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Alnylam Reports Final 24-Month Results from Phase 2 Open-Label Extension Study of Patisiran, an Investigational RNAi Therapeutic in Development for the Treatment of Hereditary ATTR (hATTR) Amyloidosis

- Patisiran Achieves Mean 7.0 Point Decrease in Modified Neuropathy Impairment Score (mNIS+7), Comparing Favorably with Expected Mean 26-30 Point Increase Estimated from Historical Data -

- In New Post-Hoc Analysis, Evidence for Potential Halting or Improvement of Neuropathy Progression Seen Across Broad Range of Baseline Neuropathy Severity -

- In Addition, Company Reports First-Ever Histological Evidence for Decrease in Dermal TTR Amyloid Burden Associated with Patisiran Administration -

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, announced today final 24-month results from its Phase 2 open-label extension (OLE) study of patisiran, an investigational RNAi therapeutic targeting transthyretin (TTR) for the treatment of hATTR amyloidosis. These clinical data are being presented at the American Academy of Neurology (AAN) 2017 Annual Meeting, held April 22 - 28, 2017 in Boston, Massachusetts. New results (N=26) showed a mean decrease in the modified neuropathy impairment score (mNIS+7) at 24 months that provides continued evidence that patisiran has the potential to halt or improve neuropathy progression in patients with hATTR amyloidosis. In a new post-hoc analysis, patisiran showed a mean improvement in mNIS+7 across the full range of neuropathy severity at baseline. Moreover, patisiran administration was found to be associated with statistically significant decreases in TTR amyloid deposition as measured from a blinded analysis of skin biopsy samples. Finally, patisiran was found to be generally well tolerated, with no drug-related serious adverse events (SAEs) for up to 25 months of treatment or drug-related discontinuations. Dosing continues for all eligible Phase 2 OLE patients (N=25) who have now transitioned into the ongoing APOLLO-OLE study. The Company remains on track to present top-line results from its ongoing APOLLO Phase 3 study of patisiran in mid-2017.

"We are encouraged to see the final 24-month results from our Phase 2 OLE which provide continued evidence suggesting that patisiran can potentially halt or improve neuropathy progression in patients with hATTR amyloidosis. We are also pleased to present the first-ever clinical evidence that patisiran administration is associated with a decrease in dermal TTR amyloid burden, which we believe further supports the therapeutic hypothesis that TTR knockdown can potentially lead to reduction of amyloid deposits in the body," said Eric Green, Vice President, General Manager, TTR Program. "All eligible Phase 2 OLE patients have now rolled over to the ongoing, global APOLLO-OLE trial, and we plan to present 36-month data from this cohort of patients in late 2017."

Final 24-month results from the Phase 2 OLE study showed a mean decrease in mNIS+7 of 7.0 points after 24 months of patisiran administration. This compares favorably to an expected mean increase in mNIS+7 of 26 to 30 points at 24 months estimated from an analysis of historical data sets in untreated hATTR amyloidosis patients with similar baseline characteristics (Adams *et al., Neurology,* 2015;85:675-682; Berk *et al., JAMA,* 2013;310:2658-67). In an analysis of individual responses, 74 percent of patients showed either an improvement or no change in mNIS+7 at 24 months, with a maximal 34.6-point decrease. In a new post-hoc analysis exploring the relationship between baseline neuropathy severity and change in mNIS+7, the potential effect of patisiran was observed across the full range of disease severity, including patients with a high degree of neurologic impairment at baseline (N=9 with baseline NIS of 46-93 points). Specifically, in this group, patisiran administration was associated with a mean 7.4-point decrease in mNIS+7. These results demonstrate that patisiran has the potential to halt or improve neuropathy progression across a broad range of neurologic impairment.

Over the 24-month period, patients with evidence of cardiac amyloid involvement at study entry (N=11) showed stability in their cardiac biomarkers, echocardiographic measures, and 10-meter walk test (gait speed). Additional results for patisiran in these hATTR amyloidosis patients with cardiac involvement will be presented at the European Society of Cardiology Heart Failure (ESC-HF) Congress, being held April 29 - May 2, 2017 in Paris, France, on Saturday, April 29th at 5:06 am ET. The data presentation will be posted on Capella at that time.

Serum TTR levels were also measured throughout the Phase 2 OLE study and showed patisiran-mediated TTR knockdown of up to 97 percent, with mean maximal knockdown of 93 percent and a mean knockdown of approximately 82 percent over 24 months.

In the first post-hoc exploratory analysis of its kind, the change in dermal TTR amyloid content over 24 months was assessed through blinded evaluation of tandem skin punch biopsies from the distal thigh and distal leg. Patisiran administration was associated with a median reduction of up to 78 percent in dermal amyloid content over time as compared to baseline, with statistically significant mean decreases in dermal amyloid content at 24 months in both the distal thigh and distal leg (p less than 0.05). This decrease in mean dermal amyloid content is consistent with the statistically significant mean increase in sweat gland nerve fiber density observed from the same skin biopsy samples over 24 months. Taken together, these exploratory analyses support the therapeutic hypothesis that reduction of mutant and wild-type TTR can potentially lead to reduction of TTR amyloid deposition and increased nerve regeneration.

Patisiran administration was found to be generally well tolerated in patients with hATTR amyloidosis out to 25 months, with no drug-related serious adverse events (SAEs) reported. Drug-related or possibly drug-related adverse events (AEs) in four or more patients were flushing (22.2%) and infusion-related reactions (22.2%), all of which were mild in severity and did not result in any discontinuations. There were ten reports of serious adverse events (SAEs) in seven patients, all of which were unrelated to study drug, including two previously reported deaths. There were no clinically significant changes in liver function tests, renal function, or hematologic parameters, including platelets. Following treatment in the Phase 2 OLE study, all 25 eligible patients enrolled in the APOLLO-OLE study; 20 have received at least 36 months of dosing as of April 12, 2017.

To view all the results presented by Alnylam at the AAN and ESC-HF meetings, please visit www.alnylam.com/capella.

About the Patisiran Phase 2 OLE Study

The patisiran Phase 2 OLE study was an open-label, multi-center trial designed to evaluate the long-term safety and tolerability of patisiran administration in patients with polyneuropathy due to hereditary ATTR (hATTR) amyloidosis that were previously enrolled in a Phase 2 study. Patisiran was administered once every 3 weeks at a dose of 0.3 mg/kg by intravenous infusion. The study measured a number of clinical endpoints every six months, including mNIS+7, which is an evaluation of muscle weakness, sensory and autonomic function, and nerve conductance, where neuropathy progression leads to an increased score over time. The change in the mNIS+7 measurement from baseline to 18 months is the primary endpoint in the Company's APOLLO Phase 3 trial of patisiran in patients with hATTR amyloidosis. Patients who completed the Phase 2 OLE study were eligible to screen for the global APOLLO-OLE study, in which they have the opportunity to receive patisiran on an ongoing basis.

About the APOLLO Phase 3 Study

The APOLLO Phase 3 trial is 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 is the difference in the change in mNIS+7 between patisiran and placebo at 18 months. Secondary endpoints include: the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) score; NIS-weakness; modified BMI; timed 10-meter walk; and the COMPASS-31 autonomic symptom score. The trial enrolled 225 hATTR amyloidosis patients that were randomized 2:1, patisiran:placebo, with patisiran administered at 0.3 mg/kg once every three weeks for 18 months. The study was designed with 90 percent power to conservatively detect as little as a 37.5 percent difference in change in mNIS+7 between treatment groups, with a two-sided alpha of 0.05. The placebo mNIS+7 progression rate was derived from an Alnylam analysis of natural history data from 283 hATTR amyloidosis patients. All patients completing the APOLLO Phase 3 study are eligible to screen for the global APOLLO-OLE study, in which they have the opportunity to receive patisiran on an ongoing basis.

Sanofi Genzyme Alliance

In January 2014, Alnylam and Sanofi Genzyme, the specialty care global business unit of Sanofi, formed an alliance to accelerate and expand the development and commercialization of RNAi therapeutics across the world. The alliance is structured as a multi-product geographic alliance in the field of rare diseases. Alnylam retains product rights in the United States, Canada and Western Europe, while Sanofi Genzyme obtained the right to access certain programs in Alnylam's current and future Genetic Medicines pipeline in the rest of the world (ROW) through the end of 2019, together with certain broader co-development/co-commercialization rights and global rights for certain products. In the case of patisiran, Alnylam will advance the product in the United States, Canada and Western Europe, while Sanofi Genzyme will advance the product in the ROW.

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 produced primarily in the liver and is normally a carrier of vitamin A. Mutations in TTR 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. hATTR amyloidosis represents a major unmet medical need with significant morbidity and mortality,

affecting approximately 50,000 people worldwide. hATTR amyloidosis patients have a life expectancy of 2.5 to 15 years from symptom onset, and the only approved treatment options for early stage disease are liver transplantation and tafamidis (approved in Europe, Japan, and certain countries in Latin America). There is a significant need for novel therapeutics to treat patients with hATTR amyloidosis.

About LNP Technology

Alnylam has licenses to Arbutus Biopharma LNP intellectual property for use in RNAi therapeutic products using LNP technology.

About RNAi

RNAi (RNA interference) is a revolution in biology, representing a breakthrough in understanding how genes are turned on and off in cells, and a completely new approach to drug discovery and development. Its discovery has been heralded as "a major scientific breakthrough that happens once every decade or so," and represents one of the most promising and rapidly advancing frontiers in biology and drug discovery today which was awarded the 2006 Nobel Prize for Physiology or Medicine. RNAi is a natural process of gene silencing that occurs in organisms ranging from plants to mammals. By harnessing the natural biological process of RNAi occurring in our cells, the creation of 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, target the cause of diseases by potently silencing specific mRNAs, thereby preventing disease-causing proteins from being made. RNAi therapeutics have the potential to treat disease and help patients in a fundamentally new way.

About Alnylam Pharmaceuticals

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 patients who have limited or inadequate treatment options. Based on Nobel Prize-winning science, RNAi therapeutics represent a powerful, clinically validated approach for the treatment of a wide range of 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 three product candidates that are in late-stage development or will be in 2017. 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. For more information about our people, science and pipeline, please visit www.alnylam.com and engage with us on Twitter at @Alnylam.

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 for RNAi therapeutics, including the continued development of patisiran in the ongoing APOLLO Phase 3 study and APOLLO-OLE study, its expectations regarding the expected timing for reporting top-line data from the APOLLO study of patisiran, and its expectations regarding the safety and tolerability of its products in clinical development, including patisiran, 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, including actions by regulators concerning product candidates, which may affect the initiation, timing and progress of clinical trials, 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 Annual Report on Form 10-K 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.

The scientific information discussed in this news release relating to Alnylam's investigational therapeutic patisiran is preliminary and investigative. Patisiran has not 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 its safety or effectiveness.

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