Alnylam Presents New Analyses of Clinical Results from APOLLO Phase 3 Study of Patisiran at 2018 Peripheral Nerve Society Annual Meeting

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− Patisiran-Treated Patients Showed Improvements in Overall Health Status Compared to Placebo −

− Indirect Analysis Shows Patisiran's Impact on Measures of Neuropathy and Quality of Life in APOLLO Study Relative to those Measured in Randomized Study of Tafamidis −

− Improvements in Neuropathy Impairment with Patisiran Treatment Associated with Ambulatory Status −

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jul. 23, 2018-- Alnylam Pharmaceuticals, Inc. (Nasdaq:ALNY), the leading RNAi therapeutics company, announced today that the Company presented new analyses from the APOLLO Phase 3 study of patisiran, an investigational RNAi therapeutic for the treatment of hereditary ATTR (hATTR) amyloidosis, in six presentations at the 2018 Peripheral Nerve Society (PNS) Annual Meeting being held July 22-25, in Baltimore, MD.

"We are pleased to continue to share new analyses from the APOLLO Phase 3 study with six presentations at the PNS annual meeting. We believe the new data presented underscore the potential clinical benefit of patisiran for patients with hATTR amyloidosis. First, the results of the exploratory EQ-5D-5L and EQ-VAS assessments show that patisiran treatment, relative to placebo, may help patients maintain or improve mobility and independence, reduce anxiety and depression, and favorably impact overall health status," said Eric Green, Vice President and General Manager, TTR Program at Alnylam. "Further, we believe the results of an indirect analysis between patisiran and tafamidis highlight the therapeutic potential of patisiran, if approved. Finally, with patients on placebo experiencing substantial worsening in neuropathy in as little as nine months and irrespective of baseline disease severity, our new analyses show a clear need to intervene early in the course of this disease."

Results on Overall Health Status Endpoints

Overall health status was an exploratory endpoint assessed in APOLLO using EuroQOL-5-dimension 5-level (EQ-5D-5L), a standardized measure of health status based on five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and the EuroQOL visual analogue scale (EQ-VAS), a measure of a patient's global impression of their overall health as evaluated on a scale of zero (worst possible health) to 100 (best possible health). At 18 months, a larger proportion of patients on patisiran than placebo, respectively, showed preservation (defined as no change in score) or improvement relative to baseline in each EQ-5D-5L domain: mobility, 70 versus 22 percent; self-care, 66 versus 21 percent; usual activities, 72 versus 25 percent; pain/discomfort, 73 versus 31 percent; anxiety/depression, 81 versus 45 percent. Overall health, as measured by EQ-VAS, improved by an average of 2.4 points in patients on patisiran, while declining by an average of 7.1 points in placebo patients, indicating a 9.5 point difference (nominal p value less than 0.001).

Results from an Indirect Treatment Comparison (ITC) of Tafamidis and Patisiran

We also presented results from an ITC of patisiran and tafamidis (a transthyretin tetramer stabilizer) using the standard pairwise Bucher method. The analysis was based on publicly available randomized trial efficacy data for tafamidis in hATTR amyloidosis with polyneuropathy[1-2]. Importantly, there are limitations to this approach, and there have been no head-to-head studies comparing the safety and effectiveness of patisiran and tafamidis. With those caveats, indirect comparisons were conducted for endpoints or components of endpoints measured in both trials: change from baseline in NIS-LL (Neuropathy Impairment Score of the Lower Limbs), NIS-LL response (less than two point increase in NIS-LL from baseline), Norfolk QoL-DN, and mBMI (modified body mass index). Safety was not compared as part of this analysis. The base case analysis indirectly compared these results in patients with Stage 1 polyneuropathy after 18 months of treatment. In the base case ITC, statistically significant differences in mean change from baseline for NIS-LL (-5.5 [95% CI -10.0, -1.0]) and Norfolk QoL-DN (-13.1 [95% CI -23.6, -2.7]) at 18 months were observed favoring patisiran treatment as compared to tafamidis, and the differences were corroborated by sensitivity analyses. Favorable trends were also seen for NIS-LL response rate and mBMI.

Relationship between Improvements in Neuropathy Impairment and Ambulatory Status

The primary endpoint in APOLLO was the change from baseline in the modified Neuropathy Impairment Score + 7 (mNIS+7) relative to placebo, with patisiran demonstrating significant improvement in neuropathy. Results were presented from an analysis conducted to interrogate whether changes in mNIS+7 were associated with ambulatory status (as measured by polyneuropathy disability [PND] score) at 18 months in patisiran-treated patients. Predictive modeling analysis demonstrated that greater reduction in mNIS+7 is consistently associated with a higher probability that a patient will have improved or stabilized ambulatory status (p value less than 0.0001). Modeling also showed that patients with an mNIS+7 change of less than zero points after 18 months of patisiran treatment were predicted to have substantially greater odds of improving or stabilizing their ambulatory status compared to patients with an mNIS+7 score of greater than or equal to zero (p value less than 0.0001).

FAP (familial amyloid polyneuropathy) Stage and PND score are commonly used to indicate neuropathy severity in hATTR amyloidosis and are based largely on ambulatory ability (e.g. whether, and how many, walking aids are required). It was shown that following 18 months of treatment, a greater proportion of patisiran patients compared to placebo showed stable or improved FAP Stage (79 versus 44 percent) and PND score (73 versus 30 percent). Improvements in FAP Stage and PND score were only seen with patisiran, and worsening occurred twice as frequently with placebo compared to patisiran. The observed changes in FAP Stage and PND score were statistically significant ($p=9.5 \times 10^{-8}$ and $p=1.3 \times 10^{-10}$, respectively), and further support the clinical benefit of patisiran compared to placebo in improving or preserving ambulation.

Finally, results highlighting neuropathy progression in the placebo arm of the APOLLO study were presented. Patients randomized to placebo experienced significant neuropathy progression as early as 9 months, the first assessment time point in APOLLO. At 9 and 18 months, neuropathy

progression relative to baseline was observed with a least squares (LS) mean increase in mNIS+7 of 14.0 and 28.0 points, respectively. Placebo patients had substantial progression regardless of their baseline disease severity. The rapid disease progression observed across multiple endpoints underscores the need for early administration of an effective therapy for patients with hATTR amyloidosis to prevent disability and morbidity accumulation.

Results on Infusion-Related Reactions

Patisiran was generally well tolerated, and the common adverse events (AEs) occurring more frequently with patisiran than placebo were peripheral edema (29.7 versus 22.1 percent) and infusion-related reactions (IRRs; 18.9 versus 9.1 percent). All patients in APOLLO received premedications, consisting of corticosteroids, antihistamines (H1 and H2 blockers), and acetaminophen, prior to each infusion. A new analysis of IRRs was presented. In the patisiran-treated patients with IRRs, the majority of patients had their first IRR within the first two doses. IRR incidence rate and the number of associated symptoms decreased over time. Only one patient (less than one percent) discontinued treatment due to an IRR (moderate flushing). Thus, IRRs associated with patisiran were manageable and rarely led to treatment discontinuation.

1. Study Fx-005; NCT00409175.
2. Coelho T., *et al*., J Neurol. 2013; 260(11):2802-14.

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 in 19 countries with 39 genotypes who were randomized 2:1, patisiran:placebo, with patisiran administered at 0.3 mg/kg intravenously once every three weeks for 18 months. All patients who completed the APOLLO Phase 3 study were eligible to screen for the Global Open Label Extension (OLE) study, in which they receive patisiran on an ongoing basis.

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. Patisiran is currently under Priority Review as a Breakthrough Therapy with the U.S. Food and Drug Administration (FDA) and under accelerated assessment by the European Medicines Agency (EMA) for the treatment of patients with hATTR amyloidosis. The FDA has set a PDUFA date of August 11, 2018. The safety and efficacy of patisiran have not been evaluated by the FDA or any other health authority.

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. The only available treatment options for early stage disease are liver transplantation and, in some countries, tafamidis (approved in Europe, and certain countries in Asia and Latin America, specific indication varies by region). As such, there is a significant need for novel therapeutics 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 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 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 the results from its APOLLO Phase 3 clinical trial for patisiran, including from new analyses of the data, and the potential implications of

such results for patients, its expectations concerning the review of patisiran by regulatory authorities in the United States and Europe, its expectations regarding the potential for patisiran to improve the lives of hATTR amyloidosis patients and their families, 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.

Patisiran has not been approved by the FDA, EMA, or any other regulatory authority and no conclusions can or should be drawn regarding the safety or effectiveness of this investigational therapeutic.

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Source: Alnylam Pharmaceuticals, Inc.

Alnylam Pharmaceuticals, Inc.
Christine Regan Lindenboom, 617-682-4340
(Investors and Media)
or
Josh Brodsky, 617-551-8276
(Investors)