Alnylam Announces Publication in Circulation of Exploratory Cardiac Endpoint Data from APOLLO Phase 3 Study of Patisiran

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− Published Data From the APOLLO Study Show That Patisiran Improved Markers of Cardiomyopathy in Patients with Hereditary ATTR Amyloidosis with Polyneuropathy –

− In Exploratory Post-Hoc Analysis, Reduction of All-Cause Mortality and Hospitalization Was Observed in Patients Treated with Patisiran –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Sep. 14, 2018-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today publication of data from exploratory cardiac assessments in the APOLLO Phase 3 study of patisiran, an RNAi therapeutic for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults. The results were published online today in the journal *Circulation,* and showed that patisiran improved markers of cardiomyopathy in patients with hATTR amyloidosis with polyneuropathy.

“We are encouraged by these data from the APOLLO study on the effects of patisiran on measures of cardiac disease in hATTR amyloidosis patients with polyneuropathy,” said Pushkal Garg, M.D., Chief Medical Officer at Alnylam. “These data support the hypothesis that patisiran may favorably impact certain cardiac manifestations of hATTR amyloidosis. Accordingly, we believe these results support further study of the effects of patisiran on cardiac features of hATTR amyloidosis.”

“Our publication highlights the potential for patisiran to favorably impact certain cardiac manifestations of hATTR amyloidosis,” said Scott D. Solomon M.D., Professor of Medicine, Brigham and Women's Hospital, Harvard Medical School, lead author of the paper. “The results on exploratory endpoints of NT-proBNP – an independent predictor of survival in patients with ATTR amyloidosis – and certain echocardiographic measures of cardiac structure and function are encouraging. Together, these data support the therapeutic potential of patisiran in patients with cardiac involvement due to hATTR amyloidosis, where there is a substantially reduced lifespan and limited treatment options.”

The publication presents data on the treatment effects of patisiran relative to placebo on certain measures of cardiac structure and function in patients with echocardiographic evidence of cardiac amyloid involvement at study entry with no confounding medical history (APOLLO cardiac subpopulation*: n=126; 56 percent of total study population). In pre-specified analyses, left ventricular (LV) wall thickness was reduced by a mean of 0.9 mm (p=0.017) in patisiran-treated patients, compared to those receiving placebo. Global longitudinal strain was also significantly improved by an absolute value of -1.4 percent (p=0.015), suggesting improved systolic, or contractile, function. Differences in global longitudinal strain of this magnitude have been shown in other studies to be an independent predictor of survival in patients with ATTR and light-chain (AL) amyloidosis.[1] In addition to the favorable impact on echocardiographic measures of cardiac structure and function, a treatment effect on NT-proBNP – a cardiac biomarker released in response to ventricular wall stress – was also observed in the cardiac subpopulation, with a significant 55 percent relative reduction in NT-proBNP levels compared to placebo. This effect was noted as early as 9 months of treatment, the first assessment time point in APOLLO. In post-hoc categorical analyses, a greater proportion of patients treated with patisiran versus placebo experienced reductions in LV wall thickness, decreases in global longitudinal strain and reductions in NT-proBNP relative to baseline, providing evidence for potential improvement in markers of cardiomyopathy.

In the overall study population, the proportions of patients with cardiac adverse events (AEs) and cardiac serious AEs (SAEs) were similar in the patisiran and placebo groups. The incidence of cardiac arrhythmia AEs was lower in the patisiran group compared with placebo (18.9 versus 28.6 percent). Deaths occurred in 4.7 percent of patients treated with patisiran (3.2 per 100 patient-years) and 7.8 percent of patients treated with placebo (6.2 per 100 patient-years). In a post-hoc analysis, the exposure-adjusted rates of all-cause death and/or hospitalization were 71.8 and 34.7 per 100 patient-years in the placebo and patisiran groups, respectively, representing an approximately 50 percent reduction in event rate. A similar trend was seen for reduction of all-cause death and/or cardiac hospitalizations.

As described in U.S. prescribing information for ONPATTRO™(patisiran), four serious adverse reactions of atrioventricular (AV) heart block (2.7 percent) occurred in ONPATTRO-treated patients, including three cases of complete AV block. No serious adverse reactions of AV block were reported in placebo-treated patients.

The full manuscript titled, "Effects of Patisiran, an RNA Interference Therapeutic, on Cardiac Parameters in Patients with Hereditary Transthyretin-Mediated Amyloidosis: an Analysis of the APOLLO Study," will appear in an upcoming issue of *Circulation*.

*Patients with baseline left ventricular wall thickness ≥ 13 mm and no medical history of aortic valve disease or hypertension.

1. Quarta CC, Solomon SD, Uraizee I, Kruger J, Longhi S, Ferlito M, Gagliardi C, Milandri A, Rapezzi C, Falk RH. Left ventricular structure and function in transthyretin-related versus light-chain cardiac amyloidosis. *Circulation*. 2014;129:1840–1849.

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 echocardiographic assessments. 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 open-label extension or OLE study, which is ongoing.

About ONPATTRO™ (patisiran) lipid complex injection
Patisiran is an intravenously administered RNAi therapeutic targeting transthyretin (TTR) for the treatment of hereditary ATTR amyloidosis. It is designed to target and silence specific messenger RNA, potentially blocking the production of TTR protein before it is made. Patisiran blocks the production of transthyretin in the liver, reducing its accumulation in the body's tissues in order to halt or slow down the progression of the disease. In August 2018, patisiran received approval from the U.S. Food and Drug Administration (FDA) for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults, having been reviewed by the FDA under Priority Review and previously granted Breakthrough Therapy and Orphan Drug Designations. ONPATTRO (patisiran) is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults. ONPATTRO is the first and only RNA interference (RNAi) therapeutic approved by the FDA for this indication. In the EU, ONPATTRO (patisiran) was approved by the European Commission in August 2018 for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy. The European Medicines Agency reviewed patisiran under the accelerated assessment procedure that is granted to medicines judged to be of major interest for public health and therapeutic innovation. Additional regulatory filings in other markets, including Japan, are planned in 2018. ONPATTRO is administered through intravenous (IV) infusion once every 3 weeks following required premedication and the dose is based on actual body weight. Home infusion may be an option for some patients after an evaluation and recommendation by the treating physician and may not be covered by all insurance plans. Regardless of the setting, ONPATTRO infusions should be performed by a healthcare professional. For more information about ONPATTRO, visit ONPATTRO.com.

About hATTR amyloidosis
Hereditary transthyretin (TTR)-mediated amyloidosis (hATTR) is an inherited, progressively debilitating, and often fatal disease caused by mutations in the TTR gene. TTR protein is primarily produced in the liver and is normally a carrier of vitamin A. Mutations in the TTR gene cause abnormal amyloid proteins to accumulate and damage body organs and tissue, such as the peripheral nerves and heart, resulting in intractable peripheral sensory neuropathy, autonomic neuropathy, and/or cardiomyopathy, as well as other disease manifestations. hATTR amyloidosis represents a major unmet medical need with significant morbidity and mortality, affecting approximately 50,000 people worldwide. The median survival is 4.7 years following diagnosis, with a reduced survival (3.4 years) for patients presenting with cardiomyopathy.

IMPORTANT SAFETY INFORMATION

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, acetaminophen, 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 upper respiratory tract infections (29 percent) and infusion-related reactions (19 percent). For additional information about ONPATTRO, please see the full Prescribing Information.

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 improve 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. ONPATTRO™ (patisiran) lipid complex injection, available in the U.S. for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults, is Alnylam's first U.S. FDA-approved RNAi therapeutic. 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, Alnylam's views with respect to the data and results from its APOLLO Phase 3 clinical trial for patisiran, including its views with respect to the potential of patisiran to impact certain cardiac manifestations of hATTR amyloidosis, the expected timing for additional regulatory filings for approval of ONPATTRO in global markets, 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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