Dear Stockholders,

In 2014 and the recent period, Alnylam made significant progress in advancing RNAi therapeutics as a whole new class of innovative medicines. We are advancing our investigational RNAi therapeutics pipeline in three Strategic Therapeutic Areas, or "STArs," including: Genetic Medicines, focused on a robust pipeline for rare diseases; Cardio-Metabolic Disease, targeting unmet needs in dyslipidemia, hypertension, type 2 diabetes, and non-alcoholic steatohepatitis (NASH); and Hepatic Infectious Disease, addressing major global health burdens such as hepatitis B virus (HBV) infection. Today, we have what we believe to be one of the most exciting development pipelines in biotech, with six programs in clinical development, including two in Phase 3 trials, and well over an additional dozen programs in pre-clinical development stages.

For the past several years, we've been executing on our *Alnylam 5x15* strategy, which we launched in 2011; we now expect to exceed our original guidance with a plan to end 2015 with eight clinical stage programs. Recently, we launched our new guidance called *Alnylam 2020*, where we expect to end 2020 with three or more marketed products, with an additional 10 or more clinical stage programs, including four in late-stage development, across our three STArs. *Alnylam 2020* marks our transition from a late-stage development company to a multi-product, commercial-stage company – where we intend to maintain direct marketing and sales in North America and Europe – advancing a sustainable pipeline and robust product engine. In our view, this is a profile that has rarely been achieved in the history of the biopharmaceutical industry. We believe execution on *Alnylam 2020* will meet our commitment to bring our innovative medicines to patients and, in turn, reward our stockholders for their investment.

Alnylam's most advanced pipeline programs are in rare diseases as part of our Genetic Medicine STAr. Here, our lead programs are focused on transthyretin (TTR)-mediated amyloidosis (ATTR), an inherited progressive and debilitating disease afflicting about 50,000 people worldwide. Patisiran is our most advanced program, and is being developed for the treatment of ATTR polyneuropathy (familial amyloidotic polyneuropathy or "FAP"). During 2014, we enrolled patients in our Phase 3 APOLLO trial, which is aimed at obtaining global marketing authorization for patisiran in FAP. Results from our ongoing Phase 2 open-label extension (OLE) study of patisiran in patients with FAP were a highlight of 2014. We were able to show initial evidence for potential disease stabilization after six months of treatment in 19 patients, as compared with historical data. With the important caveat that this is an open-label study in a small number of subjects, we view these results as promising and look forward to further analysis of results after longer duration of treatment. In addition, patisiran was found to be generally well tolerated in this study. We are also advancing revusiran in ATTR, specifically in patients with ATTR cardiomyopathy (familial amyloidotic cardiomyopathy or "FAC"). During 2014, we completed our Phase 2 trial showing robust knockdown of serum TTR – the disease-causing protein – and a tolerability profile supporting further development. In addition, we initiated our Phase 3 ENDEAVOUR trial of revusiran in FAC. This is an exciting development, since revusiran is our most advanced program to employ our GalNAc-conjugate delivery platform that enables subcutaneous administration of RNAi therapeutics with a wide therapeutic index.

Also as part of our Genetic Medicine STAr, we are advancing a number of additional clinical programs. These include ALN-AT3, an investigational RNAi therapeutic targeting antithrombin (AT) for the treatment of hemophilia and other rare bleeding disorders. There remains enormous unmet need for improved management of bleeding disorders, and ALN-AT3 has the potential to become what we believe could be a disease-modifying approach and, possibly, a "functional cure." In late 2014, we presented preliminary data from our ALN-AT3 Phase 1 study showing knockdown of AT and initial evidence for potential correction of the hemophilia phenotype in a small number of patients with severe hemophilia. ALN-AT3 has been generally well tolerated in the Phase 1 study. We're also advancing ALN-CC5, an investigational RNAi therapeutic targeting complement component C5 for the treatment of complement-mediated diseases such as paroxysmal nocturnal hemoglubinuria (PNH), a rare blood disorder leading to red blood cell destruction. As a subcutaneously administered agent that consistently clamps C5 levels by greater than 98% in pre-clinical studies, we believe that ALN-CC5 has the potential to emerge as a new approach for management of complement-mediated diseases. We were pleased to recently initiate a Phase 1/2 study of ALN-CC5, including in patients with PNH. Finally, we are also advancing ALN-AS1 for the treatment of hepatic porphyrias, including acute intermittent porphyria (AIP). AIP is an ultra-rare genetic disease with enormous unmet need. For the approximately 500 AIP patients in the U.S. and Europe with recurrent attacks, ALN-AS1 could emerge as a new treatment option to prevent attack occurrence. Recently, we filed our Clinical Trial Application for ALN-AS1 and expect to start our Phase 1 study in mid-2015.

We have many additional programs in our Genetic Medicine STAr, and expect to file Investigational New Drug (IND) or equivalent applications in 2015 and beyond. A highlight in 2014 was the formation of our transformational alliance with Genzyme, a Sanofi company, for our Genetic Medicine pipeline. In this alliance, Alnylam and Genzyme are advancing RNAi therapeutics for rare diseases on a global basis, where Alnylam leads development and commercialization in North America and Western Europe, while Genzyme leads in the rest of world. Genzyme is the industry pioneer in developing and commercializing medicines for rare diseases, and we could not have a stronger partner to advance our medicines to patients worldwide.

**VISION:** *Harnessing a revolution in biology for human health®*

**MISSION:** *Build a top-tier, independent biopharmaceutical company founded on RNAi*

We are also advancing investigational RNAi therapeutics in our Cardio-Metabolic Disease STAr. Indeed, the emerging profile of our GalNAc-conjugate programs – specifically, those employing our Enhanced Stabilization Chemistry (ESC) platform – demonstrates the potential for subcutaneous administration of RNAi therapeutics with once-monthly and possibly once-quarterly dose regimens. We believe this is a compelling profile for new medicines to address unmet needs in dyslipidemia, hypertension, type 2 diabetes, and NASH. Our most advanced effort is ALN-PCSsc, an investigational RNAi therapeutic targeting PCSK9 for the treatment of hypercholesterolemia. PCSK9 is a notable disease target, since it has been validated in human genetics as a key regulator of LDL-C metabolism; elevated LDL-C, or "bad cholesterol," has been associated with increased risk and complications of coronary artery disease. PCSK9 is also the target of new monoclonal antibody drugs that are nearing potential FDA approval. Our approach is to block the synthesis of PCSK9, i.e., turn off the faucet, in comparison to the monoclonal antibodies that need to bind to PCSK9 in the blood and "mop up the floor." We believe that a PCSK9 synthesis inhibitor like ALN-PCSsc could have several advantages including the potential for a once-monthly or possibly once-quarterly subcutaneous dose administration regimen. Recently, we started our Phase 1 study of ALN-PCSsc in human volunteers with elevated LDL-C. This program is partnered with The Medicines Company. In addition to ALN-PCSsc, we are advancing additional programs for hypertriglyceridemia, mixed hyperlipidemia, and hypertensive disorders of pregnancy, including preeclampsia, amongst other currently non-disclosed programs.

Our third STAr is in Hepatic Infectious Disease, where we are advancing investigational RNAi therapeutics to treat global health burdens such as HBV infection. There are an estimated 400 million people worldwide with chronic HBV infection, including an estimated 25 million people in the U.S. and Europe. Unlike diseases such as hepatitis C virus (HCV) infection where new drugs have achieved cure rates over 90%, existing therapies – interferon and nucleoside analogs – fall far short in HBV, where cure rates are approximately 10%. Clearly, new therapies are needed, and RNAi therapeutics represent what we believe to be a potentially powerful new approach. Indeed, we have demonstrated multi-log reductions of viral load and HBV surface antigen (HBsAg) levels in chronically infected chimpanzees; HBsAg reduction is believed to be a predictor of seroconversion (i.e., a "functional cure") in patients with HBV. In 2014, we selected our Development Candidate, ALN-HBV, which employs our ESC-GalNAc-conjugate platform for subcutaneous administration with high potency and durability. In animal models, a single subcutaneous dose of ALN-HBV achieved multi-log reduction in HBsAg levels. We expect to advance ALN-HBV into the clinic in late 2015. In addition, we are advancing investigational RNAi therapeutics for other unmet needs in Hepatic Infectious Disease such as hepatitis delta virus (HDV) infection, amongst other diseases.

In addition to our focus and execution on our *Alnylam 2020* goals, we made important business progress during 2014 and in the recent period. For example, we continued to extend our leadership in RNAi therapeutics with the acquisition of Merck RNAi assets including Sirna Therapeutics. In addition, Alnylam continued to grow its intellectual property estate for RNAi therapeutics with a large number of new patent grants across our portfolio related to fundamental features of small interfering RNAs, or "siRNAs" – the molecules that mediate RNAi – and delivery approaches for siRNAs such as our GalNAc-conjugate platform. GalNAc-conjugate delivery of RNA therapeutics has now emerged as the industry-leading approach when targeting liver-expressed disease genes. We have also maintained a strong balance sheet to fund our significant pipeline development efforts. Indeed, the new capital from our 2014 Genzyme alliance and proceeds from our early 2015 follow-on equity offering have strengthened our balance sheet with well over $1 billion in cash as of February 2015. This level of capitalization enables continued execution on our *Alnylam 2020* goals. We also have opportunities for new alliances in our Cardio-Metabolic and Hepatic Infectious Disease STArs, where we plan to retain significant product rights in the U.S. and Europe.

This is certainly an exciting period for Alnylam with a rapidly expanding pipeline and many clinical data read-outs expected in 2015 and the years to come. Importantly, we are beginning to establish important "bridges" linking RNAi knockdown of disease genes with clinical outcomes. Here, our efforts remain focused first and foremost on the patient.

In closing, I'd like to thank you for your trust and confidence, as we rely on your support to fulfill the promise of RNAi therapeutics for patients, their families, and caregivers.

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*Chief Executive Officer*
Alnylam Pharmaceuticals, Inc.
March 10, 2015