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Alnylam Presents New Pre-Clinical Data on Pharmacology of GalNAc-siRNA Conjugates

— New Results Demonstrate Achievement of Steady State Liver Drug Levels During Chronic Dosing with No Evidence for Drug Accumulation —

— Steady, Long-Term Knockdown Maintained with High Level of Consistency in Absence of Tachyphylaxis or Sensitization —

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), a leading RNAi therapeutics company, announced today that it has presented new pre-clinical data on the pharmacology of GalNAc-siRNA conjugates at the 12th US-Japan Symposium on Drug Delivery Systems held December 16 — 20, 2013 in Lahaina, Maui, Hawaii. In a presentation titled "Advances in Systemic Delivery of RNAi Therapeutics," Alnylam scientists presented new data on tissue drug levels and sustained target knockdown achieved with long-term chronic dosing of GalNAc-siRNA 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. This targeted delivery platform enables subcutaneous dose administration with a wide therapeutic index, and has demonstrated potent and durable gene silencing, as well as a favorable tolerability profile, in clinical and pre-clinical studies from multiple programs in the company's "Alnylam 5x15" product pipeline.

"Our GalNAc-siRNA conjugate delivery platform is being employed in the majority of the pipeline programs within our "Alnylam 5x15" product development strategy. At Alnylam, we are at the forefront of optimizing the delivery of RNAi therapeutics using this proprietary, now clinically validated delivery approach," said Muthiah (Mano) Manoharan, Ph.D., Senior Vice President of Drug Discovery at Alnylam. "These new data show that weekly subcutaneous dosing of GalNAc conjugates results in mean steady state drug levels that compare very favorably with other oligonucleotide platforms that require 100 to 1000 times greater tissue drug levels to achieve clinically relevant gene silencing. Furthermore, these data show that chronic dosing results in sustained target gene knockdown with a high level of consistency in the absence of any evidence for tachyphylaxis or sensitization. We view these findings as very encouraging, as they will likely have significant implications for RNAi-mediated silencing with chronic dosing in the clinical setting."

The new data demonstrate the pharmacodynamic and pharmacokinetic properties of GalNAc-siRNA conjugates following repeat dosing. Specifically, in mouse studies, weekly subcutaneous dosing of ALN-AT3, an RNAi therapeutic targeting antithrombin (AT), resulted in mean steady state liver drug levels of approximately 0.4 and 1.1 micrograms per gram at doses of 0.2 and 0.5 mg/kg, respectively. These drug levels were shown to correspond to roughly 60% and 75% knockdown of serum AT, and compare very favorably with other oligonucleotide platforms requiring greater than 100 micrograms of drug per gram of tissue for similar biologic effects; this corresponds to 100- to 1000-fold lower levels of required tissue exposure for GalNAc-siRNA conjugates, which could underscore the potential for a more favorable tolerability profile. Further, no evidence of drug accumulation in liver tissue during chronic dosing was observed after the third weekly dose. In addition, data from a long-term pharmacology study were presented with a GalNAc-siRNA conjugate targeting the transthyretin (TTR) mRNA in mice. Weekly dosing at 1.0 and 2.5 mg/kg led to steady TTR knockdown of 50% and 80%, respectively, which was sustained for the entire 196-day time period analyzed. The TTR knockdown effect was found to be highly consistent with very low levels of inter-animal variation. Finally, the steady level of knockdown was achieved with no evidence of tachyphylaxis or sensitization.

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, and Alnylam's views with respect to the potential for RNAi therapeutics and GalNAc conjugates, 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 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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