Alnylam Announces Publication of APOLLO Phase 3 Clinical Study Results for Investigational RNAi Therapeutic Patisiran in The New England Journal of Medicine

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− In Patients with Hereditary ATTR Amyloidosis, Patisiran Treatment Improved Polyneuropathy and Quality of Life Relative to Placebo −

− Majority of Patients Receiving Patisiran Experienced Improvement in Polyneuropathy and Quality of Life Relative to Baseline −

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jul. 4, 2018-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today that the pivotal study results from the APOLLO Phase 3 trial of patisiran were published online today in *The New England Journal of Medicine* (NEJM). The study showed that patisiran improved measures of polyneuropathy, quality of life, activities of daily living, ambulation, nutritional status, and autonomic symptoms relative to placebo in patients with hereditary transthyretin-mediated (hATTR) amyloidosis, an inevitably progressive and generally fatal disease. Patisiran treatment also led to favorable effects on exploratory endpoints related to cardiac structure and function in patients with cardiac involvement. Further, the frequency and severity of adverse events (AEs) were similar in patients receiving patisiran and placebo, with the exception of peripheral edema and infusion-related events which were higher in patisiran-treated patients and generally mild to moderate in severity. The full manuscript, titled "Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis," will appear in the July 5, 2018 issue of NEJM.

“The publication of the APOLLO study results in NEJM underscores the potential for clinical benefit and the encouraging safety profile of patisiran, and reinforces the strong therapeutic potential of this investigational medicine for people living with hATTR amyloidosis,” said David Adams M.D., Ph.D., Department of Neurology, Coordinator of the national reference center for Familial Amyloid Polyneuropathy (FAP) and rare neuropathies, Bicêtre Hospital, Greater Paris University Hospitals, AP-HP, Principal Investigator for the APOLLO trial, and lead author of the manuscript. “The positive impact on both neurologic impairment and quality of life in patients treated with patisiran was in marked contrast to the disease progression seen in placebo-treated patients in just 18 months. In fact, we observed improvement in neuropathy manifestations and quality of life in a majority of patisiran-treated patients, with some patients showing evidence of halting or reversal of neuropathy progression during the study, including a transition from assisted to unassisted walking. The broad, international patient population recruited to APOLLO is characteristic of the wide disease spectrum seen in clinical practice, supporting the relevance of the potential beneficial effects of patisiran for patients worldwide afflicted with this progressive and generally fatal disease.”

“We are extremely pleased with the publication of this landmark manuscript, the first-ever pivotal RNAi clinical trial to be published in a top-tier, peer-reviewed medical journal,” said Akshay Vaishnaw, M.D., Ph.D., President of Research and Development at Alnylam. “Publication of the APOLLO study results in NEJM is a testament to Alnylam's decade-long effort and unwavering commitment to patients with hATTR amyloidosis, and to the goal of advancing an innovative new class of medicines that harnesses the natural RNAi mechanism of action to silence production of disease-causing proteins. Further, publication of these comprehensive efficacy and safety results highlights our commitment to scientific and clinical excellence, and the importance we place on data transparency. This work would not have been possible without all the patients and investigators who participated in APOLLO, and we are deeply indebted to them.”

The APOLLO study publication presents robust evidence for patisiran’s potential to treat a broad constellation of hATTR amyloidosis clinical manifestations and their disabling effects. Relative to placebo, data from APOLLO showed that treatment with patisiran resulted in significant and clinically meaningful improvements in measures of polyneuropathy and quality of life. In addition, compared to baseline and after 18 months of patisiran treatment, improvement was observed in a majority of patients in the primary endpoint, mNIS+7 score (a composite measure of neuropathy), and in the key secondary endpoint, Norfolk QOL-DN (a quality of life questionnaire). The improvement in mNIS+7 was shown to be correlated with degree of TTR knockdown. Significant effects on muscle strength, activities of daily living, ambulation, nutritional status, and autonomic symptoms were also noted in patisiran patients relative to placebo. Moreover, patisiran patients with echocardiographic evidence of cardiac amyloid involvement at study entry demonstrated favorable effects on exploratory endpoints related to cardiac structure and function when compared to placebo.

A lower proportion of patients randomized to patisiran than placebo discontinued treatment (7 versus 38 percent) and discontinued the study (7 versus 29 percent). The incidence and severity of AEs and the frequency of serious AEs (SAEs) and deaths were similar in patisiran- and placebo-treated patients. Compared to placebo, patisiran treatment was associated with fewer treatment discontinuations (5 versus 14 percent) due to AEs. The AEs occurring more frequently with patisiran than placebo were peripheral edema (30 versus 22 percent) and infusion-related reactions (IRRs; 19 versus 9 percent) both of which were generally mild to moderate in severity. IRRs decreased over time and led to study withdrawal in one patient (0.7 percent). No clinically-relevant changes in laboratory values related to patisiran treatment, including platelet counts and liver and kidney function tests, were observed during the study.

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 in 19 countries with 39 genotypes who were randomized 2:1, patisiran:placebo, with patisiran administered at 0.3 mg/kg intravenously 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. The safety and efficacy of patisiran 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, and certain countries in Asia and 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 800 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 the results from its APOLLO Phase 3 clinical trial for patisiran, the publication of such results, and the potential implications of such results for patients, its expectations concerning the review of patisiran by regulatory authorities in the United States and Europe, its expectations regarding the potential for patisiran to improve the lives of hATTR amyloidosis patients and their families, its plans for the commercialization of patisiran if approved by regulatory authorities, 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 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.

Patisiran has not 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 this investigational therapeutic.

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