Dear Stockholders,

Over the past year, Alnylam has continued to make excellent progress advancing our robust pipeline of investigational RNAi therapeutics toward the market with significant achievements across all three Strategic Therapeutic Areas, or "STArs," including Genetic Medicines, Cardio-Metabolic Disease and Hepatic Infectious Disease – spanning disease settings from the rare, to the common, to the global.

Last year, we launched our *Alnylam 2020* guidance to have three or more marketed products, and an additional ten or more clinical stage programs, including four in late-stage development, across our three STArs by the end of 2020. This strategy marks our transition from a late-stage development company to a multi-product, commercial-stage company with a sustainable development pipeline. We believe our reproducible and modular platform applied across the pipeline, our competitive and differentiated product profiles for each program, and the large number of opportunities for future innovative medicines will continue to fuel our journey to *Alnylam 2020* and our ultimate goal of bringing RNAi therapeutics to patients.

Genetic Medicines STAr: Small patient populations, large impact

Alnylam's most advanced programs are in our Genetic Medicines STAr, with our two lead programs focused on transthyretin (TTR)-mediated amyloidosis (ATTR amyloidosis), an inherited progressive and debilitating disease afflicting about 50,000 people worldwide. Patisiran, in development for the treatment of hereditary ATTR with polyneuropathy (familial amyloidotic polyneuropathy or "FAP") is our most advanced program. We have recently completed enrollment in our Phase 3 APOLLO trial with 225 FAP patients, putting us on track for our first Phase 3 data readout in the second half of 2017. Assuming the study is positive, we expect to submit a New Drug Application (NDA) and Marketing Authorisation Application (MAA) for patisiran in late 2017. Initial 18-month data from our Phase 2 open-label extension (OLE) study with patisiran showed continued evidence for potential halting of neuropathy progression. Further, patisiran was found to be generally well tolerated out to nearly two years of drug administration through the data cutoff date. With the important caveat that this is an open-label study in a small number of patients, we view these results as encouraging and increasingly informative as we continue advancement of patisiran to the market.

We are also developing revusiran for the treatment of hereditary ATTR with cardiomyopathy (familial amyloidotic cardiomyopathy or "FAC"). Throughout 2015, we continued to enroll FAC patients in our Phase 3 ENDEAVOUR trial, and we expect to read out data in 2018. We also reported initial 6-month data from our Phase 2 OLE study with revusiran, which showed potent and sustained TTR knockdown, representing the longest dosing experience reported to date for target gene knockdown with a subcutaneously administered GalNAc-siRNA conjugate. In the majority of patients, revusiran was generally well tolerated out to 10 months of administration through the data cutoff date. Also in 2015, we demonstrated our continued commitment to ATTR amyloidosis patients with the advancement of a Development Candidate (DC) for ALN-TTRsc02, our second generation, Enhanced Stabilization Chemistry (ESC)-GalNAc-siRNA conjugate targeting TTR with the potential for a low volume, once quarterly, subcutaneous dose regimen. We believe ALN-TTRsc02 has the potential to achieve a best-in-class profile for the treatment of ATTR amyloidosis, and as such, we plan to proceed with a streamlined clinical development plan pending positive Phase 1 results later this year and appropriate discussions with regulatory authorities.

The next program in our Genetic Medicines pipeline is fitusiran, previously known as ALN-AT3, an investigational RNAi therapeutic targeting antithrombin (AT) for the treatment of hemophilia and other rare bleeding disorders. In late 2015, we presented positive interim data from our ongoing Phase 1 study showing that monthly subcutaneous doses of fitusiran achieved AT lowering associated with statistically significant and clinically meaningful increases in thrombin generation, as well as decreases in bleeding frequency in patients with hemophilia A and B. Fitusiran was also found to be generally well tolerated through the data cutoff date, including no clinically significant increases in D-dimer, a biomarker of excessive clot formation. We are now planning to advance fitusiran into Phase 3 development, with two pivotal studies slated to start later in 2016. In addition, earlier this year Sanofi Genzyme elected to opt into the fitusiran program for development and commercialization outside of North America and Western Europe.

Also in the past year, we believe we made great progress in the advancement of ALN-CC5, an investigational RNAi therapeutic targeting complement component C5 for the treatment of complement-mediated diseases, including paroxysmal nocturnal hemoglubinuria (PNH), a rare blood disorder leading to red blood cell destruction. In late 2015, we reported positive initial data from our ongoing Phase 1/2 clinical trial showing that ALN-CC5 achieved clinically meaningful, clamped reductions in serum C5 as well as inhibition of complement activity, and was generally well tolerated through the data cutoff date. Dosing of PNH patients in Part C of the Phase 1/2 study is currently ongoing. We look forward to presenting LDH data from these patients in mid-2016, and we plan to initiate a Phase 3 study in 2017.

Alnylam® PHARMACEUTICALS

We continue to advance ALN-AS1 targeting aminolevulinic acid synthase 1 (ALAS1) for the treatment of acute hepatic porphyrias, including acute intermittent porphyria (AIP). In 2015, we presented positive initial data from our ongoing Phase 1 trial, showing significant reductions of toxic heme intermediates that mediate porphyria attacks and potent, dose-dependent, durable silencing of ALAS1 mRNA in the liver. Importantly, ALN-AS1 was found to be generally well tolerated with no clinically significant drug-related adverse events through the data cutoff date. Part C of the Phase 1 study is currently being conducted in AIP patients experiencing multiple recurrent porphyria attacks. We plan to report these initial data in late 2016 and, assuming results are positive, we expect to initiate a Phase 3 study with ALN-AS1 in 2017.

We have many additional programs in our Genetic Medicines STAr, including ALN-AAT for the treatment of alpha-1 antitrypsin (AAT) deficiency-associated liver disease and ALN-GO1 for the treatment of primary hyperoxaluria type 1 (PH1), both of which are in early clinical stages.

Our transformational alliance with Sanofi Genzyme for our Genetic Medicines pipeline, initiated in 2014, continues to enable the advancement of RNAi therapeutics for rare diseases on a global basis, where Alnylam retains commercial rights in North America and Western Europe and Sanofi Genzyme is our partner in the rest of the world, subject to certain broader rights.

Cardio-Metabolic STAr: An uncommon approach for common disease settings

We remain committed to the development of investigational RNAi therapeutics for indications like dyslipidemia, diabetes, NASH, and hypertension. Our most advanced effort is ALN-PCSsc, an investigational RNAi therapeutic targeting PCSK9 for the treatment of hypercholesterolemia. Phase 1 data presented in late 2015 demonstrated reductions in LDL cholesterol comparable to levels achieved with anti-PCSK9 monoclonal antibodies, but with durability that supports the potential for a *biannual* dose regimen as compared to a *bimonthly* dose regimen that's required with the antibodies. We believe this is a best-in-class profile for our drug, and represents a potential paradigm shift in the management of hypercholesterolemia. This program is partnered with The Medicines Company, which initiated the Phase 2 ORION-1 trial in January 2016. We have an attractive economic agreement with The Medicines Company, whereby we are eligible to receive scaled double-digit royalties up to 20 percent on global product sales and milestone payments of up to an additional $170 million, with no financial burden for development or commercialization moving forward.

Hepatic Infectious Disease STAr: Potential to alleviate health burdens on a global scale

In our Hepatic Infectious Disease STAr, we have the potential to treat global health burdens, such as hepatitis B and D, amongst other chronic liver infections. We recently filed our CTA for ALN-HBV, in development for the treatment of chronic hepatitis B virus (HBV) infection, and plan to initiate a Phase 1 trial in mid-2016. In pre-clinical studies, ALN-HBV has demonstrated multi-log reductions in HBV surface antigen levels, holding promise that this investigational RNAi therapeutic can increase the rate of "functional cures" in HBV-infected patients.

Strong Execution on Business Objectives

In addition to our significant pipeline advancements in the past year, we made important progress on our broader business objectives as we grow Alnylam in a sustainable manner and prepare for our transition to a multi-product, commercial-stage company. We have maintained a strong balance sheet to fund these R&D and market development efforts, ending 2015 with $1.28 billion in cash. Looking forward, we are building capabilities needed in the U.S. and Europe to achieve our *Alnylam 2020* goals, and will soon break ground on a manufacturing facility in Massachusetts, an important capital investment that is intended to ensure long-term commercial supply for our products in the years to come. We are also pursuing potential new alliances in our Cardio-Metabolic and Hepatic Infectious Disease STArs, with the goal of retaining significant product rights in the U.S. and Europe.

This is certainly an exciting period for Alnylam, with ten or more major clinical data readouts expected in 2016. In 2017, we expect to have five or more ongoing Phase 3 trials and our first Phase 3 data readout and NDA/MAA submission. At Alnylam, we believe our fundamentals have never been stronger. We remain focused on developing medicines with the potential to transform the lives of patients, and we believe we are well on track to achieving our *Alnylam 2020* goals. I'd like to thank you sincerely for your continued support as we strive to fulfill the promise of RNAi therapeutics for patients, their families, and caregivers.

John M. Maraganore, Ph.D.
Chief Executive Officer
Alnylam Pharmaceuticals, Inc.
March 16, 2016

Alnylam® PHARMACEUTICALS