Alnylam Presents New Clinical Research Findings at the Second European Meeting of ATTR Amyloidosis for Doctors and Patients

September 3, 2019

− Neurofilament Light Chain (NfL) Identified as a Potential Biomarker of Nerve Damage and Polyneuropathy due to hATTR Amyloidosis; ONPATTRO® (patisiran) Treatment Found to Reduce NfL Levels Relative to Placebo in APOLLO Phase 3 Study–

− In Analysis of UK Biobank, Carriers of Transthyretin (TTR) "Stabilizing" T119M Variant in a General Population Setting Show No Evidence for Extended Lifespan or Protection Against Vascular Disease –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Sep. 3, 2019-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, today shared new findings at the Second European Meeting of ATTR Amyloidosis (EU-ATTR) for Doctors and Patients, being held September 2-3, in Berlin, Germany. The Company and collaborators presented results from a proteome-wide biomarker analysis of samples from the APOLLO Phase 3 study of ONPATTRO® (patisiran), an RNAi therapeutic for the treatment of the polyneuropathy of hereditary ATTR (hATTR) amyloidosis in adults. In addition, results were presented 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 – on clinical outcomes and medical history of individuals with the non-pathogenic transthyretin (TTR) "stabilizing" T119M variant.

"These new clinical research findings provide important insights on a potential biomarker for monitoring polyneuropathy and response to treatment, and highlight human genetic data showing no evidence for protection against vascular disease or life-extending advantages of a 'stabilizing' T119M gene variant associated with elevated TTR plasma levels," said Eric Green, Senior Vice President and General Manager, TTR Program at Alnylam. "Notably, our biomarker study represents the most comprehensive plasma proteomics analysis in patients with hATTR amyloidosis performed to date and the first system-wide proteomics interrogation of response to an RNAi therapeutic in humans.We believe a biomarker such as NfL could have the potential to allow for an earlier diagnosis of polyneuropathy in patients with hATTR amyloidosis."

Biomarker Analysis of APOLLO Patient Samples

A comprehensive proteomics analysis on plasma samples from patients in the APOLLO Phase 3 study was conducted to interrogate system-wide changes in the proteome in response to treatment and to identify potential biomarkers for early detection of disease. Across greater than 1000 proteins screened, a significant change was observed in the levels of 66 proteins following patisiran treatment (p less than 4.18×10^{-5}). Neurofilament light chain (NfL) – a well-described biomarker of neuroaxonal damage – was identified as having the greatest statistical significance (p equals 3.95×10^{-21}) for change relative to placebo over the 18-month study period. A correlation between changes in NfL levels and polyneuropathy, as determined by the mNIS+7 score, indicated that decreasing levels of NfL are associated with improvements in measures of polyneuropathy. Thus, these data support further evaluation of NfL as a potential biomarker for hATTR amyloidosis that may facilitate earlier diagnosis of polyneuropathy and enable monitoring of disease progression and/or regression over time, with or without treatment. Moreover, upon further evaluation, NfL may also offer an easy and convenient blood test to detect polyneuropathy in patients with mutations that predominantly cause cardiomyopathy, e.g., V122I, but where underlying nerve damage often occurs and can be overlooked.

UK Biobank Analysis of Transthyretin "Stabilizing" Variant (T119M)

Results were also presented of an analysis from the UK Biobank characterizing the association of the T119M genotype with mortality and vascular disease. The T119M variant encodes a thermodynamically and kinetically stabilized TTR protein that increases the stability of wild type and mutant TTR tetramers by slowing tetramer dissociation – a mechanism that established the therapeutic rationale for small-molecule TTR tetramer stabilizers. People with the T119M variant have higher plasma levels of TTR.

A previous Scandinavian study of 68,602 subjects and 321 carriers found an association of the T119M variant with extended lifespan and reduced vascular disease[1]. Accordingly, the potential effect of the TTR T119M variant on vascular disease and mortality was investigated in the UK Biobank cohort, representing 337,148 subjects and 2,502 carriers of the variant. The analysis showed that carriers of the TTR T119M variant were *not* protected against vascular, cardiovascular, or cerebrovascular disease, or death. Furthermore, no difference was seen between T119M carriers and non-carriers in their time to death following a diagnosis of vascular disease. These findings suggest that stabilization of the TTR tetramer and/or higher plasma levels of TTR do not confer protection against vascular disease or death in a general population setting.

To view the results presented at EU-ATTR please visit www.alnylam.com/capella.

1. Hornstrup *et al*. *Arteriscler Thromb Vasc Biol* 2013;33:1441–7.

Important Safety Information

ONPATTRO is a medicine that treats the polyneuropathy caused by an illness called hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis). ONPATTRO is used in adults only.

Infusion-Related Reactions

Infusion-related reactions (IRRs) have been observed in patients treated with ONPATTRO. In a controlled clinical study, 19 percent of ONPATTRO-treated patients experienced IRRs, compared to 9 percent of placebo-treated patients. The most common symptoms of IRRs with ONPATTRO were flushing, back pain, nausea, abdominal pain, dyspnea, and headache.

To reduce the risk of IRRs, patients should receive premedication with a corticosteroid, paracetamol, and antihistamines (H1 and H2 blockers) at least 60 minutes prior to ONPATTRO infusion. Monitor patients during the infusion for signs and symptoms of IRRs. If an IRR occurs, consider slowing or interrupting the infusion and instituting medical management as clinically indicated. If the infusion is interrupted, consider resuming at a slower infusion rate only if symptoms have resolved. In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed.

Reduced Serum Vitamin A Levels and Recommended Supplementation

ONPATTRO treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance (RDA) of vitamin A is advised for patients taking ONPATTRO. Higher doses than the RDA should not be given to try to achieve normal serum vitamin A levels during treatment with ONPATTRO, as serum levels do not reflect the total vitamin A in the body.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g. night blindness).

Adverse Reactions

The most common adverse reactions that occurred in patients treated with ONPATTRO were respiratory-tract infection (29 percent) and infusion related reactions (19 percent).

About the APOLLO Phase 3 Study

The APOLLO Phase 3 trial was a randomized, double-blind, placebo-controlled, global study designed to evaluate the efficacy and safety of patisiran in hATTR amyloidosis patients with polyneuropathy. The primary endpoint of the study was the change from baseline in modified Neuropathy Impairment Score +7 (mNIS+7) relative to placebo at 18 months. Secondary endpoints included: the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) score; NIS-weakness (NIS-W); Rasch-built Overall Disability Scale (R-ODS); timed 10-meter walk (10-MWT); modified BMI (mBMI); and the composite autonomic symptom score-31 (COMPASS-31). In addition, exploratory cardiac assessments included measurement of N-terminal pro-brain natriuretic peptide (NT-ProBNP) levels and echocardiography. The trial enrolled 225 hATTR amyloidosis patients from 19 countries with 39 genotypes who were randomized 2:1, patisiran:placebo, with patisiran administered at 0.3 mg/kg once every three weeks for 18 months. All patients who completed the APOLLO Phase 3 study were eligible to screen for the Global OLE study, in which they have the opportunity to receive patisiran on an ongoing basis.

About ONPATTRO®(Patisiran)

ONPATTRO is an RNAi therapeutic that is approved by the U.S. Food and Drug Administration (FDA) for the treatment of the polyneuropathy of hATTR amyloidosis in adults. ONPATTRO is also approved in the European Union for the treatment of hATTR amyloidosis in adults with Stage 1 or Stage 2 polyneuropathy, in Canada for the treatment of hATTR amyloidosis with polyneuropathy by Health Canada, and in Japan for the treatment of hATTR amyloidosis with polyneuropathy by the Japanese Ministry of Health, Labour and Welfare (MHLW). Based on Nobel Prize-winning science, ONPATTRO is an intravenously administered RNAi therapeutic targeting transthyretin (TTR) for the treatment of hereditary ATTR amyloidosis. It is designed to target and silence TTR messenger RNA, thereby blocking the production of TTR protein before it is made. ONPATTRO blocks the production of TTR in the liver, reducing its accumulation in the body's tissues in order to halt or slow down the progression of the disease.

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, Alnylam's views with respect to new clinical research findings regarding a potential biomarker for monitoring polyneuropathy and response to treatment and the potential of

such biomarker to allow for an earlier diagnosis of polyneuropathy in patients with hATTR amyloidosis, its views with respect to human genetic data showing no evidence for protection against vascular disease or life-extending advantages of a “stabilizing” T119M gene variant associated with elevated TTR plasma levels, 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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