Alnylam Receives Positive CHMP Opinion for ONPATTRO™ (patisiran) for the Treatment of Hereditary Transthyretin-Mediated Amyloidosis in Adults with Stage 1 or Stage 2 Polyneuropathy

July 27, 2018

– European Commission Decision Expected in September –

– Recommended Summary of Product Characteristics (SmPC) Includes Data on Secondary and Exploratory Endpoints, Including Results on Cardiac Parameters –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jul. 27, 2018-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today that the Committee for Medicinal Products for Human Use (CHMP) has adopted a Positive Opinion recommending marketing authorization of patisiran for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adults with stage 1 or stage 2 polyneuropathy. If approved by the European Commission (EC), the medicine will be commercialized under the brand name ONPATTRO ™.

"We are delighted with this positive opinion, and today's recommendation by the CHMP takes us one step closer to bringing RNAi therapeutics, an entirely new class of innovative medicines, to patients around the world," said John Maraganore, Ph.D., Chief Executive Officer of Alnylam Pharmaceuticals. "Our hope with patisiran is to transform the treatment of hATTR amyloidosis for the patients living with this devastating disease."

"hATTR amyloidosis is a progressively debilitating disease that often impacts patients and their families in the prime of their lives," said Theresa Heggie, Head of Europe, Alnylam Pharmaceuticals. "We are ready to launch patisiran following the EC decision, and hope that it will help to meet the pressing need for new treatment options for patients living with hATTR amyloidosis in Europe."

The CHMP positive opinion is based on the evaluation of the effects of patisiran in patients with hATTR amyloidosis and its safety profile as demonstrated in the APOLLO Phase 3 study. The SmPC recommended by the CHMP includes data from APOLLO primary and secondary endpoints, as well as exploratory cardiac endpoints. The results of the APOLLO study were published July 5, 2018 in *The New England Journal of Medicine* (NEJM).

The European Medicines Agency reviewed patisiran under the accelerated assessment procedure that is granted to medicines that the CHMP believes are of major interest for public health and therapeutic innovation. A CHMP positive opinion is one of the final steps before marketing authorization is granted by the European Commission. The European Commission will now review the CHMP recommendation to deliver its final decision, applicable to all 28 EU member states, plus Iceland, Liechtenstein and Norway. Patisiran is currently under priority review as a Breakthrough Therapy with the U.S. Food and Drug Administration (FDA), with an action date of August 11, 2018. Regulatory filings in other markets, including Japan, are planned for mid-2018.

About APOLLO
In APOLLO, the safety and efficacy of patisiran were evaluated in a diverse, global population of hATTR amyloidosis patients. Patients were randomized in a 2:1 ratio to receive intravenous patisiran (0.3 mg per kilogram 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. The APOLLO study used the modified Neuropathy Impairment Score +7 (mNIS+7) to assess 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 28.0-point mean increase (worsening) for patients in the placebo group, resulting in a 34.0-point mean 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 experienced significant improvement in measures of their polyneuropathy (as assessed by mNIS+7 score) relative to their own baseline with 18 months of treatment, compared to four percent of patients who received placebo.
- As measured by the Norfolk Quality of Life Diabetic Neuropathy (QoL-DN) Score, 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 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 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.

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.

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. In Europe, treatment options that can modify the course of the disease are limited and there remains a pressing need for novel medicines 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
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 data supporting the CHMP positive opinion, recommended SmPC, and ongoing regulatory reviews of patisiran, the potential implications of such data for patients, the commercial readiness of Alnylam to launch patisiran in Europe, 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.

None of Alnylam’s investigational therapeutics have been approved by the U.S. Food and Drug Administration, European Medicines Agency, or any other regulatory authority and no conclusions can or should be drawn regarding the safety or effectiveness of such investigational therapeutics.

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Source: Alnylam Pharmaceuticals, Inc.

Alnylam Pharmaceuticals, Inc.
Christine Regan Lindenboom, +1-617-682-4340
(Investors and Media)
or
Josh Brodsky, +1-617-551-8276
(Investors)
or
Fiona McMillan, +44 1628 244960
(Media, Europe)