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Alnylam Initiates Phase II Clinical Trial with ALN-TTRsc, a Subcutaneously Delivered RNAi Therapeutic Targeting Transthyretin (TTR) in Development for the Treatment of TTR-Mediated Amyloidosis (ATTR)

— Pilot Phase II Trial Now Open for Enrollment for ATTR Patients with Familial Amyloidotic Cardiomyopathy (FAC) or Senile Systemic Amyloidosis (SSA);
Study Includes a Number of Exploratory Clinical Endpoints —

— Company Expects to Present Data in Late 2014, and Start Pivotal Phase III Trial with ALN-TTRsc in TTR Cardiac Amyloidosis in Late 2014 —

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), a leading RNAi therapeutics company, announced today that it has initiated a pilot Phase II study with ALN-TTRsc, a subcutaneously delivered RNAi therapeutic targeting the transthyretin (TTR) gene in development for the treatment of TTR-mediated amyloidosis (ATTR). The Phase II trial, which is now open for enrollment, is aimed at evaluating the tolerability and preliminary clinical activity of ALN-TTRsc in TTR cardiac amyloidosis patients with familial amyloidotic cardiomyopathy (FAC) — which is caused by autosomal dominant mutations in the TTR gene, or senile systemic amyloidosis (SSA) — which is caused by idiopathic accumulation of wild-type TTR in the heart. The company expects to present data from the Phase II trial in late 2014, and assuming positive results, begin a Phase III trial in TTR cardiac amyloidosis patients by the end of 2014.

"Our recently presented Phase I study results of ALN-TTRsc demonstrated robust, up to 94% knockdown of serum TTR, which we believe provide an encouraging profile of clinical activity that warrants further advancement of this drug candidate for the treatment of TTR cardiac amyloidosis. We are pleased to announce that we have initiated our pilot Phase II trial with ALN-TTRsc, with the study now open for enrollment. Initiation of this Phase II trial highlights continued execution on our 'Alnylam 5x15' product development and commercialization strategy, which is focused on advancing RNAi therapeutics toward genetically defined targets for the treatment of diseases with high unmet medical need," said Akshay Vaishnaw, M.D., Ph.D., Executive Vice President and Chief Medical Officer of Alnylam. "This new study aims to evaluate the tolerability and preliminary clinical activity of ALN-TTRsc in patients with TTR cardiac amyloidosis. Since ALN-TTRsc achieves robust knockdown of serum TTR, the disease-causing protein in ATTR, we believe that this investigational agent has encouraging potential as a new therapeutic option for patients. Further, it is notable that ALN-TTRsc is the most advanced program in our pipeline that utilizes our GalNAc-conjugate approach for subcutaneous delivery of RNAi therapeutics, and the first to enter Phase II trials; as such, we are pleased with this important industry milestone with the continued development of RNAi therapeutics that utilize this delivery approach in clinical studies."

ATTR is caused by mutations in the TTR gene which cause abnormal TTR 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 FAC affects at least 40,000 people worldwide. 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. ALN-TTRsc is an investigational drug being developed for the treatment of TTR cardiac amyloidosis, including both FAC and SSA, and is a subcutaneously administered RNAi therapeutic that comprises a TTR-specific 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 advance in clinical development. Alnylam is also developing patisiran (ALN-TTR02), an intravenously administered RNAi therapeutic targeting TTR for the treatment of ATTR patients with FAP.

The Phase II trial is an open-label, multi-dose study of ALN-TTRsc, designed to enroll approximately 15 TTR cardiac amyloidosis patients with FAC or SSA. The primary objective of the study is to evaluate the general tolerability of ALN-TTRsc. Patients will receive 5 daily doses followed by 5 weekly doses of 5 mg/kg, with follow-up through Day 90; in the Phase I ALN-TTRsc study, this dose resulted in an up to 93% TTR knockdown and a mean nadir knockdown of approximately 88%, and was found to be generally safe and well tolerated. Secondary objectives include assessment of clinical activity as measured by knockdown of serum TTR levels and additional tests, such as cardiac imaging (including echocardiography and cardiac MRI), circulating cardiac biomarkers (NT-proBNP and troponins T and I), 6-minute walk test, New York Heart Association (NYHA) classification, and measures of heart failure symptoms and quality of life (Kansas City Cardiomyopathy Questionnaire and EQ-5D QOL). Patients completing the Phase II trial will be eligible to participate in an open-label extension (OLE) study for further assessment of general tolerability and clinical activity with long-term dosing; the ALN-TTRsc Phase II OLE study is expected to be initiated in mid-2014.

Alnylam reported positive results from a Phase I trial with ALN-TTRsc in 28 healthy volunteers at the Heart Failure Society of America 17th Annual Scientific Meeting held in September 2013. The results of the clinical study showed that ALN-TTRsc administration led to robust, consistent, and statistically significant ($p < 0.01$) knockdown of serum TTR of up to 94%. Knockdown of TTR was found to be rapid, dose-dependent, and durable. ALN-TTRsc was found to be generally safe and well tolerated in the study. Importantly, these human study results were the first to be reported for Alnylam's proprietary GalNAc-siRNA conjugate delivery platform, enabling subcutaneous dosing of RNAi therapeutics with a wide therapeutic index.

In 2012, Alnylam entered into an exclusive alliance with Genzyme, a Sanofi company, to develop and commercialize RNAi therapeutics, including patisiran 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 approved treatment options for early stage disease are liver transplantation, and tafamidis (approved in Europe). The mean survival for FAC patients is approximately 2.5 years, and there are no approved therapies. 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 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.

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 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), an intravenously delivered RNAi therapeutic targeting transthyretin (TTR) for the treatment of TTR-mediated amyloidosis (ATTR) in patients with familial amyloidotic polyneuropathy (FAP); ALN-TTRsc, a subcutaneously delivered RNAi therapeutic targeting TTR for the treatment of ATTR in patients with familial amyloidotic cardiomyopathy (FAC); ALN-AT3, an RNAi therapeutic targeting antithrombin (AT) for the treatment of hemophilia and rare bleeding disorders (RBD); ALN-AS1, an RNAi therapeutic targeting aminolevulinate synthase-1 (ALAS-1) for the treatment of porphyria including acute intermittent porphyria (AIP); ALN-CC5, an RNAi therapeutic targeting complement component C5 for the treatment of complement-mediated diseases; ALN-PCS, an RNAi therapeutic targeting PCSK9 for the treatment of hypercholesterolemia; ALN-TMP, an RNAi therapeutic targeting TMPRSS6 for the treatment of beta-thalassemia and iron-overload disorders; ALN-AAT, an RNAi therapeutic targeting alpha-1-antitrypsin (AAT) for the treatment of AAT deficiency liver disease; and ALN-ANG, an RNAi therapeutic for the treatment of genetic forms of mixed hyperlipidemia and severe hypertriglyceridemia, amongst other programs. 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, Ascletis, Monsanto, Genzyme, and The Medicines Company. In addition, Alnylam holds an 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, Cell, the 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.

About "Alnylam 5x15™"

The "Alnylam 5x15" strategy, launched in January 2011, establishes a path for development and commercialization of novel RNAi therapeutics toward genetically defined targets for the treatment of 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: patisiran (ALN-TTR02), an intravenously delivered RNAi therapeutic targeting transthyretin (TTR) in development for the treatment of TTR-mediated amyloidosis (ATTR) in patients with familial amyloidotic polyneuropathy (FAP); ALN-TTRsc, a subcutaneously delivered RNAi therapeutic targeting TTR in development for the treatment of ATTR in patients with familial amyloidotic cardiomyopathy (FAC); ALN-AT3, an RNAi therapeutic targeting antithrombin (AT) in development for the treatment of hemophilia and rare bleeding disorders (RBD); ALN-AS1, an RNAi therapeutic targeting aminolevulinate synthase-1 (ALAS-1) in development for the treatment of porphyria including acute intermittent porphyria (AIP); ALN-CC5, an RNAi therapeutic targeting complement component C5 in development for the treatment of complement-mediated diseases; ALN-PCS, an RNAi therapeutic targeting PCSK9 in development for the treatment of hypercholesterolemia; ALN-TMP, an RNAi therapeutic targeting TMPRSS6 in development for the treatment of beta-thalassemia and iron-overload disorders; ALN-AAT, an RNAi therapeutic targeting alpha-1-antitrypsin (AAT) for the treatment of AAT deficiency liver disease; and ALN-ANG, an RNAi therapeutic for the treatment of genetic forms of mixed hyperlipidemia and severe hypertriglyceridemia, amongst 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.

Alnylam Forward-Looking Statements

Various statements in this press release concerning Alnylam's future expectations, plans and prospects, including without limitation, Alnylam's expectations regarding its "Alnylam 5x15" product strategy, Alnylam's views with respect to the potential for RNAi therapeutics, including ALN-TTRsc, its expectations regarding the reporting of data from its ALN-TTRsc clinical trials, its expectations with respect to the timing and success of its clinical trials for ALN-TTRsc, and its expectations regarding the potential market opportunity for ALN-TTRsc, 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, including ALN-TTRsc, 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 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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