Alnylam Announces Approval in Japan of ONPATTRO® for the Treatment of Hereditary ATTR Amyloidosis with Polyneuropathy

June 18, 2019

− ONPATTRO istheFirst RNAi Therapeutic Approved in Japan –

− Approval Marks the Arrival of an Entirely New Treatment Approach for People Living with hATTR Amyloidosis with Polyneuropathy in Japan –

CAMBRIDGE, Mass. & TOKYO--(BUSINESS WIRE)--Jun. 18, 2019-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, today announced that the Japanese Ministry of Health, Labour and Welfare (MHLW) has approved ONPATTRO® (patisiran) for the treatment of hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy. ONPATTRO is the first approved RNAi therapeutic in Japan and Alnylam will launch and directly market it in the country.

“hATTR amyloidosis is a genetic disease that can cause a variety of debilitating symptoms and can often be fatal. Historically, treatment options for people living with this condition in Japan, where the V30M mutation of the condition is prevalent, were limited,” said Professor Yukio Ando, President of ISA (International Society of Amyloidosis) and JSA (Japan Society of Amyloidosis), Chairman and Professor/Department of Amyloidosis Research of Nagasaki International University and Professor Emeritus and Visiting Professor of Kumamoto University, Japan. “The approval of ONPATTRO, a treatment that has the potential to mitigate and potentially reverse symptoms of polyneuropathy and to improve quality of life, marks a paradigm shift in the way we approach and treat this serious disease.”

“We are very excited about the approval of ONPATTRO and are proud to be bringing this important new treatment to patients with hATTR amyloidosis with polyneuropathy in Japan,” said Masako Nakamura, Senior Vice President, Head of Asia, Alnylam. “With this approval, we look forward to working with the hATTR amyloidosis community to continue to raise disease awareness, increase diagnosis rates and ultimately provide treatment to patients suffering from this devastating disease. This is a significant milestone in our efforts to bring RNAi therapeutics to people around the world and we look forward to continuing to build our presence in Asia.”

Alnylam submitted a New Drug Application (NDA) to Japan’s Pharmaceuticals and Medical Devices Agency (PMDA) on September 27, 2018 based on the results from the APOLLO Phase 3 study, which evaluated the efficacy and safety of patisiran in hATTR amyloidosis patients with polyneuropathy. Results from the APOLLO study were published in the July 5, 2018, issue of *The New England Journal of Medicine*. Patisiran had previously received orphan drug designation from the MHLW, which made it eligible for priority review as well as 10 years of market exclusivity in Japan.

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-motor 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.

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 ONPATTRO® (Patisiran)
Patisiran, based on Nobel Prize-winning science, 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. Patisiran 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. In August 2018, Patisiran received U.S. Food and Drug Administration (FDA) approval for the treatment of the polyneuropathy of hATTR amyloidosis in adults, as well as European Medicines Agency marketing authorization for the treatment of hATTR amyloidosis in adults with Stage 1 or Stage 2 polyneuropathy. Patisiran was approved in Japan in June 2019 for the treatment of hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy.

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 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 Prizewinning science, RNAi therapeutics represent a powerful, clinically validated approach for the treatment of diseases with high unmet need. ONPATTRO® (patisiran) is the first-ever RNAi therapeutic approved by the U.S. FDA for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults and by the EMA for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy. 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 plans to launch ONPATTRO (patisiran) in Japan, plans to increase awareness of hATTR amyloidosis, increase diagnosis rates and increase Alnylam's presence in Japan, 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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