Alnylam Presents New ONPATTRO® (patisiran) Results at the 2019 Peripheral Nerve Society Annual Meeting

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− Patisiran Global Open-Label Extension (OLE) Study Demonstrates Maintained Reversal of Disease Progression and Consistent Safety Profile, with Greater Than Four Years of Patient Experience and Over 6,000 Doses Administered –

− APOLLO Patients Previously on Tafamidis Benefited from Patisiran with Improvements in Neuropathy Impairment and Quality of Life –

− Indirect Treatment Comparison Results Show Favorable Treatment Effects of Patisiran Relative to Inotersen Across All Endpoints Evaluated –

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jun. 24, 2019-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today new results from the Global Open-Label Extension (OLE) study of ONPATTRO® (patisiran), an RNAi therapeutic for the treatment of the polyneuropathy of hereditary ATTR (hATTR) amyloidosis. Results were presented at the 2019 Peripheral Nerve Society (PNS) Annual Meeting, being held June 22-26, 2019 in Genoa, Italy. In addition, the Company reported on new analyses from the APOLLO Phase 3 study of patisiran and results of an indirect treatment comparison of patisiran and inotersen.

"With over four years of patient experience with ONPATTRO and more than 6,000 doses administered in our OLE study, we are pleased to see that hATTR amyloidosis patients with polyneuropathy continue to experience durable improvement, with ONPATTRO maintaining reversal of neuropathy impairment and an encouraging safety profile," said Eric Green, Senior Vice President and General Manager, TTR Program at Alnylam. "Additional analyses from APOLLO showed that patients previously treated with tafamidis experienced improvements in both neuropathy impairment and quality of life with patisiran."

"It's encouraging to see durable evidence of improvement with patisiran. Based on its unique mechanism of action with potent knockdown of serum TTR and an encouraging tolerability profile, these long-term data continue to highlight the potential for meaningful clinical benefit with patisiran treatment," said Michael Polydefkis, M.D., MHS, Professor, Johns Hopkins Neurology. "In addition, these results also highlight the need to avoid any delays in treatment to prevent accumulation of greater disease burden in hATTR amyloidosis patients with polyneuropathy."

Results from Global OLE Study

12-month interim results were presented from the ongoing Global OLE study of patisiran evaluating the drug's long-term efficacy and safety in eligible patients (N=211) who completed the Phase 2 OLE (N=25) and Phase 3 APOLLO (N=186) studies. The data presented were as of a September 24, 2018 data cutoff date. Serum transthyretin (TTR) levels were reduced by approximately 80 percent at 6 months in patients in the placebo arm of APOLLO who started treatment with patisiran, and were durably maintained over time. Patients on treatment for 30 to 36 months demonstrated sustained improvement in neuropathy impairment and quality of life relative to corresponding parent study baselines, as demonstrated by mean negative changes in modified Neuropathy Impairment Score + 7 (mNIS+7) and Quality of Life – Diabetic Neuropathy (QOL-DN) scores, respectively. Furthermore, the rapid trajectory of disease progression among APOLLO placebo patients was halted and, in a majority of patients reversed, once patisiran treatment was initiated in the Global OLE. Nevertheless, placebo patients did not return to their parent study baseline, as measured by mNIS+7 or QOL-DN scores, due to the disease worsening experienced while on placebo in APOLLO, highlighting the important need for early treatment with patisiran.

As of September 24, 2018, patients in the Global OLE received a mean of 20.5 months (range: 1.3–39.0 months) of patisiran, with over 6,000 doses administered. The safety of patisiran was consistent with that observed and previously reported in APOLLO and Phase 2 OLE studies, with an encouraging tolerability profile. Mild or moderate infusion-related reactions (IRRs: 12 percent) represented the most common drug-related adverse events (AEs). The proportion of patients experiencing IRRs was higher in patients newly treated with patisiran (APOLLO placebo) and decreased over time, with no discontinuations attributed to IRRs. Exposure-adjusted mortality occurred at a rate of 4.8 per 100 patient years, comparing favorably with disease natural history (exposure-adjusted rates of mortality from 6.8-29 per 100 patient-years), and the observed mortality in placebo-treated patients in APOLLO (18.9 per 100 patient-years). Mortality was lowest (1.7 per 100 patient-years) among patients from the Phase 2 OLE group, who initiated patisiran treatment at an earlier stage of disease compared with those in either of the APOLLO study arms.

APOLLO Results on Patients Previously Treated with Tafamidis

In addition, results were also presented on the impact of patisiran in patients who received tafamidis (a TTR tetramer stabilizer) treatment prior to enrolling in APOLLO. Approximately one-third of patients enrolled in APOLLO were previously treated with tafamidis. Thirty-four percent of those patients discontinued treatment with tafamidis due to disease progression; the majority of other patients discontinued tafamidis to participate in the APOLLO study for unspecified reasons. Patients with prior tafamidis use who received patisiran treatment for 18 months in APOLLO experienced significant improvement from baseline in polyneuropathy and QOL compared with placebo, similar to that observed in the overall APOLLO population. As with the overall study population, improvements in neuropathy impairment were also observed as early as nine months. These data suggest that patients who experience disease progression on tafamidis, or who discontinue tafamidis, may experience improvement in their polyneuropathy and QOL upon initiating treatment with patisiran.

Results of Indirect Treatment Comparison of Patisiran versus Inotersen

Additional data presented at PNS included results from an indirect treatment comparison analysis evaluating the efficacy of patisiran versus inotersen from the Phase 3 APOLLO and NEURO-TTR studies, respectively; there have been no head-to-head clinical studies comparing patisiran with inotersen. An indirect treatment comparison is a method widely accepted by regulators and payers for deriving a comparative estimate between two treatments that have not been compared in head-to-head trials, notwithstanding the limitations of this approach, including differential durations of the

respective trials requiring interpolation of data, and the degree of missing outcome data due to higher discontinuations in the NEURO-TTR study. The indirect treatment comparison revealed favorable treatment effects of patisiran relative to inotersen across all endpoints evaluated, including mNIS+7_{Ionis}, QOL, body mass index, and polyneuropathy disability score, as calculated via various statistical models and approaches. Specifically, at 15 months, mean differences in mNIS+7_{Ionis} and QOL – key study endpoints – ranged from -6.5 to -16.2 points and from -8.2 to -11.6 points, respectively, favoring patisiran.

To view the results presented by Alnylam at PNS 2019 Annual Meeting, please visit www.alnylam.com/capella.

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 infections (29 percent) and infusion-related reactions (19 percent).

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 from 19 countries with 39 genotypes who were randomized 2:1, patisiran:placebo, with patisiran administered at 0.3 mg/kg 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 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, and in Japan for the treatment of hATTR amyloidosis with polyneuropathy by the Japanese Ministry of Health, Labour and Welfare (MHLW). 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.

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 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 views with respect to the potential benefits from treatment with patisiran, and expectations regarding "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 preclinical 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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