December 11, 2014

Alnylam Initiates ENDEAVOUR Phase 3 Clinical Trial with Revusiran (ALN-TTRsc), an Investigational RNAi Therapeutic Targeting Transthyretin (TTR) for the Treatment of TTR Cardiac Amyloidosis

- ENDEAVOUR to Evaluate Efficacy and Safety of Revusiran in Patients with Familial Amyloidotic Cardiomyopathy (FAC); Trial Now Open for Enrollment -

- First Patient Dosed in ENDEAVOUR will Trigger $25 Million Milestone to Alnylam from Genzyme, a Sanofi Company -

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), a leading RNAi therapeutics company, announced today it has initiated the ENDEAVOUR Phase 3 clinical trial of revusiran in transthyretin (TTR)-mediated familial amyloidotic cardiomyopathy (FAC). FAC is one of the predominant clinical manifestations of TTR-mediated amyloidosis (ATTR), and afflicts an estimated 40,000 people worldwide. The ENDEAVOUR trial is a randomized, double-blind, placebo-controlled, global study designed to evaluate the efficacy and safety of revusiran in patients with FAC. The co-primary endpoints of the study are the change compared to baseline in 6-minute walk distance (6-MWD) and the percent reduction in TTR burden between placebo- and revusiran-treated patients at 18 months. This study is now open for enrollment. Alnylam is eligible to receive a $25 million milestone from Genzyme when the first patient is dosed in the ENDEAVOUR study.

"We are very pleased to be announcing today that we have initiated our ENDEAVOUR Phase 3 trial and are now enrolling patients. Initiation of ENDEAVOUR highlights our continued execution on our product development strategy for our genetic medicines pipeline and, together with our APOLLO Phase 3 trial with patisiran for the treatment of familial amyloidotic polyneuropathy, represents our commitment to develop innovative medicines for patients afflicted with ATTR," said Akshay Vaishnaw, M.D., Ph.D., Executive Vice President and Chief Medical Officer of Alnylam. "The ENDEAVOUR study aims to evaluate the efficacy and safety of revusiran for the treatment of patients with FAC, a progressive and fatal inherited cardiomyopathy. Based on our discussions with regulatory authorities in the U.S. and EU, we are aligned on the use of co-primary endpoints of 6-MWD and TTR knockdown at 18 months as measures of revusiran's efficacy. We will now focus on enrollment of FAC patients in ENDEAVOUR as a high priority for Alnylam, advancing our commitment to bring this potential novel therapy to patients and their caregivers."

The ENDEAVOUR Phase 3 trial is a randomized, double-blind, placebo-controlled, global study designed to evaluate the efficacy and safety of revusiran in patients with FAC. The co-primary endpoints of the study are the change compared to baseline in 6-MWD and the percent reduction in TTR burden between placebo- and revusiran-treated patients at 18 months. Secondary endpoints include a composite endpoint of cardiovascular mortality and cardiovascular hospitalization, New York Heart Association (NYHA) class, Kansas City Cardiomyopathy Questionnaire (KCCQ), CV mortality, CV hospitalization and all-cause mortality. The trial is designed to enroll up to 200 FAC patients with a documented TTR mutation, including V122I or other mutations, in addition to amyloid deposits as identified by biopsy. Patients will be randomized 2:1, revusiran:placebo, with revusiran administered subcutaneously at 500 mg daily for five days then weekly for 18 months. The trial design was informed by natural history data from TTR cardiac amyloidosis patients, which showed a decrease in 6-MWD in FAC patients over an 18-month period. Alnylam intends to present results from this natural history dataset in early 2015. The study was designed with 90% power to detect as little as 39% difference in the 18-month change from baseline for 6-MWD between treatment groups, with a significance level of $p < 0.05$. An unblinded interim analysis for futility may be conducted when 50% of patients reach 18 months. All patients completing the ENDEAVOUR Phase 3 study will be eligible to enroll in a Phase 3 open-label extension (OLE) study.

Recently, Alnylam presented initial results from its Phase 2 trial with revusiran in TTR cardiac amyloidosis patients. In this study, revusiran was found to be generally well tolerated in TTR cardiac amyloidosis patients. The most common adverse event was injection site reaction (23% of patients). One patient had an approximate 4-fold elevation in liver transaminases that was deemed a serious adverse event (SAE) and mild in severity; this event resolved during continued dosing. There were no other significant adverse events, discontinuations or other laboratory abnormalities. Revusiran demonstrated clinical activity with an up to 98.2% knockdown of serum TTR - the disease causing protein. This included similar knockdown effects toward wild type and mutant TTR protein in V122I patients, who represent the most common FAC genotype. As expected following a five-week course of treatment, there were no significant changes observed in a number of exploratory clinical measurements. Revusiran utilizes Alnylam's proprietary GalNAc-conjugate delivery platform that enables subcutaneous delivery of RNAi therapeutics with a wide therapeutic index.

In January 2014, Alnylam and Genzyme, a Sanofi company, 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. In the case of revusiran, Alnylam and Genzyme are co-developing and co-commercializing the investigational RNAi therapeutic in North America and Western Europe, while Genzyme is developing and commercializing revusiran in the rest of world.

About ATTR

Transthyretin (TTR)-mediated amyloidosis (ATTR) 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. ATTR represents a major unmet medical need with significant morbidity and mortality; familial amyloidotic polyneuropathy (FAP) affects approximately 10,000 people worldwide and familial amyloidotic cardiomyopathy (FAC) is estimated to affect at least 40,000 people worldwide. FAP patients have a life expectancy of 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). FAC is fatal within 2.5 to 5 years of diagnosis and treatment is currently limited to supportive care. Senile systemic amyloidosis (SSA) is a non-hereditary form of TTR cardiac amyloidosis caused by idiopathic deposition of wild-type TTR; its prevalence is generally unknown, but is associated with advanced age. There is a significant need for novel therapeutics to treat patients with TTR amyloid polyneuropathy and/or cardiomyopathy.

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 is a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. The company is leading the translation of RNAi as a new class of innovative medicines with a core focus on RNAi therapeutics as genetic medicines, including programs as part of the company's "Alnylam 5x15™" product strategy. Alnylam's genetic medicine programs are investigational RNAi therapeutics directed toward genetically defined targets for the treatment of serious, life-threatening diseases with limited treatment options for patients and their caregivers. These include: patisiran (ALN-TTR02) targeting transthyretin (TTR) for the treatment of TTR-mediated amyloidosis (ATTR) in patients with familial amyloidotic polyneuropathy (FAP); revusiran (ALN-TTRsc) targeting TTR for the treatment of ATTR in patients with TTR cardiac amyloidosis, including familial amyloidotic cardiomyopathy (FAC) and senile systemic amyloidosis (SSA); ALN-AT3 targeting antithrombin (AT) for the treatment of hemophilia and rare bleeding disorders (RBD); ALN-CC5 targeting complement component C5 for the treatment of complement-mediated diseases; ALN-AS1 targeting aminolevulinic acid synthase-1 (ALAS-1) for the treatment of hepatic porphyrias including acute intermittent porphyria (AIP); ALN-PCSsc targeting PCSK9 for the treatment of hypercholesterolemia; ALN-AAT targeting alpha-1 antitrypsin (AAT) for the treatment of AAT deficiency-associated liver disease; ALN-HBV targeting the hepatitis B virus (HBV) genome for the treatment of HBV infection; ALN-TMP targeting TMPRSS6 for the treatment of beta-thalassemia and iron-overload disorders; ALN-ANG targeting angiopoietin-like 3 (ANGPTL3) for the treatment of genetic forms of mixed hyperlipidemia and severe hypertriglyceridemia; ALN-AC3 targeting apolipoprotein C-3 (apoC3) for the treatment of hypertriglyceridemia; ALN-AGT targeting angiotensinogen (AGT) for the treatment of hypertensive disorders of pregnancy (HDP), including preeclampsia; ALN-GO1 targeting glycolate oxidase (GO) for the treatment of primary hyperoxaluria type 1 (PH1); ALN-HDV targeting the hepatitis delta virus (HDV) genome for the treatment of HDV infection; ALN-PDL targeting programmed death ligand 1 (PD-L1) for the treatment of chronic liver infections; and other programs yet to be disclosed. As part of its "Alnylam 5x15" strategy, as updated in early 2014, the company expects to have six to seven genetic medicine product candidates in clinical development - including at least two programs in Phase 3 and five to six programs with human proof of concept - by the end of 2015. The company's demonstrated commitment to RNAi therapeutics has enabled it to form major alliances with leading companies including Merck, Medtronic, Novartis, Biogen Idec, Roche, Takeda, Kyowa Hakko Kirin, Cubist, GlaxoSmithKline, Ascletis, Monsanto, and The Medicines Company. In early 2014, Alnylam and Genzyme, a Sanofi company, formed a multi-product geographic alliance on Alnylam's genetic medicine programs in the rare disease field. Specifically, Alnylam will lead development and commercialization of programs in North America and Europe, while Genzyme will develop and commercialize products in the rest of world. In addition, Alnylam and Genzyme will co-develop and co-commercialize revusiran in North America and Europe. In March 2014, Alnylam acquired Sirna Therapeutics, a wholly owned subsidiary of Merck. In addition, Alnylam holds an equity position in Regulus Therapeutics Inc., a company focused on discovery, development, and commercialization of microRNA therapeutics. Alnylam scientists and collaborators have published their research on RNAi therapeutics in over 200 peer-reviewed papers, including many in the world's top scientific journals such as *Nature, Nature Medicine, Nature Biotechnology, Cell, New England Journal of Medicine*, and *The*

Lancet. Founded in 2002, Alnylam maintains headquarters in Cambridge, Massachusetts. For more information, please visit www.alnylam.com.

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 revusiran for the treatment of FAC, the design and timing of clinical studies, its expectations regarding the triggering of a milestone payment, its "Alnylam 5x15" product strategy, and its plans regarding 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 may differ materially from those indicated by these forward-looking statements as a result of various important 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 drug candidates, the pre-clinical and clinical results for its product candidates, which may not support further development of product candidates, actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials, obtaining, maintaining and protecting intellectual property, Alnylam's ability to enforce its patents against infringers and defend its patent portfolio against challenges from third parties, obtaining regulatory approval for products, competition from others using technology similar to Alnylam's and others developing products for similar uses, Alnylam's ability to manage operating expenses, Alnylam's ability to 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, marketing, sales and distribution of products, the outcome of litigation, 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 to update any forward-looking statements.

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