Alnylam Submits Clinical Trial Authorization (CTA) Application for ALN-AAT02, an Investigational RNAi Therapeutic for the Treatment of Alpha-1 Antitrypsin Deficiency-Associated Liver Disease (Alpha-1 Liver Disease)

October 3, 2018

− ALN-AAT02 is the First Investigational RNAi Therapeutic to Utilize Alnylam's Enhanced Stabilization Chemistry Plus (ESC+) GalNAc-Conjugate Technology −

− Company Expects to Initiate Phase 1/2 Study by Year-End 2018 −

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Oct. 3, 2018-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today that it has submitted an Clinical Trial Authorization (CTA) application to the Medicines and Healthcare products Regulatory Agency (MHRA) to initiate a Phase 1/2 study of ALN-AAT02, an investigational RNAi therapeutic targeting alpha-1 antitrypsin (AAT) for the treatment of AAT deficiency-associated liver disease (alpha-1 liver disease). ALN-AAT02 is Alnylam's first investigational RNAi therapeutic utilizing the Company's enhanced stabilization chemistry plus (ESC+) GalNAc-conjugate technology.

"We are pleased to reignite our efforts to develop a treatment for alpha-1 liver disease, where there is high unmet need with liver transplantation as the only available treatment option," said Thomas Hoock, Ph.D., Vice President, Program Lead for ALN-AAT02 at Alnylam."We are also excited for ALN-AAT02 to enter the clinic as the first investigational RNAi therapeutic that will leverage the significant enhancements we have made to our GalNAc-siRNA conjugate platform.Pending feedback from the MHRA, we look forward to evaluating the safety, pharmacodynamics, and clinical activity of this molecule in a Phase 1/2 study in healthy volunteers and adults with alpha-1 liver disease, which we expect to initiate by year-end 2018."

About ALN-AAT02
ALN-AAT02 is an investigational, subcutaneously administered RNAi therapeutic targeting alpha-1 antitrypsin (AAT) in development for the treatment of AAT deficiency-associated liver disease (alpha-1 liver disease). ALN-AAT02 utilizes Alnylam's enhanced stabilization chemistry plus (ESC+)-GalNAc-conjugate technology, which enables subcutaneous dosing with increased selectivity and a wide therapeutic index. The safety and efficacy of ALN-AAT02 have not been evaluated by the FDA, EMA or any other health authority.

About Alpha-1 Antitrypsin Deficiency-Associated 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 percent 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 percent have an associated liver pathology (alpha-1 liver disease) caused by the aggregates of 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.

About ESC+
Alnylam's Enhanced Stabilization Chemistry Plus (ESC+) GalNAc-conjugates are the Company's next generation delivery platform utilizing the Glycol Nucleic Acid (GNA) modification which confers enhanced specificity and therapeutic index. ESC+ siRNA conjugates exhibit minimal off-target activity and sustained on-target potency. All future investigational siRNA candidates entering early-stage clinical development, starting with ALN-AAT02, are planned to employ ESC+ design.

About RNAi
RNAi (RNA interference) is a natural cellular process of gene silencing that represents one of the most promising and rapidly advancing frontiers in biology and drug development today. Its discovery has been heralded as "a major scientific breakthrough that happens once every decade or so," and was recognized with the award of the 2006 Nobel Prize for Physiology or Medicine. By harnessing the natural biological process of RNAi occurring in our cells, a major new class of medicines, known as RNAi therapeutics, is now a reality. Small interfering RNA (siRNA), the molecules that mediate RNAi and comprise Alnylam's RNAi therapeutic platform, function upstream of today's medicines by potently silencing messenger RNA (mRNA) – the genetic precursors – that encode for disease-causing proteins, thus preventing them from being made. This is a revolutionary approach with the potential to transform the care of patients with genetic and other diseases.

About Alnylam Pharmaceuticals
Alnylam (Nasdaq: ALNY) is leading the translation of RNA interference (RNAi) into a whole new class of innovative medicines with the potential to transform the lives of people afflicted with rare genetic, cardio-metabolic, hepatic infectious, and central nervous system (CNS) diseases. Based on Nobel Prize-winning science, RNAi therapeutics represent a powerful, clinically validated approach for the treatment of a wide range of severe and debilitating diseases. Founded in 2002, Alnylam is delivering on a bold vision to turn scientific possibility into reality, with a robust discovery platform. Alnylam's first U.S. FDA-approved RNAi therapeutic is ONPATTRO™ (patisiran) lipid complex injection, available in the U.S. for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults. In the EU, ONPATTRO is approved for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy. Alnylam has a deep pipeline of investigational medicines, including three product candidates that are in late-stage development. Looking forward, Alnylam will continue to execute on its "Alnylam 2020" strategy of building a multi-product, commercial-stage biopharmaceutical company with a sustainable pipeline of RNAi-based medicines to address the needs of patients who have limited or inadequate treatment options. Alnylam employs over 800 people worldwide and is headquartered in Cambridge, MA. For more information about our people, science and pipeline, please visit www.alnylam.com and engage with us on Twitter at @Alnylam or on LinkedIn.

Alnylam Forward Looking Statements
Various statements in this release concerning Alnylam's future expectations, plans and prospects, including, without limitation, the expected enhancements of its ESC+ GalNAc-conjugate technology utilized in ALN-AAT02, Alnylam's filing of a CTA for ALN-AAT02 and its expectations regarding the anticipated timing for initiation of a Phase 1/2 study, and expectations regarding its “Alnylam 2020” guidance for the advancement and 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 its 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, successfully launching, marketing and selling its approved products globally, Alnylam’s ability to successfully expand the indication for ONPATTRO in the future, 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.

ALN-AAT02 has not been evaluated by the FDA, EMA, or any other regulatory authority and no conclusions can or should be drawn regarding the safety or effectiveness of this investigational therapeutic.

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