Alnylam Reports New Platform Innovations for RNAi Therapeutics at the Oligonucleotide Therapeutics Society 2018 Annual Meeting

October 2, 2018

− Achieves Robust and Durable Target Gene Silencing with Central Nervous System Delivery of Novel siRNA Conjugates in Non-Human Primates −

− Extends Progress on Extrahepatic Delivery with Ocular Disease Targets −

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Oct. 2, 2018-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today further progress on the Company's platform efforts in extrahepatic delivery of novel siRNA conjugates, including central nervous system (CNS) and ocular delivery in rat and non-human primates (NHPs). Preclinical results were presented at the Oligonucleotide Therapeutics Society (OTS) 2018 Annual Meeting held September 30 to October 3 in Seattle, WA.

"We are pleased to report on our continued progress on broadening the therapeutic potential of RNAi by demonstrating successful delivery to extrahepatic tissues such as the CNS and eye. The *in vivo* activity of our novel CNS and ocular siRNA conjugates is consistent across species and targets with potent and highly durable mRNA silencing. As we have seen with liver target gene silencing, we anticipate a highly competitive profile for our siRNA conjugates with increased potency, extended duration of action, and encouraging safety margins," said Kevin Fitzgerald, Ph.D., Senior Vice President, Research at Alnylam. "We are excited to grow the potential universe of tissues, targets, and diseases addressable by RNAi therapeutics, expanding our efforts to reach patients in need of new therapies. We believe that the demonstration of potent, safe, and infrequent dosing may allow us to develop innovative RNAi therapeutics directed to these new targets."

In NHP studies, a single intrathecal (IT) injection of a siRNA conjugate targeting the ubiquitously expressed β-catenin mRNA transcript resulted in broadly distributed target gene silencing across the brain and spinal cord. Robust and durable silencing of β-catenin mRNA was observed after a single dose at day 31 post injection. Specifically, a single 72 mg dose (approximately 24 mg/kg) resulted in over 80 percent target silencing in the spinal cord and approximately 50 percent silencing across regions of the brain. Widespread distribution of the novel siRNA conjugate was observed across the CNS, including the frontal and temporal cortex, deep brain structures such as basal ganglia and dentate gyrus, cerebellum, brain stem and spinal cord, with evidence for cellular localization in neurons, astrocytes, and microglia. In additional rat studies, further optimization of novel conjugates was reported using siRNAs targeting superoxide dismutase 1 (SOD1), a genetically defined disease gene implicated in amyotrophic lateral sclerosis (ALS). Additional optimization of the conjugate design resulted in an over ten-fold improvement in potency, with a dose as low as 0.07 mg (approximately 0.25 mg/kg) resulting in approximately 50 percent SOD1 silencing across the CNS. In both rat and NHP studies, intrathecal administration of these novel siRNA conjugates was found to be generally well tolerated. Consistent with previous guidance, Alnylam expects to select its first CNS Development Candidate (DC) by the end of 2018 with an initial Investigational New Drug (IND) or equivalent application in late 2019 or early 2020.

Alnylam scientists also presented new preclinical results with novel siRNA conjugates targeting transthyretin (TTR), demonstrating delivery to ocular tissue in rats and NHPs. Efficient and durable silencing of ocular TTR mRNA in rat was achieved following a single intravitreal injection, with siRNAs localizing to the relevant cell types in the eye, retinal pigment epithelium (RPE) and ciliary epithelia (CE), where amyloid deposits can occur in approximately 10 percent of hereditary ATTR (hATTR) amyloidosis patients. The ocular target gene silencing effect was recapitulated in NHPs with approximately 98 percent silencing of TTR mRNA in RPE and near complete knockdown of TTR protein at day 31, as measured in immunohistochemical analyses. In NHP studies, there were no notable safety findings related to administration of ocular siRNA conjugates.

Additional OTS presentations by Alnylam scientists and collaborators included results on:

- Further optimization of the Company's enhanced stabilization chemistry plus (ESC+) conjugate platform
- Safety evaluation of 2'-Fluoro-modified nucleotides embedded in GalNAc-conjugate siRNAs
- Simultaneous silencing of two different gene transcripts with Bis-RNAi conjugates.

For the full breadth of results presented by the Company at OTS please visit the Capella section of the Alnylam website.

We are also pleased to share that Alnylam's publication of results from the APOLLO Phase 3 pivotal trial of patisiran featured in the July 5, 2018 issue of *The New England Journal of Medicine* has been selected as the OTS "2018 Paper of the Year" – an award designed to honor the year's most impactful paper in the field of oligonucleotide therapeutics.

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 potential opportunity for extrahepatic delivery of novel siRNA conjugates, including in the central nervous system and eye based upon preclinical studies in rat and non-human primates, the expected timing for identification of its first CNS program DC and filing of an IND or equivalent application for a CNS program, 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.

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