Alnylam® PHARMACEUTICALS

Vision: Harnessing a revolution in biology for human health®
Mission: Build a top-tier biopharmaceutical company founded on RNAi

Dear Shareholders,

For Alnylam, 2012 was a remarkable period of accomplishment as we advance our RNAi therapeutic scientific and clinical efforts. In particular, it was a year where we achieved positive clinical results from multiple programs including ALN-TTR02, an RNAi therapeutic targeting the gene transthyretin (TTR) for the treatment of TTR-mediated amyloidosis (ATTR), and ALN-PCS, an RNAi therapeutic targeting the gene PCSK9 for the treatment of hypercholesterolemia. These data points now clearly demonstrate that RNAi works in man. Indeed, based on these data, we believe RNAi can be harnessed to create a whole new class of innovative medicines. With this solid foundation, Alnylam is poised in 2013 to advance our pipeline into late-stage development and towards patients in need of new therapeutic options.

We continued to advance our product strategy, *Alnylam 5x15*, where we are focused on development and commercialization of RNAi therapeutics toward genetically defined targets in diseases with very high unmet need. Several other selection criteria are core to our strategy; these include the ability to leverage current Alnylam delivery technologies targeting genes expressed in the liver, the availability of biomarkers demonstrating early clinical activity, and the potential for a streamlined development path to patients. Our plan is to progress five such programs into clinical development — including programs in advanced stages — by the end of 2015. As part of this strategy, we also intend to directly commercialize certain programs in North and South America, Europe, and other parts of the world, while seeking partners for product commercialization in Japan and the Pacific Rim; this strategy should allow Alnylam to retain significant value in these product opportunities. We 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 RNAi therapeutics for the treatment of ATTR, a progressive, fatal disease that afflicts approximately 50,000 patients worldwide; the disease manifests in patients as a neuropathy and/or cardiomyopathy. In mid-2012, we were very pleased to present positive clinical data for ALN-TTR02, an intravenously administered RNAi therapeutic. Specifically, we showed that a single dose of ALN-TTR02 resulted in rapid, dose-dependent, durable, and specific knockdown of serum TTR — the disease-causing protein — of up to 94% in healthy volunteer subjects. With these positive results in hand, we are now enrolling ATTR patients in a Phase II study with results expected in mid-2013. If these results are positive, we expect to start our Phase III study for ALN-TTR02 in neuropathy patients by the end of this year.

Another highlight in 2012 was the progress we made on subcutaneous (SC) delivery of RNAi therapeutics with our proprietary GalNAc-conjugate platform. We view this approach as significant to our future plans with RNAi therapeutics, as SC administration could markedly broaden the range of clinical settings for our products. In late 2012, we filed a regulatory application to start our Phase I clinical trial with ALN-TTRsc in healthy volunteer subjects. We have recently initiated this study, and results are also expected in mid-2013. Assuming we achieve positive results, we intend to initiate a Phase II study of ALN-TTRsc in ATTR patients with cardiomyopathy in late 2013

and to initiate a Phase III study with this product candidate in 2014. We believe that ALN-TTR02 and ALN-TTRsc could represent best-in-class, breakthrough medicines for patients afflicted with ATTR, resulting in disease stabilization and potentially disease regression. In the fall of 2012, we formed a partnership with Genzyme Corporation, a Sanofi company, to develop and commercialize our TTR program in Japan and the Pacific Rim, while retaining full development control and commercial rights in the rest of the world.

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An additional *Alnylam 5x15* program is ALN-AT3, an RNAi therapeutic targeting antithrombin. This product candidate may represent a fundamentally new way to reset blood coagulation in patients with hemophilia and rare bleeding disorders, including patients with "inhibitors" against their replacement factor. In 2012, we reported initial data from this program showing that SC administration of ALN-AT3 can normalize thrombin generation in pre-clinical models of hemophilia. We aim to file an investigational new drug (IND) application for this program in mid-2013 and plan to start our Phase I study by year's end. We are very excited about the potential of this program to provide effective prophylaxis for the unmet needs that afflict hemophilia patients. In a similar vein, we are also pleased to advance ALN-AS1, an RNAi therapeutic for the treatment of an ultra-rare orphan disease called acute intermittent porphyria (AIP). Patients with AIP suffer acute, life-threatening, painful attacks that can often occur on a recurrent basis. ALN-AS1 could represent a breakthrough therapy for these patients, and we aim to initiate clinical studies in 2014.

Another highlight in 2012 was demonstration of positive clinical data for ALN-PCS, an RNAi therapeutic targeting PCSK9 — one of the most important disease target genes in molecular medicine today. Our clinical study, performed in the absence of concomitant statin therapy, showed rapid, dose-dependent, and durable knockdown of plasma PCSK9 by up to 84% with lowering of LDLc (so called 'bad cholesterol') of up to 50%. RNAi therapeutics have a unique mechanism of action, as compared with anti-PCSK9 monoclonal antibodies which are also in development. We believe this differentiation could be important in achieving optimal LDLc lowering in patients with hypercholesterolemia. We are advancing this program in a recently formed, global alliance, with The Medicines Company, a leading company in the advancement of innovative cardiovascular medicines.

Alnylam continues to lead the advancement of RNAi therapeutics to patients, and we view our scientific and clinical progress in 2012 as an important inflection point for the company's progress in 2013 and beyond. Without a doubt, our achievements speak to the unrelenting passion and commitment of our employees and advisors. And as always, we are grateful to you, our shareholders, for your continued interest and support.

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