Alnylam® PHARMACEUTICALS

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

Dear Shareholders,

As Alnylam looks to celebrate its 10th anniversary in 2012, we have never been better positioned to execute on our mission of building a top-tier biopharmaceutical company founded on RNAi. Indeed, the past year has been a remarkable period of accomplishment in our scientific and our clinical development efforts, with positive results in three clinical programs including: human proof of RNAi mechanism in our ALN-VSP liver cancer program; human proof of concept in our ALN-TTR transthyretin (TTR)-mediated amyloidosis (ATTR) program; and clinical efficacy in our ALN-PCS severe hypercholesterolemia program. These results confirm what we have always believed: RNAi can be harnessed in man to create a whole new class of innovative medicines.

Our path forward is clear. It is to execute on our *Alnylam 5x15* strategy, where we are focused on development and commercialization of RNAi therapeutics for genetically defined targets and diseases. Several selection criteria underlie programs encompassed by our *Alnylam 5x15* strategy; these include a high level of unmet medical need, the ability to leverage current Alnylam delivery technologies such as lipid nanoparticles (LNPs) and conjugates, the availability of early biomarkers in early clinical development, and the potential for a streamlined path to the market based on endpoints in late-stage development. In short, *Alnylam 5x15* defines a rapid path for innovative RNAi therapeutic medicines that really matter. Our plan is to progress five such programs into clinical development, including programs in advanced stages, by the end of 2015. We expect to ultimately market and commercialize some of these programs in the U.S. and other countries on our own, and in other cases, form partnerships for program advancement. We believe this strategy defines a compelling opportunity for Alnylam to build an exciting product-driven company for the future.

In the immediate period, our focus is on our ALN-TTR program where we are developing an RNAi therapeutic targeting the TTR gene for the treatment of ATTR, and our ALN-APC program where we are developing an RNAi therapeutic targeting protein C for the treatment of hemophilia. We are focusing our efforts on these programs as they define what we believe are the highest value opportunities for Alnylam in the near term. We aim to enter into alliances to advance additional programs – ALN-PCS for severe hypercholesterolemia, ALN-HPN for refractory anemia, and ALN-TMP for hemoglobinopathies such as beta-thalassemia and sickle cell anemia.

Our ALN-TTR program for ATTR, a devastating and fatal genetic disease, is our leading *Alnylam 5x15* effort. We were very pleased to report positive clinical results for ALN-TTR01 in the fall of 2011. Specifically, we showed that this RNAi therapeutic, which utilized first-generation LNP delivery, achieved statistically significant knockdown of the disease-causing protein in patients with ATTR. After just a single dose, the knockdown effect was rapid - occurring within days, and durable - lasting for weeks. ALN-TTR01 was found to be generally safe and well tolerated. With this positive human proof of concept in hand, we have initiated clinical studies with our ALN-TTR02 product candidate utilizing second-generation LNP delivery. Assuming positive results, our goal is to rapidly advance ALN-TTR02 into pivotal trials in 2013 and, ultimately, to the market. We believe that ALN-TTR02 will be a breakthrough medicine for patients afflicted with ATTR, resulting in disease stabilization and potentially disease regression.

Our RNAi therapeutic for hemophilia defines our second key *Alnylam 5x15* program. Hemophilia is a major bleeding disorder resulting from a genetic deficiency in certain clotting factors. Our approach in this program is to knockdown the endogenous

anticoagulant pathway that normally acts to stop blood coagulation; in the setting of hemophilia, we expect this will result in increased thrombin generation and improved hemostasis. Our product candidate in this program is ALN-APC, an RNAi therapeutic targeting protein C. In pre-clinical studies, we have shown that we can silence the protein C messenger RNA and knockdown protein levels in the blood. We aim to have this program in the clinic in the first half of 2013, and, assuming positive results, expect it to move rapidly in development in high unmet need segments of hemophilia disease management.

A notable accomplishment in 2011 and in the recent period was our progress in our severe hypercholesterolemia program, ALN-PCS. As our first RNAi therapeutic utilizing second-generation LNP delivery to enter human studies, this program highlights the clinical performance we expect going forward. ALN-PCS targets a disease gene called "PCSK9," a key regulator of LDL cholesterol (LDL-C, or "bad" cholesterol) metabolism and one of the most exciting targets in molecular medicine today. In a clinical study in healthy volunteers with elevated LDL-C, ALN-PCS demonstrated rapid, dose-dependent, and durable knockdown of the PCSK9 target of up to 84%, resulting in marked reductions in LDL-C of up to 50%. These statistically significant results mark the first-ever demonstration of clinical efficacy for an RNAi therapeutic, since LDL-C is a validated risk factor for coronary artery disease and myocardial infarction. ALN-PCS was shown to be safe and well tolerated in this study. We aim to advance this program into Phase II studies with a partner.

Alnylam continues to lead the advancement of RNAi therapeutics to products, and we are very proud of our critical clinical accomplishments in 2011. These achievements speak to the enormous passion, dedication, 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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