Alnylam Pharmaceuticals Announces Initiation of APOLLO-B Phase 3 Study of Patisiran for the Treatment of Transthyretin Amyloidosis with Cardiomyopathy

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– APOLLO-B Will Enroll Patients with Both Hereditary and Wild-Type Amyloidosis –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Sep. 16, 2019-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, today announced that the Company has initiated APOLLO-B, a global Phase 3 placebo-controlled clinical trial of patisiran, an intravenously administered RNAi therapeutic, for the treatment of transthyretin amyloidosis (ATTR amyloidosis) with cardiomyopathy. The primary endpoint is the change from baseline in the 6-minute walk test (6-MWT) at 12 months. Secondary endpoints will evaluate the efficacy of patisiran on quality of life using the Kansas City Cardiomyopathy Questionnaire Overall Summary, and composite endpoints of mortality and hospitalization.

“ATTR amyloidosis is a rare, debilitating, and life-threatening disease encompassing hereditary ATTR (hATTR) amyloidosis and wild-type ATTR (wtATTR) amyloidosis. Based on the encouraging exploratory results on cardiac endpoints in the Phase 3 APOLLO study, we are investigating the potential for patisiran to treat cardiovascular-related manifestations of ATTR amyloidosis,” said Eric Green, Senior Vice President and General Manager, TTR Program. “The initiation of APOLLO-B represents a significant milestone in our commitment to explore the full potential of patisiran for patients living with all types of ATTR amyloidosis.”

Patisiran is the non-branded drug name for ONPATTRO®.It 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, Canada, and Japan.

APOLLO-B Phase 3 Study Design
The APOLLO-B Phase 3 trial is a randomized, double-blind, placebo-controlled multicenter global study designed to evaluate the efficacy and safety of patisiran in approximately 300 adult patients with ATTR amyloidosis (hereditary or wild type) with cardiomyopathy. Patients will be randomized on a 1:1 basis to receive 0.3 mg/kg of patisiran or placebo intravenously administered every three weeks over a 24-month treatment period. After 12 months, all patients will receive patisiran in an open-label treatment period. For more information on APOLLO-B (NCT03997383), including the full list of eligibility criteria, please visit www.clinicaltrials.gov, email clinicaltrials@alnylam.com or call 877-256-9526 in North America and +31 20 369 7861 in Europe.

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). Patisiran is also being investigated in patients with ATTR amyloidosis (hereditary [hATTR] or wild type [wtATTR]) with cardiomyopathy in the APOLLO-B study. 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.

ONPATTRO Indication and 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, 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 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

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, hepatic infectious, and central nervous system (CNS)/ocular 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. 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 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 1,200 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 plans concerning the APOLLO-B study of patisiran and the potential for patisiran to treat cardiovascular-related manifestations of ATTR amyloidosis in patients qualifying for the study, 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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