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Alnylam Initiates Phase I Clinical Study for ALN-TTRsc, a Subcutaneously Administered RNAi Therapeutic Targeting Transthyretin (TTR) for the Treatment of TTR-Mediated Amyloidosis (ATTR)

– ALN-TTRsc is Company’s First Subcutaneously Delivered RNAi Therapeutic to Enter Clinical Trials –

– Data from Trial Expected Mid-2013 –

Cambridge, Mass., March 18, 2013 – Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), a leading RNAi therapeutics company, announced today that it has initiated dosing in its Phase I clinical trial with ALN-TTRsc, an RNAi therapeutic targeting transthyretin (TTR) for the treatment of TTR-mediated amyloidosis (ATTR). ATTR is caused by mutations in the TTR gene which cause abnormal amyloid protein deposits to accumulate in various tissues including peripheral nerves and heart, resulting in 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) affects at least 40,000 people worldwide. ALN-TTRsc, which is being developed for the treatment of FAC, is a subcutaneously administered RNAi therapeutic that comprises an siRNA conjugated to a GalNAc ligand that enables receptor-mediated delivery to the liver. ALN-TTRsc is the first GalNAc-siRNA and the first subcutaneously delivered, systemic RNAi therapeutic to enter clinical development stages.

“RNAi therapeutics hold great promise for the treatment of ATTR since they have demonstrated rapid, potent, and durable knockdown of TTR, the disease-causing protein. We are advancing what we believe to be the industry leading effort in ATTR; this includes ALN-TTRsc for the treatment of FAC and ALN-TTR02 for the treatment of FAP which is currently enrolling patients in a Phase II trial,” said Akshay Vaishnaw, M.D., Ph.D., Executive Vice President and Chief Medical Officer of Alnylam. “The start of this Phase I trial with ALN-TTRsc represents the first for an RNAi therapeutic that utilizes our proprietary GalNAc conjugate delivery platform. It also marks the first subcutaneously delivered, systemic RNAi therapeutic for the industry. We look forward to the continued advancement of ALN-TTRsc for the treatment of FAC.”
The Phase I trial of ALN-TTRsc is being conducted in the U.K. as a randomized, double-blind, placebo-controlled, single- and multi-dose, dose-escalation study, enrolling up to 40 healthy volunteer subjects. The primary objective of the study is to evaluate the safety and tolerability of single and multiple doses of subcutaneously administered ALN-TTRsc. Secondary objectives include assessment of clinical activity of the drug as measured by serum TTR levels. Alnylam expects to present data from this trial in mid-2013. Upon completion of the Phase I trial, the company plans to start a Phase II clinical study of ALN-TTRsc in FAC patients by the end of 2013 and, assuming positive results, expects to start a pivotal trial for ALN-TTRsc in FAC patients in 2014.

“ATTR is a genetic disease with significant unmet medical need and limited treatment options for patients. RNAi therapeutics are a novel and compelling approach for the treatment of ATTR, as this novel modality has been shown to achieve robust knockdown of serum levels of both wild-type and mutant TTR,” said Philip Hawkins, FMedSci., Professor of Medicine, University College London Medical School. “I am encouraged by the clinical and pre-clinical data to date with Alnylam’s ALN-TTR program and look forward to the continued advancement of this effort for patients suffering from either the cardiomyopathy or polyneuropathy manifestations of this devastating disease.”

ATTR is an autosomal dominant inherited disease caused by mutations in the TTR gene, which is expressed predominantly in the liver. Pre-clinical studies have shown that subcutaneous administration of ALN-TTRsc resulted in potent and sustained suppression of TTR. In non-human primates, ALN-TTRsc administration resulted in an approximately 80% reduction of TTR at doses as low as 2.5 mg/kg. In single- and multi-dose pre-clinical safety studies in rodents and non-human primates, ALN-TTRsc was found to be generally safe and well tolerated. Specifically, at doses as high as 300 mg/kg in non-human primates, ALN-TTRsc was well tolerated with no clinical signs, no adverse laboratory or histopathologic findings, no elevations in cytokines or complement, and no significant injection site reactions.

Alnylam entered into an exclusive alliance with Genzyme, a Sanofi company, to develop and commercialize RNAi therapeutics, including ALN-TTR02 and ALN-TTRsc, for the treatment of ATTR in Japan and the broader Asian-Pacific region. Alnylam plans to develop and commercialize the ALN-TTR program in North and South America, Europe, and rest of the world.

About Transthyretin-Mediated Amyloidosis

Transthyretin (TTR)-mediated amyloidosis (ATTR) is an inherited, progressively debilitating, and fatal disease caused by mutations in the TTR gene. TTR protein is produced primarily in the liver and is normally a carrier for retinol binding protein. 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) affects at least 40,000 people worldwide. FAP patients have a life expectancy of five to 15 years from symptom onset, and the only treatment options for early stage disease are liver transplantation and tafamidis
The mean survival for FAC patients is approximately 2.5 years, and there are no approved therapies. There is a significant need for novel therapeutics to treat patients who have inherited mutations in the TTR gene.

**About GalNAc Conjugates**
GalNAc-siRNA conjugates are a proprietary Alnylam delivery platform and are designed to achieve targeted delivery of RNAi therapeutics to hepatocytes through uptake by the asialoglycoprotein receptor. Research findings demonstrate potent and durable target gene silencing, as well as a wide therapeutic index, with subcutaneously administered GalNAc-siRNAs from multiple “Alnylam 5x15” programs. GalNAc-siRNAs are being employed in Alnylam’s ALN-TTRsc, ALN-AT3, and ALN-AS1 RNAi therapeutic programs for the treatment of transthyretin-mediated amyloidosis (ATTR), hemophilia and rare bleeding disorders, and acute intermittent porphyria, respectively, among other ‘Alnylam 5x15’ programs.

**About RNA Interference (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 for the treatment of genetically defined diseases, including ALN-TTR for the treatment of transthyretin-mediated amyloidosis (ATTR), ALN-AT3 for the treatment of hemophilia and rare bleeding disorders (RBD), ALN-AS1 for the treatment of acute intermittent porphyria (AIP), ALN-PCS for the treatment of hypercholesterolemia, and ALN-TMP for the treatment of hemoglobinopathies. As part of its “Alnylam 5x15™” strategy, the company expects to have five RNAi therapeutic products for genetically defined diseases in clinical development, including programs in advanced stages, on its own or with a partner by the end of 2015. Alnylam has additional partnered programs in clinical or development stages, including ALN-RSV01 for the treatment of respiratory syncytial virus (RSV) infection and ALN-VSP for the treatment of liver cancers. The company’s leadership position on RNAi therapeutics and intellectual property have enabled it to form major alliances with leading companies including Merck, Medtronic, Novartis, Biogen Idec, Roche, Takeda, Kyowa Hakko Kirin, Cubist, Asclepis, Monsanto, Genzyme, and The Medicines Company. In addition, Alnylam holds a significant equity position in Regulus Therapeutics Inc.
a company focused on discovery, development, and commercialization of microRNA therapeutics. Alnylam has also formed Alnylam Biotherapeutics, a division of the company focused on the development of RNAi technologies for applications in biologics manufacturing, including recombinant proteins and monoclonal antibodies. Alnylam’s VaxiRNA™ platform applies RNAi technology to improve the manufacturing processes for vaccines; GlaxoSmithKline is a collaborator in this effort. Alnylam scientists and collaborators have published their research on RNAi therapeutics in over 100 peer-reviewed papers, including many in the world’s top scientific journals such as Nature, Nature Medicine, Nature Biotechnology, and Cell. Founded in 2002, Alnylam maintains headquarters in Cambridge, Massachusetts. For more information, please visit www.alnylam.com.

About “Alnylam 5x15™”
The “Alnylam 5x15” strategy, launched in January 2011, establishes a path for development and commercialization of novel RNAi therapeutics directed toward genetically defined targets for diseases with high unmet medical need. Products arising from this initiative share several key characteristics including: a genetically defined target and disease; the potential to have a major impact in a high unmet need population; the ability to leverage the existing Alnylam RNAi delivery platform; the opportunity to monitor an early biomarker in Phase I clinical trials for human proof of concept; and the existence of clinically relevant endpoints for the filing of a new drug application (NDA) with a focused patient database and possible accelerated paths for commercialization. By the end of 2015, the company expects to have five such RNAi therapeutic programs in clinical development, including programs in advanced stages, on its own or with a partner. The “Alnylam 5x15” programs include ALN-TTR for the treatment of transthyretin-mediated amyloidosis (ATTR), ALN-AT3 for the treatment of hemophilia and rare bleeding disorders (RBD), ALN-AS1 for the treatment of acute intermittent porphyria (AIP), ALN-PCS for the treatment of hypercholesterolemia, ALN-TMP for the treatment of hemoglobinopathies, and other programs. Alnylam intends to focus on developing and commercializing certain programs from this product strategy itself in North and South America, Europe, and other parts of the world; these include ALN-TTR, ALN-AT3, and ALN-AS1; the company will seek global development and commercial alliances for other programs.

Alnylam Forward-Looking Statements
Various statements in this release concerning Alnylam’s future expectations, plans and prospects, including without limitation, statements regarding Alnylam’s views with respect to the potential for RNAi therapeutics and its proprietary GalNAc-siRNA delivery platform, its expectations regarding the development of ALN-TTR02 and ALN-TTRsc, as well as other “Alnylam 5x15” programs, its expectations with respect to the timing and success of its clinical trials, including for ALN-TTR02 and ALN-TTRsc, its expectations regarding the reporting of data from its ALN-TTRsc clinical trial, and its expectations regarding its “Alnylam 5x15” product strategy, 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, successfully demonstrate the safety and efficacy of its drug candidates, including drug candidates utilizing GalNAc-siRNA delivery, the pre-clinical and clinical results for these product candidates, which may not support further development of such product
candidates, actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials for such product candidates, obtaining, maintaining and protecting intellectual property, obtaining regulatory approval for products, competition from others using technology similar to Alnylam’s and others developing products for similar uses, and Alnylam’s ability to establish and maintain strategic business alliances and new business initiatives, as well as those risks more fully discussed in the “Risk Factors” section of its Annual Report on Form 10-K for the year ended December 31, 2012 on file with the Securities and Exchange Commission. 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 does not assume any obligation to update any forward-looking statements.