Alnylam and Isis Form New Agreement, Extending Decade-Long Partnership for Leadership in RNA Therapeutics

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New Agreement Includes Cross-License on Four Disease Targets, Providing Each Company Exclusive RNA Therapeutic License Rights for Two Programs

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jan. 9, 2015-- Isis Pharmaceuticals, Inc. (Nasdaq:ISIS) and Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), leaders in RNA-targeted therapeutics, announced today they have formed a new agreement, extending their existing strategic partnership – formed originally in 2004 – to lead the development and commercialization of RNA therapeutics. This new agreement includes a cross-license of intellectual property (IP) on four disease targets, providing each company with exclusive RNA therapeutic license rights for two programs. The agreement also includes a non-exclusive technology IP cross-license, providing each company rights to certain of each other's technology advances for RNA therapeutics through April 2019.

"Isis and Alnylam lead the RNA-targeted therapeutics space and are innovators in understanding the science and developing the technologies to support RNA-targeted drug discovery. At Isis, we have dedicated ourselves to advancing the core understanding of RNA-based drugs, continually evolving and optimizing our technology and creating an extensive IP position. We believe that providing access to our IP supports our business strategy of generating revenue from our partners while focusing our efforts on our internal programs and promising pipeline of maturing products," said Stanley T. Crooke, M.D., Ph.D., chief executive officer of Isis Pharmaceuticals. "Since we began our collaborative efforts in 2004, Alnylam has been a great partner and has made excellent progress in its RNAi therapeutic programs. This expansion of our license agreement will enable both companies to enhance drug development efforts in particular disease areas while also sharing IP access. We look forward to continuing to innovate in the field of RNA-targeted therapeutics and advance our maturing pipeline of drugs to patients who are in need."

"We and Isis have each benefited enormously from our long-standing collaborative efforts over the last decade. We believe that our collaboration has enabled both companies to succeed as leaders in the development and commercialization of RNA therapeutics," said John Maraganore, Ph.D., chief executive officer of Alnylam. "This extended agreement adds a new feature, enabling further advancement of specific therapeutic programs on an exclusive basis, while allowing for the continued sharing of IP on technology. Based on the benefit that we believe innovative RNA therapeutics may bring to patients across a broad range of diseases, we look forward to continued success for both companies."

Per the terms of the new agreement, Alnylam and Isis are forming an IP cross-license with reciprocal economic terms on four therapeutic targets, where each company obtains exclusive license rights to two therapeutic programs. Alnylam is granting Isis an exclusive, royalty-bearing license to its chemistry, RNA-targeting mechanism and target-specific IP for oligonucleotide therapeutics against two targets: Factor XI and apolipoprotein (a) – or Apo(a). Isis is currently developing an investigational antisense drug toward Factor XI for the prevention of thrombosis. ISIS-FXI$_{Rx}$ is currently in Phase 2 clinical development. Isis is also currently developing an investigational antisense drug targeting Apo(a) to treat cardiovascular disease. ISIS-APO(a)$_{Rx}$ is currently in a Phase 2 clinical trial. In exchange, Isis is granting Alnylam an exclusive, royalty-bearing license to its chemistry, RNA-targeting mechanism and target-specific IP for oligonucleotide therapeutics against two targets: antithrombin (AT) and aminolevulinic acid synthase-1 (ALAS-1). Alnylam is currently developing an investigational RNAi therapeutic targeting AT for the treatment of hemophilia and rare bleeding disorders. ALN-AT3 is currently in a Phase 1 clinical trial enrolling hemophilia subjects. Alnylam is also currently developing an investigational RNAi therapeutic targeting ALAS-1 for the treatment of hepatic porphyrias, including acute intermittent porphyria (AIP); Alnylam has just filed a clinical trial application (CTA) to begin a Phase 1 clinical trial with ALN-AS1.

The new agreement also includes an extended technology IP cross-license. Specifically, Alnylam is granting Isis a royalty-bearing, non-exclusive license to new platform technology arising from May 2014 through April 2019 for single-stranded antisense therapeutics. In turn, Isis is granting Alnylam a royalty-bearing, non-exclusive license to new platform technology arising from May 2014 through April 2019 for double-stranded RNAi therapeutics. This IP cross-license includes chemistry, motif and mechanism patents, but excludes patent claims on formulations, manufacturing, and specific targets. Under the 2004 agreement, Isis licensed to Alnylam its patent estate related to antisense mechanisms and oligonucleotide chemistry for double stranded RNAi drugs in exchange for a technology access fee, participation in fees for Alnylam's partnering programs and future milestone and royalty payments from Alnylam for programs that incorporate Isis' IP. In turn, Alnylam non-exclusively licensed to Isis Alnylam's patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded antisense therapeutics, ssRNAi therapeutics and to research double-stranded RNAi compounds. Isis also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on a non-exclusive basis. Such licenses for RNAi therapeutics were granted by Alnylam in exchange for option fees, and future milestone and royalty payments from Isis for RNAi programs that incorporate certain Alnylam IP.

About Isis Pharmaceuticals, Inc.

Isis is exploiting its leadership position in RNA-targeted technology to discover and develop novel drugs for its product pipeline and for its partners. Isis' broad pipeline consists of 33 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO ®, in the United States and other countries for the treatment of patients with homozygous FH. Isis has numerous drugs in Phase 3 development in severe and rare and cardiovascular diseases. These include ISIS-APOCIII$_{Rx}$, a drug Isis is developing through its wholly owned subsidiary, Akcea Therapeutics, to treat patients with severely high triglycerides, such as patients with familial chylomicronemia syndrome; ISIS-TTR$_{Rx}$, a drug Isis is developing with GSK to treat patients with the polyneuropathy form of TTR amyloidosis; and, ISIS-SMN$_{Rx}$, a drug Isis is developing with Biogen Idec to treat infants and children with spinal muscular atrophy, a severe and rare neuromuscular disease. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at www.isispharm.com.

About Alnylam Pharmaceuticals

Alnylam is a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. The company is leading the translation of RNAi as a new class of innovative medicines. Alnylam's pipeline of investigational RNAi therapeutics is focused in 3 Strategic Therapeutic Areas (STArs): Genetic Medicines, with a broad pipeline of RNAi therapeutics for the treatment of rare diseases; Cardio-Metabolic Disease, with a pipeline of

RNAi therapeutics toward genetically validated, liver-expressed disease targets for unmet needs in cardiovascular and metabolic diseases; and Hepatic Infectious Disease, with a pipeline of RNAi therapeutics that address the major global health challenges of hepatic infectious diseases. In early 2015, Alnylam launched its “Alnylam 2020” guidance for the advancement and commercialization of RNAi therapeutics as a whole new class of innovative medicines. Specifically, by the end of 2020, Alnylam expects to achieve a company profile with 3 marketed products, 10 RNAi therapeutic clinical programs – including 4 in late stages of development – across its 3 STArs. The company’s demonstrated commitment to RNAi therapeutics has enabled it to form major alliances with leading companies including Merck, Medtronic, Novartis, Biogen Idec, Roche, Takeda, Kyowa Hakko Kirin, Cubist, GlaxoSmithKline, Ascletis, Monsanto, The Medicines Company, and Genzyme, a Sanofi company. In addition, Alnylam holds an equity position in Regulus Therapeutics Inc., a company focused on discovery, development, and commercialization of microRNA therapeutics. Alnylam scientists and collaborators have published their research on RNAi therapeutics in over 200 peer-reviewed papers, including many in the world’s top scientific journals such as *Nature, Nature Medicine, Nature Biotechnology, Cell, New England Journal of Medicine,* and *The Lancet*. Founded in 2002, Alnylam maintains headquarters in Cambridge, Massachusetts. For more information about Alnylam’s pipeline of investigational RNAi therapeutics, please visit www.alnylam.com.

Isis Pharmaceuticals’ Forward-looking Statemen t

This press release includes forward-looking statements regarding Isis Pharmaceuticals, the potential of Isis’ intellectual property position and the potential of the success of Isis’ collaboration with Alnylam. 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 drugs. 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, 2013, 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. Akcea Therapeutics™ is a trademark o**f**sis Pharmaceuticals, Inc. KYNAMRO® is a registered trademark of Genzyme Corporation.

Alnylam Forward-Looking Statements

Various statements in this release concerning Alnylam’s future expectations, plans and prospects, including without limitation, potential further RNA therapeutic advances enabled by the extended agreement with Isis, its expectations regarding the benefit that RNA therapeutics have the potential to provide to patients across a broad range of diseases, its STAr pipeline growth strategy, and its plans regarding commercialization of RNA 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, without limitation, Alnylam’s ability to discover and develop novel drug candidates and delivery approaches, successfully demonstrate the efficacy and safety of its drug candidates, the pre-clinical and clinical results for its product candidates, which may not support further development of product candidates, actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials, obtaining, maintaining and protecting intellectual property, Alnylam’s ability to enforce its patents against infringers and defend its patent portfolio against challenges from third parties, obtaining regulatory approval for products, competition from others using technology similar to Alnylam’s and others developing products for similar uses, Alnylam’s ability to manage operating expenses, Alnylam’s ability to obtain additional funding to support its business activities and establish and maintain strategic business alliances and new business initiatives, Alnylam’s dependence on third parties for development, manufacture, marketing, sales and distribution of products, the outcome of litigation, and unexpected expenditures, as well as those risks more fully discussed in the “Risk Factors” filed with Alnylam’s most recent Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) and in other filings that Alnylam makes with the SEC. 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 explicitly disclaims any obligation to update any forward-looking statements.

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