Dear Stockholders,

Alnylam made enormous progress in 2013 and the recent period, bringing our medicines closer to patients and the market. Amongst many accomplishments over this period, we launched our company's first Phase 3 trial, we advanced additional programs into Phase 2 and Phase 1 studies, and we demonstrated human proof-of-concept for our GalNAc-conjugate platform, enabling subcutaneous dose administration for investigational RNAi therapeutics with a wide therapeutic index. On the business side, we formed a transformative relationship with Genzyme, a Sanofi company, where Alnylam will advance our genetic medicine programs in North America and Western Europe while Genzyme becomes our partner in the rest of world. We also acquired the assets of Merck's Sirna Therapeutics subsidiary, continuing to cement Alnylam leadership on intellectual property and technology for RNAi therapeutics. I am pleased to report that Alnylam is well positioned for continued growth of its pipeline and potential transition to a commercial stage company in the next several years.

In early 2011, we introduced our product strategy, *Alnylam 5x15™*, where we proposed to focus on development and commercialization of RNAi therapeutics toward genetically defined targets in diseases with very high unmet need. Our plan was to progress five such programs into clinical development – including programs in advanced stages – by the end of 2015. Based on our continued success, we recently *increased* our guidance to now have six to seven programs in clinical development by the end of 2015, including two programs in Phase 3 and five to six programs with human proof-of-concept results. Alnylam intends to directly commercialize these programs in North America and Western Europe, while Genzyme may develop and commercialize these programs in the rest of world. We continue to believe that *Alnylam 5x15* defines a compelling path forward to build an exciting, product-driven, commercial biopharmaceutical company, fulfilling our company's vision and mission.

Our lead effort is focused on developing RNAi therapeutics for the treatment of transthyretin (TTR)-mediated amyloidosis (ATTR), a progressive, fatal disease that afflicts approximately 50,000 patients worldwide; the disease manifests in patients as a neuropathy and/or cardiomyopathy. Having demonstrated positive Phase 1 and 2 results, we were excited to advance patisiran (formerly ALN-TTR02) into our APOLLO Phase 3 study in late 2013. APOLLO is a randomized, double-blind, placebo-controlled study of patisiran in ATTR patients with familial amyloidotic polyneuropathy (FAP). If this study is successful, we expect it to support regulatory filings in 2017 for marketing approval in the U.S. and the European Union. We are also advancing ALN-TTRsc, an investigational RNAi therapeutic targeting TTR utilizing our GalNAc-conjugate platform, which enables subcutaneous dosing with a wide therapeutic index. In 2013, we presented positive Phase 1 results for ALN-TTRsc – with up to 94% knockdown of serum TTR, the disease causing protein – supporting continued advancement of this program and also providing our first human proof-of-concept for our entire GalNAc-conjugate platform. Based on these positive results – in addition to an encouraging tolerability profile – we advanced ALN-TTRsc into a pilot Phase 2 study in ATTR patients with cardiomyopathy and intend to start a Phase 3 trial in late 2014.

We are also advancing ALN-AT3, an investigational RNAi therapeutic targeting antithrombin (AT). This product candidate represents a new approach to rebalance the blood coagulation system in patients with hemophilia and other rare bleeding disorders, including patients with "inhibitors" against their replacement factor. In 2013, we reported pre-clinical data from this program showing that subcutaneous administration of ALN-AT3 can normalize thrombin generation and improve hemostasis in models of hemophilia. In early 2014, we filed an investigational new drug (IND) application for this

program and started our Phase 1 study in human volunteers. We recently reported positive top-line results from this program showing AT knockdown at the lowest dose tested (n=4; 3:1 randomization of ALN-AT3:placebo), demonstrating a markedly improved potency for our GalNAc-conjugated siRNAs that employ our "enhanced stabilization chemistry" (ESC) platform. We are now evaluating the safety and clinical activity of ALN-AT3 in people with hemophilia, and are very excited about the potential of this program to provide effective prophylaxis for the unmet needs that afflict patients with bleeding disorders.

Importantly, we have a robust pipeline of additional genetic medicine programs that are progressing at Alnylam. These include ALN-CC5, an RNAi therapeutic targeting complement factor C5 for the treatment of complement-mediated diseases. We expect to file our IND for this program in late 2014 and are encouraged by the pre-clinical data we have reported to date, where we are seeing a highly competitive and favorably differentiated profile as compared with anti-C5 monoclonal antibodies directed toward the same disease target. We are also developing ALN-AS1, an RNAi therapeutic in development for the treatment of hepatic porphyrias. This represents a potential breakthrough therapy in an ultra-rare orphan disease where there is a very high unmet need for new therapeutic options. Here, too, we expect to file an IND in late 2014. Other key genetic medicine programs in our pipeline include ALN-AAT, an RNAi therapeutic targeting alpha-1-antitrypsin (AAT) for the treatment of AAT deficiency-associated liver disease.

As we advance our genetic medicine programs in rare, orphan diseases, we also see strong potential for our pipeline in cardio-metabolic and hepatic infectious diseases. Our ALN-PCSsc program aims to extend our initial clinical data with an RNAi therapeutic targeting PCSK9, a key protein in the regulation of the LDL receptor and LDLc (so called 'bad cholesterol') metabolism. We recently presented non-human primate study results from this program supporting the potential for once-monthly or possibly once-quarterly subcutaneous dose administration. We believe this could be a game-changer in the advancement of anti-PCSK9 therapies, and our collaboration with The Medicines Company is aimed at bringing ALN-PCSsc into the clinic by the end of 2014. We also see a strong potential for RNAi therapeutics for the treatment of hepatic infectious diseases. In this regard, we are advancing ALN-HBV, an RNAi therapeutic targeting the hepatitis B virus (HBV) genome for the treatment of HBV infection; we obtained this program through our Sirna Therapeutics acquisition. Millions of people are chronically infected with HBV, and there is no effective treatment option that results in a 'functional cure' for infection. We believe our approach could be a major advance in the treatment of this disease.

At Alnylam, we continue to lead the advancement of RNAi therapeutics to patients. In our view, our scientific and clinical progress in 2013 demonstrates the strong potential of our therapeutic approach for new medicines. We remain committed and passionate in our efforts to bring our medicines to patients. To us, this is what matters. As always, we are grateful to you, our stockholders, for your continued interest and support. We very much look forward to updating you on our progress in the coming year.

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