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Alnylam Presents Clinical and Non-Clinical Data Demonstrating Continued RNAi Platform Optimization and Leadership in the Development of RNA-Based Therapeutics at 12th Annual Meeting of the Oligonucleotide Therapeutics Society

- Clinical Data from Phase 1/2 Study of ALN-AAT, an Investigational RNAi Therapeutic Targeting Alpha-1 Antitrypsin (AAT) for the Treatment of AAT Deficiency-Associated Liver Disease, Demonstrate Dose-Dependent and Durable AAT Knockdown -

- Company to Pursue Follow-On Candidate with Improved Tolerability Profile; Expects to File Clinical Trial Application in 2017 -

- In Addition, Alnylam Presents Non-Clinical Data on RNAi Therapeutics, Including Extensive Review of Toxicology Results of GalNAc Conjugates Demonstrating Wide Therapeutic Index, With Lack of Thrombocytopenia or Pro-Inflammatory Effects -

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today new clinical and non-clinical research results demonstrating continued RNAi therapeutics platform innovation and optimization, including improved potency, durability, metabolic stability and tolerability with its GalNAc platform, as well as clinical translation across multiple pipeline programs. The research was presented at the 12th Annual Meeting of the Oligonucleotide Therapeutics Society (OTS), held from September 25 - 28, 2016 in Montreal, Quebec. These data were presented in a series of 10 posters and oral presentations highlighting progress on the Company's GalNAc platform and its clinical translation. Among the presentations from Alnylam scientists and clinicians, clinical data were presented from the Phase 1/2 study of ALN-AAT, an investigational RNAi therapeutic targeting alpha-1 antitrypsin (AAT) for the treatment of AAT deficiency-associated liver disease, also known as alpha-1 liver disease. Results showed that ALN-AAT administration provided potent, dose-dependent, and durable knockdown of serum AAT, although three instances of asymptomatic, transient elevations of liver enzymes were detected in the highest dose groups. As a result, the Company is finalizing selection of a new Development Candidate with plans to rapidly advance this new RNAi therapeutic toward submission of a Clinical Trial Application (CTA) in 2017. In addition, new non-clinical platform data were presented, including an extensive review of data from toxicology studies with GalNAc conjugates.

"We continue to optimize Alnylam's RNAi therapeutics platform to achieve improved potency, durability, tolerability, and metabolic stability, and we're pleased to share this progress across 10 presentations at this year's OTS meeting," said Akshay Vaishnaw, M.D., Ph.D., Executive Vice President of R&D and Chief Medical Officer at Alnylam. "We also presented clinical results from our ALN-AAT program showing potent, dose-dependent, and durable knockdown of the target protein, just as we've seen in clinical data presented from all of the other RNAi candidates in our pipeline to date. In this case, however, we observed a low incidence of asymptomatic, transiently elevated liver enzymes. We plan to advance a follow-on molecule in efforts to optimize the tolerability profile for this program, and we aim to file a CTA for ALN-AAT02 in 2017. We remain committed to developing RNAi therapeutics for alpha-1 liver disease, a rare genetic disease with significant unmet need where liver transplantation is the only treatment option beyond supportive care."

New clinical data were presented from the Phase 1/2 trial of ALN-AAT, in which the safety and efficacy of ALN-AAT were evaluated in normal healthy volunteers, and are as of a data transfer date of June 30, 2016. In this study, subjects in Part A (N=20) were enrolled into 5 ascending dose groups (N=4 per group, randomized 3:1 drug:placebo), and received a single subcutaneous dose of ALN-AAT at doses ranging from 0.1 mg/kg to 6 mg/kg. Subjects in Part B (N=6, randomized 4:2 drug:placebo) received 4 doses of ALN-AAT at 1 mg/kg administered every 28 days. ALN-AAT administration resulted in potent, dose-dependent and durable knockdown of serum AAT. A single 6 mg/kg dose of ALN-AAT attained an AAT knockdown of up to 88.9% with a mean maximal knockdown of 83.9 ± 2.6%. The pharmacodynamic effects of ALN-AAT were highly durable, where a single dose at 6 mg/kg maintained mean AAT knockdown of 75.0 ± 1.2% at approximately six months.

ALN-AAT was shown to be generally well tolerated in healthy adult volunteers. There were no drug-related serious adverse events (SAEs), discontinuations due to adverse events (AEs), or injection site reactions reported. Transient, asymptomatic, and dose-dependent increases in liver enzymes were observed in 3 out of 15 healthy volunteers exposed to single doses of ALN-AAT. Since the target patient population for ALN-AAT has established liver disease, Alnylam plans to advance a follow-on molecule targeting a different sequence for further development. Specifically, the Company is finalizing selection of a new Development Candidate - ALN-AAT02 - and plans to rapidly advance this compound towards the clinic, with a planned CTA filing in 2017.

In addition, several posters were presented by Alnylam researchers describing significant advances made in optimizing Alnylam's Enhanced Stabilization Chemistry (ESC)-GalNAc platform, including improved potency, duration of activity, and tolerability, based on a greater mechanistic understanding of GalNAc conjugate features. Amongst other talks, a comprehensive review of non-clinical data from toxicology studies of multiple GalNAc conjugates was presented, highlighting a wide therapeutic index, with no evidence of thrombocytopenia or pro-inflammatory effects, across the platform. In contrast, thrombocytopenia, pro-inflammatory effects, and nephrotoxicity have been reported with phosphorothioate-containing antisense oligonucleotides (ASOs) (Frazier, *Toxicol Pathol,* 43:78-89(2015)). In an additional presentation, comparative studies of GalNAc conjugated siRNAs and ASOs revealed differences in efficacy and PK across the two RNA platforms. Finally, early research presented in a poster showed that recent advances in siRNA design from Alnylam's ESC-GalNAc platform could potentially be translated to robust RNAi-mediated silencing in muscle using cholesterol conjugates, demonstrating the future potential of the platform for extra-hepatic delivery.

To view the clinical and non-clinical data described in this press release, please visit www.alnylam.com/capella.

About Alpha-1 Antitrypsin (AAT), AAT Deficiency, and Alpha-1 Liver Disease
Alpha-1 antitrypsin deficiency is an autosomal disorder that results in disease of the lungs and liver. AAT is a liver-produced serine proteinase inhibitor with the primary function of protecting the lungs from neutrophil elastase and other irritants that cause inflammation. About 95% of people with alpha-1 antitrypsin deficiency are homozygous and carry two copies of the abnormal Z allele (PiZZ) which expresses the Z-AAT protein. In the liver, misfolding of the mutant Z-AAT protein hinders its normal release into the blood, thereby causing it to aggregate in hepatocytes, leading to liver injury, fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). There are estimated to be approximately 120,000 individuals with the PiZZ mutation in the U.S. and major European countries, and of these, about 10% have an associated liver pathology (alpha-1 liver disease) caused by the misfolded Z-AAT protein. The only treatment options presently available for alpha-1 liver disease patients are supportive care and, in the case of advanced cirrhosis, liver transplantation. RNAi-mediated inhibition of AAT in people with alpha-1 liver disease may represent a promising new way to treat this rare disease.

Sanofi Genzyme Alliance
In January 2014, Alnylam and Sanofi Genzyme, the specialty care global business unit of Sanofi, formed an alliance to accelerate and expand the development and commercialization of RNAi therapeutics across the world. The alliance is structured as a multi-product geographic alliance in the field of rare diseases. Alnylam retains product rights in North America and Western Europe, while Sanofi Genzyme obtained the right to access certain programs in Alnylam's current and future Genetic Medicines pipeline, including ALN-AAT, in the rest of the world (ROW) through the end of 2019, together with certain broader co-development/co-commercialization rights and global product rights for certain products.

About GalNAc Conjugates and Enhanced Stabilization Chemistry (ESC)-GalNAc Conjugates
GalNAc-siRNA conjugates are a proprietary Alnylam delivery platform and are designed to achieve targeted delivery of RNAi therapeutics to hepatocytes through uptake by the asialoglycoprotein receptor. Alnylam's Enhanced Stabilization Chemistry (ESC)-GalNAc-conjugate technology enables subcutaneous dosing with increased potency and durability, and a wide therapeutic index. This delivery platform is being employed in nearly all of Alnylam's pipeline programs, including programs in clinical development.

About RNAi
RNAi (RNA interference) is a revolution in biology, representing a breakthrough in understanding how genes are turned on and off in cells, and a completely new approach to drug discovery and development. Its discovery has been heralded as "a major scientific breakthrough that happens once every decade or so," and represents one of the most promising and rapidly advancing frontiers in biology and drug discovery today which was awarded the 2006 Nobel Prize for Physiology or Medicine. RNAi is a natural process of gene silencing that occurs in organisms ranging from plants to mammals. By harnessing the natural biological process of RNAi occurring in our cells, the creation of a major new class of medicines, known as RNAi therapeutics, is on the horizon. Small interfering RNA (siRNA), the molecules that mediate RNAi and comprise Alnylam's RNAi therapeutic platform, target the cause of diseases by potently silencing specific mRNAs, thereby preventing disease-causing proteins from being made. RNAi therapeutics have the potential to treat disease and help patients in a fundamentally new way.

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 Ionis, Novartis, Roche, Takeda, Merck, Monsanto, The Medicines Company, and Sanofi Genzyme. 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.

Alnylam Forward Looking Statements
Various statements in this release concerning Alnylam's future expectations, plans and prospects, including without limitation, Alnylam's views with respect to the potential for RNAi investigational therapeutics, its expectations regarding the selection of a Development Candidate and filing of a Clinical Trial Application for ALN-AAT02, its expectations regarding its STAr pipeline growth strategy, and its plans regarding commercialization of 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 and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other 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 product candidates, the pre-clinical and clinical results for its product candidates, which may not be replicated or continue to occur in other subjects or in additional studies or otherwise support further development of product candidates for a specified indication or at all, actions or advice of regulatory agencies, which may affect the design, initiation, timing, continuation and/or progress of clinical trials or result in the need for additional pre-clinical and/or clinical testing, delays, interruptions or failures in the manufacture and supply of our product candidates, obtaining, maintaining and protecting intellectual property, Alnylam's ability to enforce its intellectual property rights against third parties and defend its patent portfolio against challenges from third parties, obtaining and maintaining regulatory approval, pricing and reimbursement for products, progress in establishing a commercial and ex-United States infrastructure, competition from others using technology similar to Alnylam's and others developing products for similar uses, Alnylam's ability to manage its growth and operating expenses, 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 and distribution of products, the outcome of litigation, the risk of government investigations, 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, except to the extent required by law, to update any forward-looking statements.

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