNA interference (RNAi). The issued patent is owned by Isis and is licensed exclusively to Alnylam for double-stranded RNAi therapeutic applications pursuant to the terms of their 2004 collaboration and license agreement.

"Our intellectual property estate continues to yield issued patents stemming from our pioneering efforts in the discovery and development of RNA-based therapies, including RNAi and other antisense mechanisms," said C. Frank Bennett, Ph.D., Senior Vice President, Research for Isis. "This new patent is particularly important for the emerging field of RNAi therapeutics, where our strategic alliance with Alnylam has aligned our intellectual property assets with what we believe is the leading company in the field."

"We deeply value our relationship with Isis and recognize the significance of their early contributions to and continued leadership in the field of oligonucleotide therapeutics. Indeed, our alliance with Isis represents a key component of Alnylam's overall patent estate for the development and commercialization of RNAi therapeutics," said John Maraganore, Ph.D., President and Chief Executive Officer of Alnylam. "This newly issued patent broadly covers certain chemical modifications that are used to improve potency, stability, and selectivity of siRNAs, including so-called 'no-ribose' or 'siNA' derivatives."

The new '517 patent stems from the Cook patent series that includes three previously issued U.S. patents (U.S. Patent Nos. 5,670,633; 6,005,087; and 6,531,584), and its claims broadly cover oligonucleotide compositions containing more than one 2'-ribose modifications such as 2'-O-methyl and 2'-fluoro groups. These chemical modifications can be used to improve potency and stability of siRNAs (Journal of Medicinal Chemistry 2005, 48, 901-904) and can also be used to optimize their selectivity.

About Isis Intellectual Property (IP) Licensed to Alnylam for RNAi Therapeutics

Isis Pharmaceuticals, Inc. controls more than 150 issued patents pertaining to chemical modification of oligonucleotides for therapeutic applications. These patents have been exclusively licensed to Alnylam for double-stranded RNAi therapeutics and include, but are not limited to:

-- The Crooke Patents: U.S. 5,898,031 and U.S. 6,107,094 cover compositions, methods, and uses of modified oligonucleotides to inactivate a target mRNA mediated by a double-stranded RNase;

-- Phosphorothioate and 2'-O-methyl modifications (Buhr, U.S. Patent No. 6,476,205); and,

-- 2'-Ribose modifications (Cook, U.S. Patent Nos. 5,670,633; 6,005,087; 6,531,584; and 7,138,517).

About Alnylam Intellectual Property (IP)

Alnylam's IP estate includes issued or granted fundamental patents in many of the world's major pharmaceutical markets that claim the broad structural and functional properties of synthetic RNAi therapeutic products. As it applies to the U.S. and Europe, these include:

-- The Tuschl II '704 patent (U.S. Patent No. 7,056,704) issued in June 2006 and exclusively licensed to Alnylam, which broadly covers methods of making siRNAs to silence any and all disease targets;

-- The Tuschl II '196 patent (U.S. Patent No. 7,078,196) issued in July 2006 and exclusively licensed to Alnylam, which broadly covers methods of making siRNAs with or without chemical modifications;

-- The Kreutzer-Limmer I '623 patent (EP 1144623) granted in August 2002, upheld in June 2006 and owned by Alnylam, covering methods, medicaments, and uses of siRNAs having, among other structural features, a length of 15-21 base pairs;

-- The Kreutzer-Limmer I '945 patent (EP 1214945) granted in June 2005 and owned by Alnylam, covering compositions, methods, and uses of siRNAs with a length between 15 and 49 nucleotides;

-- Additional fundamental patents and patent applications licensed to Alnylam on an exclusive or non-exclusive basis, including those of Fire and Mello (U.S. Patent No. 6,506,559) and Glover et al. (EP 1230375); and,

-- Several divisional patent applications pending of the aforementioned issued or granted patents and additional patent applications pending including Tuschl I.

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 are targeted 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 Isis Pharmaceuticals, Inc.

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 14 drugs in development. Isis' drug development programs are aimed at treating cardiovascular, metabolic and inflammatory diseases. Isis' partners are focused in disease areas such as ocular, viral and neurodegenerative diseases, and cancer. In its Ibis Biosciences™ division, Isis is developing and commercializing the Ibis T5000™ 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 approximately 1,500 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

About Alnylam

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 building a pipeline of RNAi therapeutics; its lead program is in Phase I human clinical trials for the treatment of respiratory syncytial virus (RSV) infection, which is the leading cause of hospitalization in infants in the U.S. 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 Merck, Medtronic, Novartis, and Biogen Idec. The company, founded in 2002, maintains global headquarters in Cambridge, Massachusetts, and has an additional operating unit in Kulmbach, Germany. Alnylam is honored to be the "emerging/mid-cap" company recipient of the 2006 James D. Watson Helix Award, the biotechnology industry's award for outstanding achievement. For more information, visit www.alnylam.com.

Isis Forward-Looking Statements

This press release includes forward-looking statements regarding Isis Pharmaceuticals' business, its intellectual property portfolio, and the therapeutic and commercial potential of the Company's technologies and products in development. 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, 2005, and its quarterly report on Form 10-Q for the quarter ended September 30, 2006, which are on file with the SEC. Copies of these and

other documents are available from the Company.

Alnylam Forward-Looking Statements

Various statements in this release concerning Alnylam's future expectations, plans and prospects, including its views with respect to the timing and the future issuance of patents, the importance and scope of its intellectual property rights and expectations with respect to the potential for RNAi therapeutics, constitute forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by these forward-looking statements as a result of various important factors, including risks related to: Alnylam's approach to discover and develop novel drugs, which is unproven and may never lead to marketable products; obtaining, maintaining and protecting intellectual property utilized by Alnylam's products; Alnylam's ability to enforce its patents against infringers and to defend its patent portfolio against challenges from third parties; Alnylam's ability to obtain additional funding to support its business activities; Alnylam's dependence on third parties for development, manufacture, marketing, sales and distribution of products; the successful development of Alnylam's product candidates, all of which are in early stages of development; obtaining regulatory approval for products; competition from others using technology similar to Alnylam's and others developing products for similar uses; Alnylam's dependence on collaborators; and Alnylam's short operating history; as well as those risks more fully discussed in the "Risk Factors" section of its most recent quarterly report on Form 10-Q on file with the Securities and Exchange Commission. In addition, any forward-looking statements represent Alnylam's views only as of today and should not be relied upon as representing its views as of any subsequent date. Alnylam does not assume any obligation to update any forward-looking statements.

Ibis Biosciences™ is a trademark of Isis Pharmaceuticals, Inc.

Ibis T5000™ is a trademark of Isis Pharmaceuticals, Inc.

CONTACT: Isis Pharmaceuticals, Inc.
Vice President, Corporate Development
Kate Corcoran, Ph.D., 760-603-2712

or

Alnylam Pharmaceuticals, Inc.

Investors:

Cynthia Clayton, 617-551-8207

or

Media:

KMorrisPR

Kathryn Morris, 845-635-9828

SOURCE: Alnylam Pharmaceuticals, Inc. and Isis Pharmaceuticals, Inc.