Alnylam Presents New Evidence Demonstrating Significant Association of V122I, a Highly Prevalent, Pathogenic Transthyretin (TTR) Mutation, with Clinical Diagnosis of Polyneuropathy

September 13, 2019

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Sep. 13, 2019-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, today presented new results from an analysis of the UK Biobank – a prospective cohort study with genetic, physical, and health data on approximately 500,000 individuals across the United Kingdom – demonstrating a significant association of the V122I mutation, a highly prevalent mutation in the transthyretin (TTR) gene, with a clinical diagnosis of polyneuropathy. These results were presented at the Heart Failure Society of America (HFSA) 23rd Annual Scientific Meeting being held September 13-16, in Philadelphia, PA.

"The data we and collaborators presented at HFSA indicate that carriers of V122I – a TTR mutation previously thought to be associated with a phenotype presenting primarily with cardiac manifestations – have a significantly increased likelihood of a clinical diagnosis of polyneuropathy," said Eric Green, Senior Vice President and General Manager, TTR Program at Alnylam. "These findings demonstrate an association of V122I with the presence of a mixed clinical phenotype, supporting the need for a broader assessment of a patient's overall health to look for multisystem manifestations of hereditary ATTR amyloidosis, which often include both cardiomyopathy and polyneuropathy."

The V122I variant is the most common pathogenic TTR mutation implicated in hereditary ATTR (hATTR) amyloidosis in the U.S., with a reported prevalence of approximately four percent in African Americans[1]. Historically, the V122I variant has been associated with a predominantly cardiac phenotype. We presented findings from a phenome-wide association study demonstrating a significant association of the TTR V122I genotype with a clinical diagnosis of polyneuropathy (based on International Classification of Diseases, 10th revision [ICD10] diagnosis codes) in the black subpopulation of the UK Biobank. Among the 6,063 unrelated black participants, 243 subjects (mean age of 52.6 years) were carriers of the TTR V122I mutation, equating to an allele frequency of two percent. Among the carriers, polyneuropathy was significantly associated with the V122I genotype (odds ratio [OR] equals 11.2; 95% confidence interval [CI]; p equals 1.1×10^{-6}). The significant association of V122I with polyneuropathy was further replicated in the Penn Medicine Biobank from 5,737 black participants with 190 subjects who were V122I carriers.

In addition, there was nominally significant evidence that carriers of V122I were at an increased risk for other signs and symptoms of hATTR amyloidosis, including carpal tunnel syndrome and urinary retention. There was no association of V122I with cardiomyopathy, potentially due to the younger age of the carriers in the UK Biobank at the time of analysis (mean age of 52.6 years) as compared to the age at which hATTR amyloidosis with cardiomyopathy typically presents (over 65 years in the V122I population, as reported in the literature[2]).

Other presentations at HFSA include:

- **Identifying Mixed Phenotype: Evaluating the Presence of Polyneuropathy in Patients with Hereditary Transthyretin-Mediated Amyloidosis with Cardiomyopathy**
  Lead Author: Grogan M
  Date/Time: Saturday, September 14, 2019 at 6:15 pm ET.

- **Risk Factors for Mortality in Patients with Hereditary Transthyretin-Mediated Amyloidosis: Analysis of APOLLO and Global Open Label Extension Studies**
  Lead Author: Polydefkis M
  Date/Time: Saturday, September 14, 2019 at 6:15 pm ET.

- **Impact of Patisiran, an RNAi Therapeutic, on Orthostatic Intolerance in Patients with Hereditary Transthyretin-Mediated Amyloidosis**
  Lead Author: Judge DP
  Date/Time: Friday, September 13, 2019 at 6:15 pm ET.

- **Alnylam Act®: Heterogenous Disease Manifestations of Hereditary Transthyretin-Mediated Amyloidosis**
  Lead Author: Malladi R
  Date/Time: Friday, September 13, 2019 at 6:15 pm ET.

To view these results presented at HFSA please visit www.alnylam.com/capella.

Alnylam will host an RNAi Roundtable to discuss the latest progress with its TTR programs on Monday, September 16, at 1:00 pm ET. This event will be webcast live on the Investors page of the Company's website, www.alnylam.com, and a replay will be posted on the Alnylam website approximately three hours after the event.

1. Dhamarajan *et al*. *J Am Geriatr Soc* 2012;60:765-74.
2. Ruberg and Berk, *Circulation* 2012;126:1286-1300.

About Transthyretin (ATTR) Amyloidosis
Transthyretin amyloidosis (ATTR) amyloidosis is a rare, serious, life-threatening, multisystemic disease encompassing hereditary ATTR (hATTR)

amyloidosis and wild-type ATTR (wtATTR) amyloidosis, which result from either hereditary (genetic mutation) or nonhereditary (ageing) causes, respectively. In ATTR amyloidosis, misfolded TTR proteins accumulate as amyloid fibrils in multiple organs and tissue types. hATTR amyloidosis can include sensory and motor, autonomic and cardiac symptoms and is estimated to impact 50,000 people worldwide. wtATTR amyloidosis predominantly manifests as cardiomyopathy and heart failure symptoms, although patients may experience other manifestations due to extra-cardiac amyloid deposition. The disease is estimated to impact 200,000 – 300,000 people worldwide.

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 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 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/ocular diseases. Based on Nobel Prize-winning science, RNAi therapeutics represent a powerful, clinically validated approach for the treatment of diseases with high unmet need. Alnylam’s first commercial RNAi therapeutic is ONPATTRO® (patisiran), approved in the U.S., EU, Canada, and Japan. Alnylam has a deep pipeline of investigational medicines, including five product candidates in Phase 3 studies and one in registration. 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. Headquartered in Cambridge, MA, Alnylam employs over 1,200 people worldwide. 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, expectations regarding the implications of data indicating that carriers of the TTR mutation V122I have a significantly increased likelihood of a clinical diagnosis of polyneuropathy, including the need for a broader assessment of a patient’s overall health to look for the multisystem manifestations of hereditary ATTR amyloidosis, 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 or marketing 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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