

# Isis Receives Notices of Allowance That Significantly Expand the Scope of Key RNA Therapeutic Patents

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*Allowances by U.S. Patent Office Enhance the "Crooke" Patent Estate by Adding Broad Claims That Cover RNA-Based Product Compositions and Methods of Treatment*

*Expands Intellectual Property Position of Alnylam for RNAi Therapeutics and Regulus for microRNA Therapeutics*

**CAMBRIDGE, Mass. and CARLSBAD, Calif., September 4, 2008** – Isis Pharmaceuticals, Inc. (Nasdaq: ISIS), Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), and the companies' joint venture Regulus Therapeutics LLC, announced today that the United States Patent and Trademark Office (USPTO) has granted notices of allowance for two U.S. patent applications that further enhance the scope of Isis' "Crooke" patent estate, which broadly covers RNA-containing therapeutics. The Crooke patent estate is a family of patents stemming from the pioneering research of Dr. Stanley Crooke and others at Isis to identify and design RNA molecules that harness cellular RNase enzymes as antisense drugs, including RNAi and microRNA therapeutics. The newly allowed claims cover pharmaceutical compositions and methods of treating patients, expanding coverage of the Crooke patents to include RNA-based drugs and treatment methods.

"Isis has an unparalleled intellectual property position that covers our innovative RNA-based technology and drug discovery platform. The Crooke patent series provides broad protection against competitors who are developing RNA-based drugs, including siRNAs," said Stanley Crooke, M.D., Ph.D., Chairman and Chief Executive Officer of Isis. "At Isis, we have dedicated ourselves to advancing the core understanding of RNA-based drugs, continually evolving and optimizing our technology. Our efforts, combined with those of our partner Alnylam and our joint venture Regulus, have broadened the understanding and potential of many of the different approaches that antisense has to offer."

The Crooke patent estate is owned by Isis and licensed to Alnylam for the development of double-stranded RNAi therapeutics, and to Regulus Therapeutics for microRNA-based therapeutics. 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 and double-stranded (siRNA) antisense compounds but also targeting other RNAs, such as microRNAs. The newly allowed claims in U.S. Patent Application No. 10/281,312 cover methods of treating patients by administering an siRNA or a single-stranded RNA-containing compound; and those in U.S. Patent Application No. 10/281,297 cover pharmaceutical compositions containing single-stranded RNA-like compounds. These allowances further strengthen Isis' broadly applicable intellectual property (IP) estate covering RNA-based drug discovery, development, and therapeutic uses.

"Our exclusive license from Isis for the Crooke patent series represents a key component of Alnylam's dominant IP position for the development and commercialization of RNAi therapeutics," said John Maraganore, Ph.D., Chief Executive Officer of Alnylam. "The allowance of these new patents is particularly important because they broaden the scope of our IP covering pharmaceutical compositions and methods of treating patients with RNAi therapeutics."

"Since our inception nearly a year ago, Regulus has made important progress in the advancement of microRNA therapeutics," said Kleanthis Xanthopoulos, Ph.D., Chief Executive Officer of Regulus Therapeutics. "The significant consolidation of the Isis and Alnylam IP estates with Regulus for microRNA therapeutics has created an unmatched opportunity for the advancement of this new technology. These new patent allowances significantly strengthen our efforts to advance microRNA therapeutic products to patients."

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 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 and metabolic diseases. Isis' partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. Ibis Biosciences, Inc., Isis' majority-owned subsidiary, is developing and commercializing the Ibis T5000™ Biosensor System, a revolutionary system to identify infectious organisms. Isis is a joint owner of Regulus Therapeutics LLC, a joint venture focused on the discovery, development and commercialization of microRNA therapeutics. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of over 1,500 issued patents worldwide. Additional information about Isis is available at [www.isispharm.com](http://www.isispharm.com).

## **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. In addition, the company is developing RNAi therapeutics for the treatment of a wide range of disease areas, including liver cancers, hypercholesterolemia, and Huntington's disease. 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, and Kyowa Hakkō Kogyo. To reflect its outlook for key scientific, clinical, and business initiatives, Alnylam has established "RNAi 2010" 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 Therapeutics LLC, a joint venture focused on the discovery, development, and commercialization of microRNA therapeutics. Founded in 2002, Alnylam maintains headquarters in Cambridge,

Massachusetts. For more information, visit [www.alnylam.com](http://www.alnylam.com).

### **About Regulus**

Regulus Therapeutics LLC is a biopharmaceutical company formed to discover, develop, and commercialize microRNA-based therapeutics. Regulus aspires to translate one of the most important new discoveries in biology into a novel new approach for innovative medicine and to build the leading microRNA company. Created as a joint venture by Alnylam Pharmaceuticals and Isis Pharmaceuticals, Regulus benefits from oligonucleotide drug discovery expertise, an established technology, and a broad intellectual property estate created and consolidated by its parent companies for the development and commercialization of microRNA-based therapeutics. Regulus' patent estate includes over 600 patents and more than 300 pending patent applications, pertaining primarily to chemical modifications of oligonucleotides targeting microRNA for therapeutic applications. In addition, Regulus has collaborations with academic researchers to build on the company's understanding of more than 60 microRNAs. In April 2008, Regulus formed a major alliance with GlaxoSmithKline to explore microRNA therapeutics for inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. Regulus, founded in September 2007, maintains facilities in Carlsbad, California. For more information, visit [www.regulusrx.com](http://www.regulusrx.com).

### **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 and its Regulus joint venture. 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. 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, 2007, 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 Isis.

Isis Pharmaceuticals is a registered trademark of Isis Pharmaceuticals, Inc. Ibis Biosciences and Ibis T5000 are trademarks of Ibis Biosciences, Inc. Regulus Therapeutics is a trademark of Regulus Therapeutics LLC.

### **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 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; 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 ability to realize future milestones and royalties as well as co-development and co-commercialization opportunities; Alnylam's dependence on third parties for development, manufacture, marketing, sales and distribution of products; 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.