Alnylam Announces Submission of New Drug Application in Japan for ONPATTRO™ (patisiran sodium) for Treatment of Hereditary ATTR Amyloidosis

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CAMBRIDGE, Mass.--(BUSINESS WIRE)--Sep. 28, 2018-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today that it has submitted a New Drug Application (NDA) to Japan's Pharmaceuticals and Medical Devices Agency (PMDA) for approval of patisiran for the treatment of hereditary transthyretin-mediated (hATTR) amyloidosis. Patisiran has orphan drug designation from the Ministry of Health, Labor and Welfare (MHLW), which makes it eligible for priority review as well as 10 years of market exclusivity, if approved. Based on the priority review timeline, Alnylam expects a decision from the MHLW and PMDA in mid-2019.

Patisiran – which will be commercialized under the brand name ONPATTRO ™ – is Alnylam's first drug submitted for regulatory review in Japan, and if approved, will be the first product to be launched and marketed by Alnylam in the country. The Company established operations in Japan this summer.

"The NDA submission highlights Alnylam's continued commitment to bring RNAi therapeutics to patients in need with the potential to make a meaningful impact on serious rare diseases that have devastating effects on the lives of patients and their families," said Masako Nakamura, Senior Vice President, Head of Asia, Alnylam. "Hereditary ATTR amyloidosis is endemic in Japan, with V30M being the most common mutation. We look forward to working with the PMDA during the review process so that we can make patisiran available to patients as expeditiously as possible."

The NDA submission is based on positive data 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*.

In APOLLO, the safety and efficacy of patisiran were evaluated in a diverse, global population of hATTR amyloidosis patients in 19 countries, with a total of 39 TTR mutations. Of the 225 patients enrolled, 16 patients were from Japan. Patients were randomized in a 2:1 ratio to receive intravenous patisiran (0.3 mg per kg of body weight) or placebo once every 3 weeks for 18 months. 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 adult patients with hATTR amyloidosis with polyneuropathy. The primary endpoint of the APOLLO study was the modified Neuropathy Impairment Score +7 (mNIS+7), which assesses motor strength, reflexes, sensation, nerve conduction and postural blood pressure.

- Patients treated with patisiran had a mean 6.0-point decrease (improvement) in mNIS+7 score from baseline compared to a mean 28.0-point increase (worsening) for patients in the placebo group, resulting in a mean 34.0-point difference relative to placebo, after 18 months of treatment.
- While nearly all patisiran-treated patients experienced a treatment benefit relative to placebo, 56 percent of patisiran-treated patients after 18 months of treatment experienced improvement of neuropathy impairment (as assessed by mNIS+7 score) relative to their own baseline, compared to four percent of patients who received placebo.
- Patients treated with patisiran had a mean 6.7-point decrease (improvement) in Norfolk Quality of Life Diabetic Neuropathy (QoL-DN) score from baseline compared to a mean 14.4-point increase (worsening) for patients in the placebo group, resulting in a mean 21.1-point difference relative to placebo, after 18 months of treatment.
- As measured by Norfolk QoL-DN, 51 percent of patients treated with patisiran experienced improvement in quality of life at 18 months relative to their own baseline, compared to 10 percent of the placebo-treated patients.
- Over 18 months of treatment, patients treated with patisiran experienced significant benefit vs. placebo for all other secondary efficacy endpoints, including measures of activities of daily living, walking ability, nutritional status, and autonomic symptoms.
- Patisiran was associated with favorable effects on exploratory endpoints related to cardiac structure and function in the prespecified subpopulation of patients with cardiac involvement.
- The incidence and severity of adverse events were similar in patients receiving patisiran and placebo. The most common adverse events that occurred more frequently with patisiran than with placebo were peripheral edema and infusion-related reactions. To reduce the risk of infusion-related reactions, patients received premedications prior to infusion.

About ONPATTRO™ (patisiran)
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 U.S. Food and Drug (FDA) approval 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. Also, in August 2018, patisiran received European Commission marketing authorization for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy. The European Medicines Agency (EMA) reviewed patisiran under the accelerated assessment procedure that is granted to medicines judged to be of major interest for public health and therapeutic innovation. In Japan, the non-proprietary adopted name (JAN) for patisiran is patisiran sodium.

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.

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 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, expectations regarding the filing of its first regulatory application in Japan for ONPATTRO and the expected timing of a decision from the PMDA on such application, the potential impact of an approval for patients and their families, expectations for the potential commercialization of ONPATTRO in Japan, if approved, 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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