Alnylam Presents New Clinical Results from the APOLLO Phase 3 Study of Patisiran at the 16th International Symposium on Amyloidosis

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− Patisiran Demonstrated Improvement of Cardiomyopathy in Prospectively Defined Subgroup of Patients with Cardiac Amyloid Involvement, Relative to Placebo −

− Long-term Treatment with Patisiran in Global Open-Label Extension (OLE) Study Demonstrates Maintenance of Efficacy and Consistent Safety −

− Degree of Patisiran-Mediated TTR Knockdown Found to Correlate with Neurologic Improvement –

− New Phase 1 Data on ALN-TTRsc02, an Investigational, Subcutaneously Administered RNAi Therapeutic for the Treatment of ATTR Amyloidosis, Support Low Dose and Volume, Quarterly Dosing Regimen −

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Mar. 28, 2018-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today that the Company presented new results from the APOLLO Phase 3 study of patisiran, an investigational, RNAi therapeutic for the treatment of hereditary ATTR (hATTR) amyloidosis at the 16th International Symposium on Amyloidosis (ISA), being held March 26-29, 2018 in Kumamoto, Japan. In addition, the Company presented new data from the Phase 1 study of ALN-TTRsc02, an investigational, subcutaneously administered RNAi therapeutic in development for the treatment of ATTR amyloidosis.

“We are pleased to share important new data from our TTR program across ten distinct presentations at ISA today. The clinical results presented further highlight the robust profile of patisiran and provide evidence supporting patisiran as a potentially transformative treatment approach for patients with hATTR amyloidosis. We believe that, if approved, these results position patisiran as a best-in-class therapeutic option for patients with hATTR amyloidosis,” said Eric Green, Vice President and General Manager, TTR Program at Alnylam. “Moreover, we believe that the positive correlation between the degree of TTR knockdown and improvement in neurologic impairment validates the hypothesis that reducing hepatic production of TTR confers clinical benefit. Finally, we’re reporting new results with ALN-TTRsc02, in development for the treatment of both wild-type and hereditary ATTR amyloidosis, where potent and highly durable TTR reduction was achieved in a Phase 1 study, with a low dose and volume subcutaneous injection.”

Cardiac Subpopulation Results

Fifty-six percent of the APOLLO study participants (N=126) were included in the predefined cardiac subpopulation*. The data presented at ISA highlighted that treatment with patisiran was associated with significant improvements in measures of cardiomyopathy, the leading cause of death in patients with hATTR amyloidosis, relative to placebo. Specifically, there were improvements in cardiac structure (reduction in mean left ventricular [LV] wall thickness) and function (reduction in LV-end diastolic volume and global longitudinal strain) at 18 months. Patisiran was also associated with a favorable effect on gait speed in the cardiac subpopulation, relative to placebo. Furthermore, patisiran treatment led to a significant reduction in levels of a cardiac stress biomarker, NT-proBNP, relative to placebo at 9 and 18 months ($p = 7.7 \times 10^{-8}$). Higher levels of NT-proBNP are associated with increased mortality in cardiac amyloidosis. The frequency of cardiac adverse events (AEs) and serious AEs (SAEs) were similar in patisiran- and placebo-treated patients in the overall APOLLO study population. Deaths occurred with similar frequency in the patisiran (4.7 percent) and placebo (7.8 percent) arms.

“The results presented at ISA highlight the potential of patisiran to alleviate the cardiac manifestations of hATTR amyloidosis through notable improvements in cardiac structure and function relative to placebo-treated patients. These improvements, in conjunction with demonstrated benefits in neurologic impairment, appear to be associated with favorable effects on gait speed, an important indicator of functional status,” said Arnt Kristen M.D., Heidelberg University Hospital, Heidelberg. “Improvements across a range of echocardiographic parameters, including left ventricular wall thickness and contractile strength, and a positive effect on a cardiac stress biomarker, speak to the potential for significant benefits of patisiran for patients with hATTR amyloidosis with cardiac involvement.”

Long-Term Use of Patisiran: Preliminary Results from Global OLE Study

The Company also presented preliminary results from the ongoing Global OLE Study of patisiran evaluating the drug’s long-term efficacy and safety in eligible patients who completed the Phase 2 OLE and Phase 3 APOLLO studies. The data presented were as of the December 1, 2017 data cut. Twenty-five patients, originally in the Phase 2 study, have now received patisiran for up to four years. These patients show sustained mean improvements in neuropathy as assessed by the modified Neurologic Impairment Score (mNIS+7) at month 36, relative to baseline. Patients (N=52) originally in the patisiran arm of APOLLO continue to demonstrate sustained benefit in neurologic impairment, relative to APOLLO study baseline, after 12 months of further treatment in the Global OLE. After 12 months of patisiran treatment, patients (N=17) originally in the placebo arm of APOLLO – who had previously shown disease progression – now demonstrate stabilization of neuropathy, with a mean improvement in mNIS+7 score of negative 0.6 points, relative to Global OLE baseline. The safety profile of all patients in the Global OLE (N=211) was consistent with that observed in APOLLO, with infusion-related reactions (IRRs, 10.4 percent) representing the most common drug-related AE. There were two patients with reports of drug-related SAEs; one with phlebitis secondary to drug extravasation at the infusion site, cellulitis and hypotension, and one with abdominal discomfort, with the latter resulting in withdrawal from study. With up to 48 months of treatment, there were 11 deaths in the Global OLE study, with four events (2.9 percent) occurring in patients previously receiving patisiran and seven events (14.3 percent) in patients previously receiving placebo; causes of death were consistent with natural history and none were considered related to study drug. In the Global OLE, a home infusion option was made available to patients in regions where permitted. As of December 1, 2017, 25 patients (11.8 percent) have received over 269 infusions at home. One patient had a mild IRR at home that did not require treatment.

Relationship Between TTR Knockdown and Change in mNIS+7

Alnylam also presented results of an exploratory analysis from the Phase 2 OLE and Phase 3 APOLLO studies examining the relationship between the degree of patisiran-mediated TTR knockdown with changes in mNIS+7 – the primary endpoint in APOLLO, relative to baseline. A strong correlation between the degree of TTR knockdown and change in mNIS+7 was observed. Specifically, higher degrees of TTR knockdown resulted in greater levels of mNIS+7 improvement. At a population level, TTR knockdown of greater than 80 percent was associated with negative changes in mNIS+7, indicating reversal of disease manifestations, relative to baseline. The Company believes these data support the therapeutic hypothesis that reducing hepatic production of TTR by RNAi has the potential to halt or improve disease progression in patients with hATTR amyloidosis.

ALN-TTRsc02 Phase 1 Results

The Phase 1 study of ALN-TTRsc02 was a randomized, ascending fixed dose (5 mg to 300 mg) study in 80 healthy volunteers. Single doses of ALN-TTRsc02 demonstrated robust TTR knockdown (mean maximum up to 97 percent) maintained over 320 days. There were no SAEs or study discontinuations due to AEs. AEs were mild in severity and reported in 77 percent of ALN-TTRsc02 versus 50 percent of placebo patients. There were no reports of clinically significant changes in hematologic parameters (including platelets), renal function, electrocardiogram, vital signs or physical exam. One subject in the 200 mg dose group experienced a transient, asymptomatic elevation in liver alanine aminotransferase levels greater than three times the upper limit of normal that was not reported as an AE. Sustained TTR knockdown observed on study to date and modeling data both support the potential for a low dose (25 mg), low volume (less than 1 mL), and once quarterly subcutaneous dosing regimen for ALN-TTRsc02 to achieve levels of TTR knockdown comparable to those observed with patisiran in the APOLLO Phase 3 study. Consistent with previous guidance, the Company expects to advance ALN-TTRsc02 into a comprehensive pivotal Phase 3 program in late 2018.

All results presented at ISA can be viewed on the Capella section of the Alnylam website.

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

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 Neurologic 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 Patisiran
Patisiran is an investigational, intravenously administered RNAi therapeutic targeting transthyretin (TTR) in development 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. This may help to reduce the deposition and facilitate the clearance of TTR amyloid in peripheral tissues and potentially restore function to these tissues. Patisiran is currently under Priority Review as a Breakthrough Therapy with the U.S. Food and Drug Administration (FDA) and under accelerated assessment by the European Medicines Agency (EMA) for the treatment of patients with hATTR amyloidosis. The FDA has set a PDUFA date of August 11, 2018.

About ALN-TTRsc02
ALN-TTRsc02 is an investigational, subcutaneously administered RNAi therapeutic targeting transthyretin (TTR) in development for the treatment of ATTR amyloidosis. It is designed to target and silence specific messenger RNA, potentially blocking the production of TTR protein before it is made. This may help to reduce the deposition and facilitate the clearance of TTR amyloid in peripheral tissues and potentially restore function to these tissues. The safety and efficacy of ALN-TTRsc02 have not been evaluated by the FDA or any other health authority.

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. The only available treatment options for early stage disease are liver transplantation and, in some countries, tafamidis (approved in Europe, Japan, and certain countries in Latin America, specific indication varies by region). As such, there is a significant need for novel therapeutics to help treat patients with hATTR amyloidosis.

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 on the horizon. 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, and hepatic infectious 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 and deep pipeline of investigational medicines, including four 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 700 people in the U.S. and Europe 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 data presented for patisiran and ALN-TTRsc02, and the potential implications of such data for patients, including patients with hATTR amyloidosis with cardiac involvement, its expectations regarding the timing of regulatory reviews and potential regulatory approvals for patisiran in the United States and the EU, and the timing of initiation of a comprehensive Phase 3 program for ALN-TTRsc02, 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, 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 Annual Report on Form 10-K 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.

Neither patisiran nor ALN-TTRsc02 have been approved by the FDA, EMA, or any other regulatory authority and no conclusions can or should be drawn regarding the safety or effectiveness of these investigational therapeutics.

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