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Alnylam Presents New Pre-Clinical Data on RNAi Therapeutic Programs for Cardio-Metabolic Diseases at American Heart Association Scientific Sessions 2014

- New Non-Human Primate Data on ALN-PCSsc Show Clamped Knockdown of PCSK9 up to 92% and LDL-C Reductions of up to 77% with Monthly Subcutaneous Dosing Regimen; Phase 1 Study with ALN-PCSsc on Track to Start This Year with Initial Data Expected in Mid-2015 -

- New Pre-Clinical Data Presented for ALN-AC3 Targeting Apolipoprotein C3, and ALN-ANG Targeting ANGPTL3, Supports Advancement of Both Programs for the Treatment of Genetic and Acquired Dyslipidemias -

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), a leading RNAi therapeutics company, announced today that it has presented new pre-clinical data from its investigational RNAi therapeutic programs toward genetically validated targets in development for the treatment of cardiovascular metabolic diseases, including: ALN-PCSsc targeting PCSK9 for the treatment of hypercholesterolemia; ALN-AC3 targeting apolipoprotein C3 (apoC3) for the treatment of hypertriglyceridemia; and ALN-ANG targeting angiopoietin-like 3 (ANGPTL3) for the treatment of genetic forms of mixed hyperlipidemia and severe hypertriglyceridemia. These new data are being presented at the American Heart Association (AHA) Scientific Sessions 2014 in a poster presentation titled "Development of Monthly to Quarterly Subcutaneous Administration of RNAi Therapeutics Targeting the Metabolic Disease Genes PCSK9, ApoC3 and ANGPTL3." Among other data, Alnylam presented new pre-clinical multi-dose data in non-human primates (NHPs) with over six months of dosing for ALN-PCSsc showing robust and clamped knockdown of PCSK9 of up to 92% and reductions in LDL-C of up to 77% with a once-monthly subcutaneous dosing regimen. Recently, Alnylam filed and received approval for a Clinical Trial Application (CTA) for ALN-PCSsc, and now expects to start the Phase 1 trial before year's end with initial clinical data expected in mid-2015.

"ALN-PCSsc is a first-in-class PCSK9 synthesis inhibitor that we believe represents an innovative, differentiated, and well-validated approach for the treatment of hypercholesterolemia. Our new non-human primate studies confirm the potential for a once-monthly, and possibly once-quarterly, low volume subcutaneous dose regimen. Further, the mechanism of action for ALN-PCSsc enables LDL-C lowering independent of baseline PCSK9 plasma levels, which we believe could result in additive or even synergistic activity in combination with statins. Together with our partners at The Medicines Company, we look forward to the start of our Phase 1 clinical trial in the coming weeks, with initial data expected in mid-2015," said Rachel Meyers, Ph.D., Vice President, Research and RNAi Lead Development at Alnylam. "We also presented new data at AHA on our ALN-AC3 and ALN-ANG programs, which expand our pipeline of investigational RNAi therapeutics toward genetically validated targets for cardio-metabolic diseases. Indeed, we see this as an attractive area for continued investment by Alnylam given the significant disease burden and unmet need for new medicines, the large number of liver-expressed disease-causing genes important in cardio-metabolic disease, and the emerging tolerability, activity, and durability profile of our GalNAc-conjugate platform."

ALN-PCSsc is a subcutaneously administered RNAi therapeutic that utilizes Alnylam's proprietary Enhanced Stabilization Chemistry (ESC)-GalNAc-siRNA conjugate delivery platform. ESC-GalNAc-siRNA conjugates are designed to achieve targeted delivery of RNAi therapeutics to hepatocytes through uptake by the asialoglycoprotein receptor, and enable subcutaneous dosing with increased potency and durability and a wide therapeutic index. The new pre-clinical NHP studies showed that monthly subcutaneous administration of ALN-PCSsc resulted in PCSK9 knockdown of up to 92% and LDL-C lowering, in the absence of statin co-administration, of up to 77%; mean maximum knockdown of PCSK9 was 83.2% +/- 7.2%, and mean maximum LDL-C reduction was 59.0% +/- 13.3%. As a PCSK9 synthesis inhibitor, ALN-PCSsc showed rapid, durable, and clamped knockdown of PCSK9 and reduction of LDL-C, which contrasts with the cyclical variation in LDL-C observed with monthly dose regimens of anti-PCSK9 monoclonal antibodies (Stein, *Curr Opin Lipidol* 2013, 24:510-517). Based on current human translational data with ESC-GalNAC-conjugates, the projected human dose levels are expected to be less than 1 mg/kg at a subcutaneous injection volume of less than 1 mL administered once-monthly. In aggregate, these pre-clinical data are supportive of a once-monthly, and possibly once-quarterly, dosing regimen for ALN-PCSsc, which the company believes could represent a highly competitive target product profile.

Alnylam's CTA for a Phase 1 trial with ALN-PCSsc has been approved and the company now expects to initiate this study before the end of this year, with initial data expected to be reported in mid-2015. The Phase 1 trial of ALN-PCSsc will be conducted as a randomized, single-blind, placebo-controlled, single- and multi-dose, dose-escalation study. The study is designed to enroll up to 76 healthy volunteer subjects with elevated baseline LDL-C (≥ 100 mg/dL), with subjects randomized 3:1, drug:placebo. The study will be performed in two phases: a single ascending dose (SAD) phase and a multiple dose (MD) phase. In the MD phase, subjects will receive two doses of either ALN-PCSsc or placebo administered four weeks apart. The MD phase will also include subjects both on and off statin co-medication. The primary objective of the Phase 1 study is to evaluate the safety and tolerability of ALN-PCSsc. Secondary objectives include assessment of clinical activity as determined

by knockdown of plasma PCSK9 levels and serum LDL-C levels, as well as pharmacokinetics of ALN-PCSsc. In support of the approved CTA, Alnylam has completed toxicology studies in rodents and NHPs. In both species, the no observed adverse effect level (NOAEL) was determined to exceed 250 mg/kg, the top dose in both studies, with no adverse findings in clinical, hematology, laboratory chemistry, and histopathology assessments. Alnylam is collaborating with The Medicines Company on the advancement of ALN-PCSsc.

Alnylam also presented data from its ALN-AC3 program at AHA. ALN-AC3 is a subcutaneously administered investigational RNAi therapeutic targeting apoC3 for the treatment of hypertriglyceridemia. ApoC3 is a component of lipoprotein particles in the blood; it inhibits lipoprotein lipase and hepatic lipase, reducing hepatic uptake of triglyceride-rich particles. Polymorphisms in apoC3 have been associated with hypertriglyceridemia; specifically, a gain-of function phenotype leads to higher apoC3 and triglyceride levels, and reduced triglyceride clearance. In contrast, loss-of-function mutations in apoC3 result in greater triglyceride hydrolysis into free fatty acids and increased triglyceride clearance; heterozygous individuals have lower triglycerides and lower levels of very low density lipoprotein (VLDL). Recent studies have identified rare loss of function variants in apoC3 that appear to be cardioprotective (Tachmazidou *et al., Nat. Comm*, 2013; Bochem *et.al. Clin Genet*., 2014). The new data presented were from studies conducted in mouse models that match human genetics. Specifically, a single 3 mg/kg dose of a GalNAc-conjugated siRNA targeting apoC3 resulted in knockdown of apoC3 levels of up to 94%, with more than 60% knockdown sustained for at least 30 days. In a multi-dose study, results showed that dosing of 3 mg/kg every other week resulted in 96% knockdown of human apoC3 through day 35, the last time point in the study. Alnylam plans to continue to conduct additional pre-clinical work in this program to finalize its Development Candidate.

In addition to ALN-PCSsc and ALN-AC3, Alnylam is also advancing ALN-ANG, an investigational RNAi therapeutic targeting ANGPTL3 for the treatment of genetic forms of mixed hyperlipidemia and severe hypertriglyceridemia. ANGPTL3 is an inhibitor of cellular lipases involved in the metabolism of lipoproteins. Human genetic as well as exome sequencing studies have identified a statistically significant relationship of loss-of-function mutations in ANGPTL3 with decreased levels of triglycerides and LDL-C (Musunuru *et al., N. Engl. J. Med* (2010) 363:2220-2227). New data presented at AHA demonstrated that a single dose of a GalNAc-siRNA targeting ANGPTL3 led to robust, dose-dependent knockdown of serum ANGPTL3 protein of up to 99%, with a single dose ED_{90} of approximately 1 mg/kg. In studies performed in an "ob/ob" mouse model of obesity and mixed hyperlipidemia, ALN-ANG treatment as a single 3 mg/kg dose resulted in a greater than 80% reduction in levels of triglycerides and LDL-C. In addition, total cholesterol was reduced up to 68%. These data with ALN-ANG support further advancement of this program for the treatment of genetic forms of mixed hyperlipidemia and severe hypertriglyceridemia, which are associated with increased risk of coronary artery disease and/or recurrent pancreatitis. Alnylam is conducting additional pre-clinical research to finalize its Development Candidate for the ALN-ANG program.

About Hypercholesterolemia

Hypercholesterolemia is a condition characterized by very high levels of cholesterol in the blood which is known to increase the risk of coronary artery disease, the leading cause of death in the U.S. Some forms of hypercholesterolemia can be treated through dietary restrictions, lifestyle modifications (e.g., exercise and smoking cessation) and medicines such as statins. However, a large proportion of patients with hypercholesterolemia are not achieving adequate LDL-C levels with currently available therapies including statins, including genetic familial hypercholesterolemia (FH) patients, acute coronary syndrome patients, high-risk patient populations (e.g., patients with coronary artery disease, diabetics, symptomatic carotid artery disease, etc.) and other patients that are statin intolerant. Severe forms of hypercholesterolemia are estimated to affect more than 500,000 patients worldwide, and as a result, there is a significant need for novel therapeutics to treat patients with hypercholesterolemia whose disease is inadequately managed by existing therapies.

About Mixed Hyperlipidemia and Hypertriglyceridemia

Mixed hyperlipidemia is a genetically inherited condition characterized by very high levels of cholesterol and triglycerides in the blood, both of which are known to increase the risk of coronary artery disease, the leading cause of death in the U.S. It is estimated that as many as 1 out of every 100 individuals have mixed hyperlipidemia and are at increased risk of developing cardiovascular disease. Some forms of mixed hyperlipidemia can be treated through dietary restrictions, lifestyle modifications (e.g., exercise and smoking cessation), and medicines such as statins or fibrates; however, a large portion of mixed hyperlipidemia patients are unable to reach either their LDL-C and/or triglyceride goals with the current standard of care. Patients with severe, inherited forms of hypertriglyceridemia (e.g., familial chylomicronemia syndrome, or "FCS") are at extremely high risk of developing recurrent pancreatitis. FCS is a rare orphan genetic disease that affects 1 to 2 individuals per million.

About GalNAc Conjugates and Enhanced Stabilization Chemistry (ESC) 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. Alnylam's Enhanced Stabilization Chemistry (ESC) GalNAc-conjugate technology enables subcutaneous dosing with increased potency, durability, and a wide therapeutic index, and is being employed in several of Alnylam's genetic medicine programs, including programs in clinical development.

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 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 ALN-PCSsc for the treatment of hypercholesterolemia; ALN-AC3 targeting apolipoprotein C-3 (apoC3) for the treatment of hypertriglyceridemia; and ALN-ANG for the treatment of genetic forms of mixed hyperlipidemia and severe hypertriglyceridemia; including the timing of beginning clinical studies and reporting data, the potential therapeutic opportunities for ALN-PCSsc, ALN-AC3, and ALN-ANG, as well as its expectations regarding its "Alnylam 5x15" product strategy, and its plans regarding commercialization of RNAi therapeutics, including ALN-PCSsc, ALN-AC3 and ALN-ANG, 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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