

Isis Receives Notice of Allowance That Expands the Scope of Key RNA Therapeutic Patents for Single-Stranded RNAi Technology

September 10, 2009

CAMBRIDGE, Mass. and CARLSBAD, Calif., Sept. 10 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) and Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY) announced today that the United States Patent and Trademark Office (USPTO) has allowed an Isis patent application that further expands the scope of the "Crooke" patent estate. The newly allowed patent broadly covers methods of cleaving a target RNA via a double-stranded ribonuclease mechanism, including the RNAi mechanism, with chemically modified, single-stranded RNA-containing drugs. Last year, Isis was awarded patents covering the compositions and methods of treating patients with a double-stranded or a single-stranded RNA-containing compounds, including double-stranded small interfering RNA (siRNA), which further strengthened Isis' broadly applicable intellectual property estate covering RNA-based drug discovery and development.

Isis' Crooke patent estate is a family of patents stemming from the innovative research of Stanley Crooke, M.D., Ph.D., and others at Isis to identify and design RNA molecules that utilize numerous different antisense mechanisms. Isis continues this research effort by utilizing its RNA expertise with its broad oligonucleotide medicinal chemistry endeavors to design drugs that are optimal to exploit each different mechanism and have attractive pharmaceutical properties. The Crooke patents are part of Isis' patent estate, which includes more than 1,600 issued patents worldwide and broadly covers the design and use of RNA-containing drugs. The Crooke patent estate is owned by Isis and licensed co-exclusively to Alnylam for RNAi drugs, and exclusively licensed to Regulus Therapeutics for microRNA-based drugs.

"The Crooke patents are a product of our pioneering efforts to investigate and understand the mechanisms by which antisense drugs work and to create attractive antisense drugs that exploit those mechanisms. The Crooke patents have evolved into a formidable set of intellectual property that cover our innovative advances to develop chemically modified antisense drugs optimized for each individual antisense mechanism. This patent estate provides us with broad protection against competitors who are developing RNA-based drugs," said Stanley Crooke, M.D., Ph.D., Chairman and Chief Executive Officer of Isis. "When combined with our existing patents, this new allowance extends our coverage for the development of single-stranded RNA-containing compounds that work through the RNAi pathway. Furthermore, the timing of this allowance comes on the heels of our newly announced, single-stranded RNAi technology collaboration with our partner Alnylam. We believe that with our experience in developing powerful single-stranded antisense drugs and Alnylam's expertise in the field of RNAi therapeutics, we can advance single-stranded RNAi technology to create innovative new drugs with different and potentially enhanced pharmaceutical properties that act through the RNAi mechanism."

"We are pleased with the decision by the USPTO to allow this additional patent in the Crooke patent family for ssRNAi technology. There should be no doubt that the pioneering efforts at Isis have been at the forefront of new discovery for all oligonucleotide therapeutic classes," said John Maraganore, Ph.D., Chief Executive Officer of Alnylam. "As we continue our primary focus on double-stranded siRNAs, we believe that ssRNAi technology has significant potential to advance the field of RNA therapeutics broadly. While there's more to do, we are excited to combine our expertise with Isis' in advancing this promising initiative."

Issued patents in the Crooke estate already include U.S. Patent No. 5,898,031 covering RNA-containing therapeutic compounds, and U.S. Patent No. 6,107,094 covering methods of using these compounds to interfere with target RNA function, including not only interrupting protein production with single-stranded and double-stranded (siRNA) antisense compounds but also targeting other RNAs, such as microRNAs. U.S. Patent No. 7,432,250 covering methods of treating patients by administering siRNA or single-stranded RNA-like compounds; and claims in U.S. Patent No. 7,432,249 cover pharmaceutical compositions containing single-stranded RNA-like compounds. The newly allowed claims in U.S. Patent Application No. 10/281,349 cover methods of cleaving a target mRNA by a double-stranded ribonuclease (e.g. RNAi) mechanism by contacting the target mRNA with a chemically modified, single-stranded, RNA-containing therapeutic compound.

These claims further strengthen Isis' broadly applicable intellectual property estate covering RNA-based drug discovery, development, and therapeutic uses.

Following a Notice of Allowance, the process resulting in final issuance of a patent involves several administrative steps that are typically completed within a year.

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 Kirin. 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 Kirin, 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 is a joint owner of Regulus, a company focused on the discovery, development, and commercialization of microRNA-based therapeutics. Founded in 2002, Alnylam maintains headquarters in Cambridge, Massachusetts. For more information, please visit www.alnylam.com.

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 19 drugs in development. Isis' drug development programs are focused on treating cardiovascular, metabolic and severe neurodegenerative diseases and cancer. 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 Statement

Various statements in this release concerning Alnylam's future expectations, plans and prospects, 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 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.

Isis Forward-Looking Statement

This press release includes forward-looking statements regarding Isis Pharmaceuticals' proprietary patent estate, the therapeutic and commercial potential of the Isis' 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. 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, 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.

Isis Pharmaceuticals is a registered trademark of Isis Pharmaceuticals, Inc. Regulus Therapeutics is a trademark of Regulus Therapeutics Inc.

SOURCE Isis Pharmaceuticals, Inc.; Alnylam Pharmaceuticals, Inc.

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