ALNYLAM PHARMACEUTICALS, INC.
Form 10-K
February 19, 2013
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UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

þ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2012

OR

¨ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the transition period from to

Commission File Number 000-50743

ALNYLAM PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**77-0602661**
(State or Other Jurisdiction of Incorporation or Organization)	*(I.R.S. Employer Identification No.)*

300 Third Street, Cambridge, MA 02142

(Address of Principal Executive Offices) (Zip Code)

Registrant s telephone number, including area code: (617) 551-8200

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock, $0.01 par value per share	**The Nasdaq Global Market**

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes þ No ¨

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ¨ No þ

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes þ No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes þ No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. þ

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ¨	Accelerated filer þ	Non-accelerated filer ¨	Smaller reporting company ¨

(Do not check if a smaller reporting company)

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ¨ No þ

The aggregate market value of the registrant s common stock, $0.01 par value per share (Common Stock), held by non-affiliates of the registrant, based on the last sale price of the Common Stock at the close of business on June 30, 2012, was $532,319,660. For purposes hereof, shares of Common Stock held by each executive officer and director of the registrant and holder of ten percent or more of the outstanding Common Stock have been excluded from the foregoing calculation because such persons and entities may be deemed to be affiliates of the registrant. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

At January 31, 2013, the registrant had 61,866,821 shares of Common Stock, $0.01 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant s definitive proxy statement for its 2013 annual meeting of stockholders, which the registrant intends to file pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant s fiscal year end of December 31, 2012, are incorporated by reference into Part II, Item 5 and Part III of this Form 10-K.

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ALNYLAM PHARMACEUTICALS, INC.

ANNUAL REPORT ON FORM 10-K

For the Year Ended December 31, 2012

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This annual report on Form 10-K contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, that involve risks and uncertainties. All statements other than statements relating to historical matters should be considered forward-looking statements. When used in this report, the words believe, expect, anticipate, may, could, intend, will, plan, target, goal and similar expressions are intended to identify forward-looking statements, although all forward-looking statements contain these words. Our actual results could differ materially from those discussed in the forward-looking statements as a result of a number of important factors, including the factors discussed in this annual report on Form 10-K, including those discussed in Item 1A of this report under the heading Risk Factors, and the risks discussed in our other filings with the Securities and Exchange Commission. Readers are cautioned not to place undue reliance on these forward-looking statements, which reflect management s analysis, judgment, belief or expectation only as of the date hereof. We explicitly disclaim any obligation to update these forward-looking statements to reflect events or circumstances that arise after the date hereof.

PART I

ITEM 1. BUSINESS

Overview

We are a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. RNAi is a naturally occurring biological pathway within cells for selectively silencing and regulating the expression of specific genes. Since many diseases are caused by the inappropriate activity of specific genes, the ability to silence genes selectively through RNAi could provide a new way to treat a wide range of human diseases. We believe that drugs that work through RNAi have the potential to become a broad new class of drugs, like small molecule, protein and antibody drugs. Using our intellectual property and the expertise we have built in RNAi, we are developing a set of biological and chemical methods and know-how that we apply in a systematic way to develop RNAi therapeutics for a variety of diseases.

Our core product strategy, which we refer to as Alnylam 5x15, is focused on the development and commercialization of novel RNAi therapeutics for the treatment of genetically defined targets for diseases with high unmet medical need. Under our core product strategy, we expect to have five RNAi therapeutic programs in clinical development, including programs in advanced stages, on our own or with one or more collaborators, by the end of 2015. As part of this strategy, our goal is to develop product candidates with the following shared characteristics: a genetically defined target and disease; the potential to have a significant impact in high unmet need patient populations; the ability to leverage our existing RNAi delivery platform; the opportunity to monitor an early biomarker in Phase I clinical trials for human proof of concept; and the existence of clinically relevant endpoints for the filing of a new drug application, or NDA, with a focused patient database and possible accelerated paths for commercialization. We are currently advancing five core programs in clinical or pre-clinical development: ALN-TTR, comprised of ALN-TTR02 and ALN-TTRsc, for the treatment of transthyretin-mediated amyloidosis, or ATTR; ALN-AT3 for the treatment of hemophilia and rare bleeding disorders, or RBD; ALN-AS1 for the treatment of acute intermittent porphyria, or AIP; ALN-PCS for the treatment of hypercholesterolemia; and ALN-TMP for the treatment of hemoglobinopathies, including beta-thalassemia. We are also advancing other early stage programs, including ALN-AAT, an RNAi therapeutic targeting the mutant Z-allele in alpha-1-antitrypsin deficiency, or AAT deficiency, for the treatment of AAT deficiency-associated liver disease. We intend to focus on developing and commercializing ALN-TTR02, ALN-TTRsc, ALN-AT3 and ALN-AS1 on our own in North and South America, Europe and other parts of the world. In February 2013, we entered into a global alliance with The Medicines Company, or MedCo, to advance our ALN-PCS program. We also intend to enter into global alliances to advance our ALN-TMP, ALN-AAT and potentially other programs.

While focusing our efforts on our core product strategy, we also intend to continue to advance additional development programs through existing or future alliances. We have two partner-based programs in clinical development, including ALN-RSV01 for the treatment of respiratory syncytial virus, or RSV, infection, and ALN-VSP for the treatment of liver cancers, as well as one candidate in pre-clinical development, ALN-HTT for the treatment of Huntington s disease, or HD.

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We also continue to work internally and with third-party collaborators with the goal of developing new technologies to deliver our RNAi therapeutics both directly to specific sites of disease, and systemically by intravenous or subcutaneous administration. We have numerous RNAi therapeutic delivery collaborations and intend to continue to collaborate with academic and corporate third parties, as well as government entities, to evaluate different delivery options.

We believe that the strength of our intellectual property portfolio relating to the development and commercialization of small interfering RNAs, or siRNAs, as therapeutics provides us a leading position with respect to this therapeutic modality. Our intellectual property portfolio includes ownership of, or exclusive rights to, issued patents and pending patent applications claiming fundamental features of siRNAs and RNAi therapeutics as well as those claiming crucial chemical modifications and promising delivery technologies. We believe that no other company possesses a portfolio of such broad and exclusive rights to the patents and patent applications required for the commercialization of RNAi therapeutics. Given the importance of our intellectual property portfolio to our business operations, we intend to vigorously enforce our rights and defend against challenges that have arisen or may arise in this area.

In addition, our expertise in RNAi therapeutics and broad intellectual property estate have allowed us to form alliances with leading pharmaceutical and life sciences companies, including Isis Pharmaceuticals, Inc., or Isis, Medtronic, Inc., or Medtronic, Novartis Pharma AG, or Novartis, Biogen Idec Inc., or Biogen Idec, F. Hoffmann-La Roche Ltd, or Roche (which assigned its rights and obligations to Arrowhead Research Corporation, or Arrowhead during 2011), Takeda Pharmaceutical Company Limited, or Takeda, Kyowa Hakko Kirin Co., Ltd., or Kyowa Hakko Kirin, Cubist Pharmaceuticals, Inc., or Cubist, Ascletis Pharmaceuticals (Hangzhou) Co., Ltd., or Ascletis, Monsanto Company, or Monsanto, Genzyme Corporation, or Genzyme, and MedCo. We have previously entered, and in the future, we may enter, into contracts with government agencies. We also have established collaborations with and, in some instances, received funding from major medical and disease associations, including CHDI Foundation, Inc., or CHDI. Finally, to further enable the field and monetize our intellectual property rights, we also grant licenses to biotechnology companies for the development and commercialization of RNAi therapeutics for specified targets in which we have no direct strategic interest under our InterfeRx program, and to research companies that commercialize RNAi reagents or services under our research product licenses.

We also seek to form or advance new ventures and opportunities in areas outside our primary focus on RNAi therapeutics. In 2007, we and Isis established Regulus Therapeutics Inc., or Regulus, a company focused on the discovery, development and commercialization of microRNA therapeutics. In October 2012, Regulus completed its initial public offering and currently, we own 17% of Regulus outstanding common stock. Through an internal effort we refer to as Alnylam Biotherapeutics, we are advancing the application of RNAi technology to improve the manufacturing processes for biologics, including recombinant proteins and monoclonal antibodies. We have formed, and may form additional, collaborations through this effort with third-party biopharmaceutical companies. In October 2011, we entered into a collaboration with GlaxoSmithKline, or GSK, for influenza vaccine production, with our VaxiRNA platform, an RNAi technology developed under our Alnylam Biotherapeutics initiative, for the enhanced production of viruses used in the manufacture of vaccine products. Given the broad applications for RNAi technology, in addition to our efforts on Alnylam Biotherapeutics and VaxiRNA, we believe new ventures and opportunities will be available to us.

Recent Developments

In December 2012, we filed an automatically effective shelf registration statement with the Securities and Exchange Commission, or SEC, for an indeterminate number of shares. In January 2013, we sold an aggregate of 9,200,000 shares of our common stock through an underwritten public offering at a price to the public of $20.13 per share. As a result of the offering, we received aggregate net proceeds of approximately $173.6 million, after deducting underwriting discounts and commissions and other estimated offering expenses of approximately $11.6 million. We intend to use these proceeds for general corporate purposes, ultimately focused on advancing our clinical pipeline, in particular our ALN-TTR02, ALN-TTRsc, ALN-AT3 and ALN-AS1 programs, as well as for potential acquisitions of new businesses, technologies or products, working capital, capital expenditures and general and administrative expenses.

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On February 4, 2013, we and MedCo entered into a license and collaboration agreement pursuant to which we granted to MedCo an exclusive, worldwide license to develop, manufacture and commercialize RNAi therapeutics targeting proprotein convertase subtilisin/kexin type 9, or PCSK9, including ALN-PCS02 and ALN-PCSsc, for the treatment of hypercholesterolemia and other human diseases. These RNAi therapeutics are referred to as licensed products under the MedCo agreement. ALN-PCS02 is an intravenously administered RNAi therapeutic, for which we have completed a Phase I clinical trial, and ALN-PCSsc is a subcutaneously administered RNAi therapeutic currently in pre-clinical development.

In consideration for the rights granted to MedCo under the MedCo agreement, MedCo paid us an upfront cash payment of $25.0 million. In addition, MedCo is required to make payments to us upon the achievement of specified clinical development, regulatory approval and commercialization milestones totaling up to $180.0 million, and to pay us scaled double-digit royalties based on annual worldwide net sales, if any, of licensed products by MedCo, its affiliates and sublicensees, subject to reduction under specified circumstances. A description of our agreement with MedCo is included below under the heading Strategic Alliances.

On February 6, 2013, Cubist notified us that it would not exercise its opt-in right for our ALN-RSV01 program for the treatment of RSV in lung transplant patients under our license and collaboration agreement. In light of this determination, we and Cubist mutually agreed to terminate our license and collaboration agreement. As a result of the termination, the parties have no further rights and obligations under the license and collaboration agreement, notwithstanding anything to the contrary in the agreement. A description of our agreement with Cubist is included below under the heading Strategic Alliances.

On February 19, 2013, we and Genzyme entered into an amendment to our license and collaboration agreement to remove a specified provision relating to the termination of clinical development by us or Genzyme under certain circumstances. A description of our agreement with Genzyme is included below under the heading Strategic Alliances.

RNA Interference

RNAi is a natural biological pathway that occurs within cells and can be harnessed to selectively silence the activity of specific genes. The discovery of RNAi first occurred in plants and worms in 1998, and two of the scientists who made this discovery, Dr. Andrew Fire and Dr. Craig Mello, received the 2006 Nobel Prize for Physiology or Medicine.

Opportunity for Therapeutics Based on RNAi

Beginning in 1999, our scientific founders described and provided evidence that the RNAi mechanism occurs in mammalian cells and that its immediate trigger is a type of molecule known as an siRNA. They showed that laboratory-synthesized siRNAs could be introduced into the cell and suppress production of specific target proteins by cleaving and degrading the messenger RNA, or mRNA, of the specific gene that encodes that specific protein. Because it is possible to design and synthesize siRNAs specific to any gene of interest, the entire human genome is accessible to RNAi, and we therefore believe that RNAi therapeutics have the potential to become a broad new class of drugs.

In May 2001, one of our scientific founders, Dr. Thomas Tuschl, published the first scientific paper demonstrating that siRNAs can be synthesized in the laboratory using chemical or biochemical methods and, when introduced or delivered into mammalian cells, can silence the activity of a specific gene. Since the Tuschl publication and issuance of the seminal Tuschl II patent, which is licensed exclusively to us for therapeutic applications, the use of siRNAs has been broadly adopted by academic and industrial researchers for the fundamental study of the function of genes. This has resulted in a significant number of publications focused on the use of RNAi and has made the Tuschl publication one of the most cited papers in basic biologic research. Reflecting this, siRNAs are a growing segment of the market for research reagents and related products and services.

Beyond its use as a basic research tool, we believe that RNAi can form the basis of a broad new class of drugs for the treatment of genetically defined targets for diseases with high unmet medical need. Drugs based on the RNAi mechanism could offer numerous opportunities and benefits, which may include:

Ability to target proteins that cannot be targeted effectively by existing drug classes. Over the last decade, the understanding of human disease has advanced enormously, and many proteins that play

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fundamental roles in human disease have been identified. Paradoxically, greater than 80% of these key proteins cannot be targeted effectively with existing drug approaches like small molecules or proteins such as monoclonal antibodies. These so called undruggable targets are potentially accessible to siRNAs as they are made by mRNAs that can be targeted with RNAi.

Ability to treat a broad range of diseases. The ability to make siRNAs that target virtually any gene to suppress the production of virtually any protein whose presence or activity causes disease suggests a broad potential for application in a wide range of diseases.

Inherently potent and natural mechanism of action. We expect the inherent catalytic nature of the RNAi mechanism to allow for a high degree of potency and durability of effect for RNAi-based therapeutics, which we believe distinguishes RNAi from other approaches. In addition, since RNAi therapeutics harness a natural mechanism for gene silencing, we believe that this approach will demonstrate improved safety and tolerability as compared with other RNA-targeting approaches.

Simplified discovery of product candidates. In contrast to the often arduous and slow drug discovery process for proteins and small molecules, the identification of siRNA product candidates has been, and we expect will continue to be, much simpler, quicker and less costly because it involves relatively standard processes that are directed by the known gene target sequences and can be applied in a similar fashion to many successive product candidates.

We have reported on our advances in developing siRNAs as potential drugs in a large number of peer-reviewed publications and meetings, including publications by Alnylam scientists in the journals *Nature, Nature Medicine, Nature Biotechnology, Cell* and *Proceedings of the National Academy of Sciences,* or *PNAS.*

Our Product Platform

Our product platform provides a capability for a systematic approach to identifying RNAi therapeutic product candidates through sequence selection, potency selection, stabilization by chemical modification, improvement of biodistribution and cellular uptake by various chemical conjugates and formulations. Key to the therapeutic application of siRNAs is the ability to successfully deliver siRNAs to target tissues and achieve cellular uptake of the siRNA into the inside of the cell where the RNAi machinery, called RNA-induced silencing complex, or RISC, is active. We have employed two predominant approaches for delivery of RNAi therapeutics: first, a formulation-based approach with lipid nanoparticles, or LNPs; and, second, a conjugate-based approach involving the modification of siRNAs with small chemical groups, such as triantennary N-acetylgalactosamine, or GalNAc, conjugates. We have demonstrated the ability to achieve delivery of siRNAs to cells in the liver with both intravenous administration using LNPs and subcutaneous administration using GalNAc conjugates. Specifically, we have demonstrated RNAi therapeutic activity with these delivery approaches in multiple species, including humans. We have also demonstrated RNAi therapeutic activity towards multiple disease genes expressed in the liver, including results from our Phase I clinical trials for ALN-TTR01, ALN-TTR02 and ALN-PCS, as well as in biopsy results from our Phase I clinical trial for ALN-VSP. In some tissues, including the respiratory tract and central nervous system, we have employed a direct RNAi delivery approach, which employs the direct or local application of siRNAs, to achieve cellular uptake and gene silencing.

We believe that we have continued to make considerable progress in developing our product platform and to make further advances relating to the delivery of RNAi therapeutics, both internally and together with our collaborators. With the progress we have made to date and expect to make in the future, we believe we are well positioned to pursue multiple therapeutic opportunities.

Our Product Pipeline

Our core product strategy is focused on the development and commercialization of novel RNAi therapeutics for the treatment of genetically defined targets for diseases with high unmet medical need. Under our core product strategy, we expect to have five RNAi therapeutic programs in clinical development, including programs in advanced stages, on our own or with one or more collaborators, by the end of 2015. As part of this strategy, our goal is to develop product candidates with the following shared characteristics: a genetically defined target

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and disease; the potential to have a significant impact in high unmet need patient populations; the ability to leverage our existing RNAi delivery platform; the opportunity to monitor an early biomarker in Phase I clinical trials for human proof of concept; and the existence of clinically relevant endpoints for the filing of an NDA, with a focused patient database and possible accelerated paths for commercialization. Our core programs currently in clinical or pre-clinical development are: ALN-TTR, including ALN-TTR02 and ALN-TTRsc, for the treatment of ATTR; ALN-AT3 for the treatment of hemophilia and RBD; ALN-AS1 for the treatment of AIP; ALN-PCS for the treatment of hypercholesterolemia; and ALN-TMP for the treatment of hemoglobinopathies, including beta-thalassemia. We intend to focus on developing and commercializing ALN-TTR02, ALN-TTRsc, ALN-AT3 and ALN-AS1 on our own in North and South America, Europe and other parts of the world. In February 2013, we entered into a global alliance with MedCo to advance our ALN-PCS program. We also intend to enter into global alliances to advance our ALN-TMP, ALN-AAT and potentially other programs.

While focusing our efforts on our core product strategy, we also intend to continue to advance additional development programs through existing or future alliances. We have two partner-based programs in clinical development, including ALN-RSV01 for the treatment of RSV and ALN-VSP for the treatment of liver cancers, as well as one candidate in pre-clinical development, ALN-HTT for the treatment of HD.

During 2012, we elected to suspend active resource allocation toward the advancement of ALN-HPN, an RNAi therapeutic targeting the hepcidin pathway for the treatment of refractory anemia, in order to focus on other higher priority pipeline programs; we may advance this program further in a potential alliance.

The following is a summary of our product development programs and our partner-based clinical development programs as of January 31, 2013:

We have spent substantial funds over the past three years to develop our product pipeline and expect to continue to do so in the future. We incurred research and development costs of $86.6 million in 2012, $99.3 million in 2011, and $106.4 million in 2010.

Core Product Development Programs

Our core product development programs are described in more detail below.

ALN-TTR TTR-Mediated Amyloidosis (ATTR)

Our most advanced core product development program, ALN-TTR, targets the transthyretin, or TTR, gene for the treatment of ATTR. ATTR is an inherited, progressively debilitating and fatal disease caused by a mutation in the TTR gene, of which over 100 mutations have been identified. TTR protein is produced primarily

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in the liver and is normally a carrier for thyroid hormone and retinol binding protein. We believe TTR is a suitable target for an RNAi therapeutic formulated to maximize delivery to liver cells, which are the primary source of TTR synthesis. Mutations in TTR result in the accumulation of toxic deposits of the wild-type and mutant protein in several body organs and tissues, including the peripheral nervous system, heart and/or gastrointestinal tract, which leads to familial amyloidotic polyneuropathy, or FAP, and/or familial amyloidotic cardiomyopathy, or FAC. FAP is associated with severe pain and loss of autonomic nervous system function, whereas FAC is associated with heart failure. ALN-TTR targets wild-type and all known mutant forms of TTR, including the V30M mutation, which is the major mutation of ATTR, particularly in FAP, and therefore is a potential therapeutic for the treatment of all forms of ATTR, including FAP and FAC. ATTR represents a major unmet medical need with significant morbidity and mortality as an orphan, or rare, disease. Based on our analysis of the available patient and market data, we estimate that FAP affects approximately 10,000 people worldwide and FAC affects at least 40,000 people worldwide. ATTR patients with FAP have a mean life expectancy of five to 15 years from symptom onset, and the only treatment options are liver transplantation and tafamidis, a small molecule stabilizer of the TTR protein for early-stage FAP patients that has been approved in the European Union, or EU. The mean survival for FAC patients is approximately 2.5 years following diagnosis, and there are no approved therapies. Although limited treatment options are available, there remains a significant need for novel therapeutics to treat patients with ATTR.

In May 2012, we reported final clinical results from our multinational ALN-TTR01 Phase I clinical trial showing that ALN-TTR01 was generally safe and well tolerated and resulted in statistically significant lowering of both wild-type and mutant TTR serum levels in ATTR patients. ALN-TTR01 employs a first-generation LNP formulation, and the ALN-TTR01 Phase I clinical trial has provided proof-of-concept data for our ALN-TTR program.

We are advancing ALN-TTR02 as our lead product candidate in our ALN-TTR program. ALN-TTR02 uses the same siRNA as ALN-TTR01, and a second generation LNP delivery technology. In July 2012, we reported clinical results from our ALN-TTR02 Phase I clinical trial, which was conducted in the United Kingdom as a randomized, single-blind, placebo-controlled, single-ascending dose study; 17 healthy volunteer subjects were enrolled. The primary objective of the clinical trial was to evaluate the safety and tolerability of a single intravenous dose of ALN-TTR02, with subjects enrolled into five sequential cohorts of increasing doses ranging from 0.01 to 0.50 mg/kg. Secondary objectives of this clinical trial included the assessment of clinical activity as measured by effects on serum TTR levels through at least day 56 following a single dose. Preliminary data from this study showed that administration of ALN-TTR02 resulted in robust knockdown of serum TTR protein levels of up to 94%; the overall results were highly statistically significant ($p<0.00001$ by ANOVA). Suppression of TTR, the disease-causing protein in ATTR, was found to be rapid, dose dependent, durable and specific after a single dose, with a nearly 80% level of TTR suppression sustained at one month after just a single dose.

ALN-TTR02 was found to be generally safe and well tolerated in this Phase I clinical trial, consistent with our broader clinical experience with LNP-formulated siRNAs. There were no serious adverse events or discontinuations in the study related to ALN-TTR02, and there were no significant adverse events associated with ALN-TTR02 up through 0.30 mg/kg. A moderate acute infusion reaction was observed in one subject receiving ALN-TTR02 at 0.50 mg/kg who was able to complete dosing with slowing of the infusion rate. There were no laboratory test abnormalities, including no changes in liver function tests, cytokines or C-reactive protein.

In June 2012, we reported the initiation of a Phase II clinical trial of ALN-TTR02. The Phase II clinical trial is designed as an open-label, multi-center, multi-dose, dose-escalation trial expected to enroll approximately 20 ATTR patients. Patients are being enrolled into cohorts of increasing doses and are receiving ALN-TTR02 once every four weeks for two cycles. The primary objectives of this clinical trial are to evaluate the safety and tolerability of multiple doses of ALN-TTR02 and to measure clinical activity based on serial measurement of circulating serum TTR levels. Assuming positive results from the Phase II clinical trial, we expect to initiate a Phase III pivotal trial of ALN-TTR02 in ATTR patients with FAP.

The Committee for Orphan Medicinal Products, or COMP, of the European Medicines Agency, or EMA, adopted a positive opinion for ALN-TTR01 designation as an orphan medicinal product for the treatment of FAP.

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In April 2011, the European Commission, or EC, officially designated ALN-TTR01 as an orphan drug. This designation also applies to ALN-TTR02. Orphan Drug Designation by the EC provides regulatory and financial incentives for companies developing orphan drugs to develop and market therapies that treat a life-threatening or chronically debilitating condition affecting no more than five in 10,000 persons in the EU. In addition to a ten-year period of marketing exclusivity in the EU after product approval, Orphan Drug Designation provides companies with protocol assistance from the EMA during the product development phase, direct access to centralized marketing authorization and reduced regulatory fees. In addition, in June 2012, we reported that the U.S. Food and Drug Administration, or FDA, provided Orphan Drug Designation to ALN-TTR02 as a therapeutic for the treatment of FAP. The FDA s Orphan Drug Designation program provides orphan status to drugs and biologics which are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the United States.

In addition to ALN-TTR02, we are also advancing ALN-TTRsc, which utilizes our GalNAc conjugate delivery technology enabling subcutaneous dose administration. In February 2013, we received acceptance from the U.K. Medicines and Healthcare products Regulatory Agency, or MHRA, to initiate a Phase I clinical trial of ALN-TTRsc. The Phase I clinical trial is designed as a randomized, double-blind, placebo-controlled, single- and multi-dose, dose escalation study, enrolling up to 40 healthy volunteer subjects. The primary objective of the study is to evaluate the safety and tolerability of ALN-TTRsc. In addition, the study will evaluate the clinical activity of ALN-TTRsc as measured by effects on serum TTR levels. Assuming positive results from the Phase I clinical trial, our goal is to initiate an exploratory Phase II clinical trial of ALN-TTRsc in ATTR patients with FAC, ultimately leading to a Phase III clinical trial in FAC patients. Pre-clinical studies have shown that once-weekly subcutaneous dosing with ALN-TTRsc enables robust and sustained silencing of TTR over a multi-week period.

As with ALN-TTR02, we intend to directly commercialize ALN-TTRsc in North and South America, Europe and other parts of the world. In October 2012, we announced that we and Genzyme entered into a license and collaboration agreement pursuant to which we granted to Genzyme an exclusive license in Japan and the Asia-Pacific region, known as the Genzyme territory, to develop and commercialize RNAi therapeutics targeting TTR, including ALN-TTR02 and ALN-TTRsc, for the treatment of ATTR and other human diseases. We retain all development and commercialization rights worldwide outside of the Genzyme territory. The Genzyme agreement is described below under the heading Strategic Alliances.

Our preliminary Phase I clinical trial data and pre-clinical findings demonstrate the potential benefit of an RNAi therapeutic targeting TTR for the treatment of ATTR. Moreover, siRNA treatment may provide benefits to ATTR patients not observed with liver transplantation or administration of tafamidis based on the ability to simultaneously reduce the expression of both mutant and wild-type TTR, both of which have a role in disease progression. ATTR is also one example of a number of orphan indications where there is a significant unmet need and the potential for early biomarker data in clinical trials, enabling rapid proof-of-concept and a clear opportunity for a large therapeutic impact in patients.

ALN-AT3 Hemophilia and Rare Bleeding Disorders (RBD)

ALN-AT3 is an RNAi therapeutic targeting antithrombin, or AT, a genetically defined target, for the treatment of hemophilia and RBD. Hemophilia is a hereditary disorder caused by deficiencies of certain blood clotting factors, resulting in recurrent bleeds into joints, muscles and other major internal organs. Hemophilia A is defined by loss-of-function mutations in factor VIII, and there are more than 40,000 registered hemophilia A patients in the United States and Europe. Hemophilia B, defined by loss-of-function mutations in factor IX, affects more than 9,500 registered patients in the United States and Europe. Standard treatment for hemophilia patients involves replacement of the missing clotting factor either as prophylaxis or on-demand therapy. However, a significant number of hemophilia A patients will develop an antibody to their replacement factor a very serious complication as these inhibitor patients become refractory to standard replacement therapy. Based on our analysis of the available patient and market data, we estimate that there are approximately 2,000 inhibitor patients in major markets and approximately 5,000 inhibitor patients worldwide. RBD are defined by congenital deficiencies of other blood coagulation factors including factors II, V, VII, X, and XI. Based on our analysis of

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the available patient and market data, we estimate that there are approximately 1,000 RBD patients worldwide with severe bleeding complications who are in need of routine prophylaxis. There exists a significant need for novel therapeutics to treat severe hemophilia patients and patients with RBD.

ALN-AT3 is a novel therapeutic approach aimed at re-balancing the coagulation cascade and normalizing hemostasis in severe hemophilia A and B patients, including patients with inhibitors against their replacement factor. ALN-AT3 also has potential as a treatment for RBD patients and patients with other bleeding disorders. In December 2012, we presented pre-clinical data showing that subcutaneous administration of ALN-AT3 in non-human primates, or NHPs, resulted in potent, dose-dependent and durable knockdown in serum AT, resulting in significant increases in thrombin generation. Specifically, a single subcutaneous dose of ALN-AT3 led to potent knockdown of serum AT, with an ED50 of approximately one mg/kg. AT suppression was durable, with effects lasting greater than six weeks after a single dose. In addition, weekly subcutaneous doses of ALN-AT3 in NHPs led to sustained AT knockdown of approximately 80% and greater than 90% at 0.5 mg/kg and 1.5 mg/kg, respectively. These data enable an estimation of an ED50 dose for weekly subcutaneous administration at 0.15-0.3 mg/kg at a volume of injection for human administration expected to be less than 0.5 mL/injection. Moreover, increased thrombin generation was closely correlated with AT reduction, with an up to four-fold increase in peak thrombin at 90% AT reduction. ALN-AT3 utilizes our GalNAc-siRNA conjugate delivery technology, enabling subcutaneous dose administration with potential for a once-weekly or twice-monthly dosing regimen. We plan to file an investigational new drug application, or IND, for ALN-AT3 and to initiate a Phase I clinical trial during 2013. We intend to directly commercialize ALN-AT3 in North and South America, Europe and other parts of the world, and we intend to seek a partner for this program in Japan and other Asian territories.

ALN-AS1 Acute Intermittent Porphyria (AIP)

ALN-AS1 is an RNAi therapeutic targeting aminolevulinate synthase 1, or ALAS-1, for the treatment of AIP. AIP is an ultra-rare autosomal dominant disease caused by loss of function mutations in porphobilinogen deaminase, or PBGD, an enzyme in the heme biosynthesis pathway. Exposure of AIP patients to certain drugs, dieting or hormonal changes can trigger strong induction of ALAS-1, another enzyme in the heme biosynthesis pathway, which can lead to accumulation of toxic intermediates upstream of PBGD that precipitate attack symptoms. Patients with AIP can suffer acute and/or recurrent life-threatening attacks with severe abdominal pain, peripheral and autonomic neuropathy, and neuropsychiatric manifestations, and possible death if left untreated. Based on our analysis of the available patient and market data, we estimate that approximately 5,000 patients in the United States and Europe suffer acute porphyria attacks annually, and we believe approximately 500 of those patients are afflicted with recurrent debilitating attacks. Treatment options for AIP patients suffering from an acute attack are limited; some patients are given intravenous heme analogues that must be administered through a central venous catheter, but these have a slow onset and can result in severe thrombophlebitis, iron overload and resistance to treatment over time. Currently, there is no approved prophylactic treatment available to prevent recurrent attacks, which often occur monthly in women associated with menses. There exists a significant need for therapies for AIP patients.

ALN-AS1 is a GalNAc conjugate siRNA targeting ALAS-1 administered subcutaneously. Inhibition of ALAS-1 is known to reduce the accumulation of heme precursors that cause the clinical manifestations of AIP. ALN-AS1 has the potential to be a therapy for the treatment of acute porphyria attacks, as well as a prophylactic approach for the prevention of recurrent attacks. We expect to select a final development candidate during 2013, with the goal of advancing ALN-AS1 into the clinic. We intend to directly commercialize ALN-AS1 in North and South America, Europe and other parts of the world, and we intend to seek a partner for this program in Japan and other Asian territories.

ALN-PCS Hypercholesterolemia

ALN-PCS is a systemically delivered RNAi therapeutic targeting PCSK9 for the treatment of hypercholesterolemia. PCSK9 is a protein involved in the regulation of low-density lipoprotein, or LDL, receptor levels on hepatocytes and the metabolism of LDL cholesterol, or LDL-c, which is commonly referred to as bad

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cholesterol. PCSK9 is produced by the liver and circulates in the bloodstream. Both intracellular and extracellular PCSK9 reduce the liver s capacity to absorb LDL-c by decreasing LDL receptor levels. Published studies indicate that, if PCSK9 activity could be reduced, the liver s uptake of LDL-c should increase and blood cholesterol levels should decrease. In fact, published case reports have shown individuals with loss-of-function genetic mutations in PCSK9 have decreased blood cholesterol levels. In turn, these individuals have been shown to have a dramatically reduced risk of coronary artery disease, or CAD, including myocardial infarction or heart attack. In addition, studies have shown that PCSK9 levels are increased by statin therapy, limiting their effect, suggesting that the introduction of a PCSK9 inhibitor to statin therapy may result in even further reductions in LDL-c levels. Some forms of hypercholesterolemia can be treated through dietary restrictions, lifestyle modifications (e.g., exercise and smoking cessation) and medicines such as statins. However, a large proportion of patients with hypercholesterolemia, including genetic familial hypercholesterolemia patients, acute coronary syndrome patients, high-risk patient populations (e.g., patients with CAD, diabetics, symptomatic carotid artery disease) and other patients that are statin intolerant, are not achieving target LDL-c goals with statin therapy. Severe forms of hypercholesterolemia are estimated to affect more than 500,000 patients worldwide, and as a result, there is a significant need for novel therapeutics to treat patients with hypercholesterolemia whose disease is inadequately managed by existing therapies.

In April 2012, we reported clinical data from our Phase I clinical trial of ALN-PCS02. ALN-PCS02 employs the same LNP formulation used for ALN-TTR02. The Phase I clinical trial was conducted in the United Kingdom as a randomized, single-blind, placebo-controlled, single-ascending dose study in healthy volunteer subjects with elevated baseline LDL-c (greater than 116mg/dL). The primary objective of the clinical trial was to evaluate the safety and tolerability of a single dose of ALN-PCS02. Secondary objectives included assessment of pharmacodynamic effects of the drug on plasma PCSK9 protein levels and evaluation of clinical efficacy as measured by LDL-c levels. The clinical trial was performed in the absence of statins or other lipid lowering therapy. A total of 32 subjects were enrolled into six sequential dose cohorts ranging from 0.015 to 0.400 mg/kg in a three-to-one randomization of drug to placebo.

In this clinical trial, as reported in April 2012, administration of ALN-PCS02 resulted in rapid, dose-dependent and durable reductions in LDL-c of up to 50% relative to baseline and placebo, with a statistically significant mean reduction of 41% ($p<0.01$) at the 0.400 mg/kg dose level. In addition, ALN-PCS administration resulted in rapid, dose-dependent and durable knockdown of PCSK9 protein levels in plasma with a maximal 84% reduction relative to baseline and placebo, with a statistically significant mean reduction of 68% in the highest dose group of 0.400 mg/kg ($p<0.0001$). There was also a dose-dependent increase in the proportion of subjects who achieved target levels of LDL-c of less than 100 mg/dL ($p<0.05$). We believe the effects of a single dose of ALN-PCS02 support a once-monthly dose administration regimen for future studies.

ALN-PCS02 was found to be safe and well tolerated in this study and there were no serious adverse events related to study drug administration. There were no drug-related discontinuations and no liver enzyme elevations. A mild, transient rash, observed in 16 subjects, including four who received placebo, is believed to be related to steroid pre-medication provided to subjects receiving both ALN-PCS, as well as those receiving placebo. There were no significant changes compared to baseline in levels of high-density lipoprotein, or HDL, also referred to as good cholesterol, consistent with the phenotype observed in human PCSK9 loss-of-function mutations.

We are also developing ALN-PCSsc, a subcutaneously administered RNAi therapeutic currently in pre-clinical development. We have presented pre-clinical data from our ALN-PCSsc program demonstrating potent knockdown of the PCSK9 target gene with an ED_{50} of less than 0.3 mg/kg after a single subcutaneous dose.

In February 2013, we and MedCo entered into a license and collaboration agreement pursuant to which we granted to MedCo an exclusive, worldwide license to develop, manufacture and commercialize RNAi therapeutics targeting PCSK9, including ALN-PCS02 and ALN-PCSsc, for the treatment of hypercholesterolemia and other human diseases. A description of our agreement with MedCo is included below under the heading Strategic Alliances.

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ALN-TMP Hemoglobinopathies

ALN-TMP is a systemically delivered RNAi therapeutic targeting transmembrane protease, serine 6, or Tmprss6, for the treatment of hemoglobinopathies, including beta-thalassemia. Hemoglobinopathies are genetic disorders defined by mutations in the globin genes that assemble to form hemoglobin, and are associated with chronic anemia, extra-medullary hematopoiesis and iron overload. Tmprss6, a genetically validated target expressed on hepatocytes, functions by cleaving hemojuvelin, resulting in reduced hepcidin levels and increased iron mobilization. By silencing Tmprss6 with RNAi, hepcidin levels would be expected to increase and iron absorption and mobilization would be decreased.

Pre-clinical animal model studies with ALN-TMP have demonstrated corrective effects on iron overload in addition to broader disease modifying effects including improvements in hemoglobin levels, spleen histopathology and globin gene expression. In December 2012, we presented pre-clinical data showing that systemic administration of ALN-TMP resulted in disease modifying effects in a model of beta-thalassemia. In addition, ALN-TMP demonstrated pre-clinical efficacy in a model of hereditary hemochromatosis. In the pre-clinical studies, ALN-TMP administration resulted in a greater than 80% silencing of Tmprss6 mRNA levels and a greater than two-fold elevation of Hamp1, the gene that encodes for hepcidin, a liver hormone that negatively regulates iron transport and absorption. Pre-clinical ALN-TMP administration resulted in an approximately 30% decrease in serum iron and non-heme liver iron, as well as a similar reduction in transferrin saturation. In a mouse model of beta-thalassemia, ALN-TMP reduced the severity of anemia as evidenced by an approximately one g/dL increase in total hemoglobin. Moreover, pre-clinical treatment with ALN-TMP was found to significantly attenuate extra-medullary hematopoiesis, including a two-to-three fold reduction in spleen size. Pre-clinical treatment with ALN-TMP also decreased ineffective erythropoiesis, with a three-to-four fold decrease in reticulocyte count, an approximate 30% increase in red blood cell count, or RBC, and a normalization of RBC morphology and lifespan. Finally, pre-clinical ALN-TMP administration was found to restore the ratio of alpha globin to beta globin, thereby correcting the genetic defect associated with ß-thalassemia with possible implications for the treatment of other hemoglobinopathies. We plan to partner our ALN-TMP program prior to initiating a Phase I clinical trial.

Partner-Based Product Development Programs

While focusing our core efforts on advancing our product development programs as described above, we also intend to continue to advance additional product development programs through existing or future alliances, including the clinical and pre-clinical programs described below.

ALN-RSV Respiratory Syncytial Virus (RSV) Infection

ALN-RSV is an RNAi therapeutic for the treatment of RSV infection. RSV is a highly contagious virus that causes infections in both the upper and lower respiratory tract. RSV infects nearly every child by the age of two years and is responsible for a significant percentage of hospitalizations of infants, children with lung or congenital heart disease, the elderly and adults with immune- compromised systems, including lung transplant recipients. A study published in 2005 in the *New England Journal of Medicine* estimates that over 170,000 elderly adults are hospitalized with RSV each year. In addition, experts estimate that the overall prevalence of lung transplants in the United States is between 8,000 to 10,000, and the annual incidence of RSV infection in lung transplant recipients can be up to ten percent.

In February 2008, we reported positive results from the GEMINI study, a double-blind, placebo-controlled, randomized Phase II clinical trial designed to evaluate the safety, tolerability and anti-viral activity of ALN-RSV01 in 88 adult subjects experimentally infected with RSV. In this clinical trial, ALN-RSV01 was found to be safe and well tolerated and demonstrated statistically significant reduction (40%) in viral infection rate ($p<0.01$) and a 95% increase in infection-free patients ($p<0.01$), as compared to placebo. In July 2009, we reported results from a Phase IIa clinical trial assessing the safety and tolerability of aerosolized ALN-RSV01 versus placebo in a randomized, double-blind trial of 24 adult lung transplant patients naturally infected with RSV. This clinical trial achieved its primary objective of demonstrating the safety and tolerability of ALN-RSV01. In particular, there were no drug-related serious adverse events or discontinuations. Prospectively defined clinical secondary

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endpoints at 90 days included recovery of lung function as measured by spirometry and clinical determination of new or progressive bronchiolitis obliterans syndrome, or BOS, an irreversible loss of function in the transplanted lung associated with approximately 50% mortality within five years. Based on the data from this small trial, ALN-RSV01 treatment was associated with a statistically significant decrease in the total incidence of new or progressive BOS at 90 days compared to placebo (p=0.02), with 50% of the placebo patients showing new or progressive BOS as compared with only 7.1% of the ALN-RSV01-treated patients.

In September 2012, we reported complete results from an international multi-center, randomized, double-blind, placebo-controlled Phase IIb clinical trial with ALN-RSV01 for the treatment of RSV infection in lung transplant patients. RSV infection in lung transplant patients represents a significant unmet medical need due to the risk of developing new or progressive BOS. The objective of this Phase IIb clinical trial was to repeat and extend the clinical results observed in the Phase IIa clinical trial described above. The primary endpoint of the clinical trial was designed as a reduction in the incidence of new or progressive BOS at 180 days after RSV infection. The clinical trial enrolled 87 patients who were randomized in a one-to-one, drug-to-placebo ratio. Based on local study site diagnosis of RSV infection, a total of 45 patients were randomized to receive ALN-RSV01 and 42 patients were randomized to receive placebo, defining the overall intent-to-treat study cohort, or ITT. Following central laboratory testing by PCR analysis, 10 patients could not be confirmed as infected for RSV; these patients happened to include nine patients randomized to receive placebo and one patient randomized to receive ALN-RSV01. Accordingly, a total of 77 patients (placebo, n=33; ALN-RSV01, n=44) comprised the intent-to-treat, or ITTc, analysis population. Baseline characteristics were generally well balanced between treatment groups. The study did not achieve the primary endpoint of reduced BOS in an ITTc analysis of confirmed RSV infected patients (p=0.058), but achieved statistically significant reductions in prospectively defined analyses of ITTc patients with their last observation carried forward, with a p-value of 0.028, and of ITTc patients treated per protocol, with a p-value of 0.025. In all analyses, ALN-RSV01 treatment was associated with a clinically meaningful treatment effect, with a reduction of over 50% in the incidence of day 180 BOS as compared with placebo. These results replicated the findings from our Phase IIa clinical trial of ALN-RSV01 in the same clinical setting.

ALN-RSV01 was found to be generally safe and well tolerated in the Phase IIb clinical trial, with a comparable incidence of reported adverse events in placebo and study drug treatment arms. There were three deaths in the study, two in placebo and one in ALN-RSV01, all of which were determined to be unrelated to treatment.

We have a collaboration with Kyowa Hakko Kirin for the development and commercialization of RNAi products for the treatment of RSV in Asia. We also had an agreement with Cubist, pursuant to which Cubist had the right to opt into collaborating with us on ALN-RSV01, subject to certain conditions. In February 2013, Cubist notified us that it would not exercise its opt-in right for ALN-RSV01. In light of this determination, we and Cubist mutually agreed to terminate our agreement.

During 2012, we met with the FDA and European regulatory authorities regarding the results of the ALN-RSV01 Phase IIb clinical trial and obtained preliminary guidance on the design of a potential Phase III clinical trial. We intend to seek another partner to advance the ALN-RSV01 program into a Phase III clinical trial and intend to finalize plans with the regulatory authorities and a new partner, if and when identified.

ALN-VSP Liver Cancer

ALN-VSP is a systemically delivered RNAi therapeutic for the treatment of advanced solid tumors with liver involvement. Cancer affecting the liver, known as either primary or secondary liver cancer, is associated with one of the poorest survival rates in oncology and represents a major unmet medical need affecting a large number of patients worldwide. Primary liver cancer, also known as hepatocellular carcinoma, is one of the most common cancers worldwide. Secondary liver cancer, also known as metastatic liver cancer, is cancer that spreads to the liver from another part of the body like the colon, stomach, pancreas, breast, lung or skin. Worldwide, more than 500,000 people are diagnosed with primary or secondary liver cancer each year. ALN-VSP contains two siRNAs formulated using a first-generation LNP formulation. ALN-VSP is designed to target two genes

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critical in the growth and development of cancer, kinesin spindle protein, or KSP and vascular endothelial growth factor, or VEGF. KSP is a key component of the cellular machinery that mediates chromosome separation during cell division, which is critical for tumor proliferation. VEGF is a potent angiogenic factor that drives the development of blood vessels that are critical to ensuring adequate blood supply to the growing tumor.

In August 2011, we announced the completion of a Phase I clinical trial for ALN-VSP, which was our first systemically delivered RNAi therapeutic to enter clinical development. This Phase I clinical trial was a multi-center, open label, dose escalation study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous ALN-VSP in patients with advanced solid tumors with liver involvement. We completed enrollment in this clinical trial during the first quarter of 2011 and reported study results in June 2011. ALN-VSP was administered to 41 patients at doses ranging from 0.1 to 1.5 mg/kg and was generally well tolerated. Results from pharmacodynamic measurements provide evidence for anti-VEGF and anti-KSP pharmacology, and tumor biopsy data demonstrated both pharmacologically relevant tissue levels of ALN-VSP and human proof-of-concept for an RNAi mechanism of action.

In June 2012, we announced results from the extension study of our Phase I clinical trial of ALN-VSP. The extension study included patients enrolled in the ALN-VSP Phase I clinical trial who achieved stable disease or better after four months of treatment; patients were eligible to continue on the extension study until disease progression. The main objectives included continued evaluation of safety and tolerability and assessment of disease response. Seven of 37 patients, or 18.9%, evaluable for response went onto the extension study. At the time of enrollment, six patients had stable disease and one had an unconfirmed partial response. For these patients treated on both the Phase I clinical trial and extension study, the average length of time on treatment was 11.3 months, with a range of five to 27 months. The results from the extension study demonstrated disease control lasting more than six months in the majority of patients treated on the extension study, including one complete response in an endometrial cancer patient who had multiple liver metastases. In this study, chronic dosing of up to 27 months with ALN-VSP was found to be generally safe and well tolerated.

In July 2012, we formed a collaboration with Ascletis, a privately held U.S.-China joint venture pharmaceutical company, for the development of ALN-VSP. Under the collaboration agreement, we granted Ascletis exclusive rights to develop and commercialize ALN-VSP in China, including Hong Kong and Macau, and Taiwan. Ascletis initial focus will be on advancing ALN-VSP into a Phase II clinical trial for the treatment of hepatocellular carcinoma. Under the collaboration agreement, Ascletis is required to pay us development and commercial milestone payments and royalties on net sales in the Ascletis territory, if any. We retain all rights to develop and commercialize ALN-VSP in the rest of the world. We may use the data generated in China by Ascletis under this strategic collaboration for development of ALN-VSP in the rest of the world and Ascletis may potentially receive sublicense payments based on any such future collaborations we may enter into to develop and/or commercialize ALN-VSP. We plan to partner our ALN-VSP program prior to initiating a Phase II clinical trial outside of the Ascletis territory.

Other Partner-Based Programs

In addition to ALN-RSV and ALN-PCS, we are also supporting the development of ALN-HTT, a novel drug-device product incorporating an RNAi therapeutic candidate targeting the huntingtin gene, delivered using an implantable infusion device, for the treatment of HD, in collaboration with Medtronic and CHDI. ALN-HTT is currently in pre-clinical development.

Our ALN-HTT-related agreements with Medtronic and CHDI are described below under Strategic Alliances.

Discovery Programs

In addition to our core development efforts on ATTR, hemophilia and RBD, AIP, hypercholesterolemia and hemoglobinopathies, including beta-thalassemia, and our additional partner-based programs in RSV, liver cancer and HD, we are conducting additional research activities to discover novel RNAi therapeutic product candidates

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that we can partner with third parties with a focus on genetically defined targets and diseases. These include ALN-AAT, an RNAi therapeutic targeting AAT deficiency for the treatment of AAT deficiency-associated liver disease, amongst others programs.

Our Collaboration and Licensing Strategy

Our business strategy is to develop and commercialize a pipeline of RNAi therapeutic products directed toward genetically defined targets for diseases with high unmet medical need. As part of this strategy, we have entered into, and expect to enter into additional, collaboration and licensing agreements as a means of obtaining resources, capabilities and funding to advance our RNAi therapeutic programs.

Our collaboration strategy is to form worldwide or specific geographic collaborations relating to RNAi therapeutic programs in our pipeline. Specifically, we intend to focus on developing and commercializing ALN-TTR02, ALN-TTRsc, ALN-AT3 and ALN-AS1 on our own in North and South America, Europe and other parts of the world, and have sought, or may seek, alliances for development and commercialization of these product candidates in Japan and other Asian territories. We intend to enter into global alliances to advance our ALN-TMP, ALN-AAT and potentially other programs. For example, during 2012, we established product alliances with Genzyme for the development and commercialization of ALN-TTR in Japan and the Asia-Pacific region, and Ascletis for the development and commercialization of ALN-VSP in China and certain other territories. In addition, in early 2013, we established a worldwide alliance with MedCo for the development and commercialization of ALN-PCS. We may also enter into RNAi platform and/or multi-target discovery alliances. For example, we have entered into a broad, non-exclusive platform license agreement with Takeda, under which we are also collaborating with Takeda on RNAi drug discovery for one or more disease targets. In addition, we have formed a platform alliance with Monsanto in the field of agriculture.

We also seek to form or advance new ventures and opportunities in areas outside our primary focus on RNAi therapeutics. In 2007, we and Isis formed Regulus to capitalize on our technology and intellectual property in the field of microRNA therapeutics. In October 2012, Regulus completed its initial public offering and currently, we own 17% of Regulus outstanding common stock. Through an internal effort we refer to as Alnylam Biotherapeutics, we are advancing the application of RNAi technology to improve the manufacturing processes for biologics, including recombinant proteins and monoclonal antibodies. We have formed, and may form additional, collaborations through this effort with third-party biopharmaceutical companies. During 2011, we also announced our progress on VaxiRNA, an RNAi technology developed under our Alnylam Biotherapeutics initiative, for the enhanced production of viruses used in the manufacture of vaccine products, and entered into a collaboration with GSK for influenza vaccine production. Given the broad applications for RNAi technology, in addition to our efforts on Alnylam Biotherapeutics and VaxiRNA, we believe new ventures and opportunities will be available to us.

To generate revenues from our intellectual property rights, we also grant licenses to biotechnology companies under our InterfeRx program for the development and commercialization of RNAi therapeutics for specified targets in which we have no direct strategic interest. We also license key aspects of our intellectual property to companies active in the research products and services market, which includes the manufacture and sale of reagents. We expect our InterfeRx and research product licenses to generate modest near-term revenues that we can re-invest in the development of our proprietary RNAi therapeutics pipeline. As of January 31, 2013, we had granted such licenses, on both an exclusive and non-exclusive basis, to approximately 20 companies.

Since delivery of RNAi therapeutics remains a major objective of our research activities, we also look to form collaboration and licensing arrangements with other companies and academic institutions to gain access to delivery technologies. For example, we have entered into agreements with Arrowhead, Tekmira Pharmaceuticals Corporation, or TPC, Protiva Biotherapeutics, Inc., a wholly owned subsidiary of TPC, and together with TPC, referred to as Tekmira, the Massachusetts Institute of Technology, or MIT, The University of British Columbia, or UBC, and AlCana Technologies, Inc., or AlCana, among others, related to various delivery technologies. We have also entered into license agreements with Isis, Max Planck Innovation GmbH (formerly known as Garching Innovation GmbH), or Max Planck Innovation, Tekmira, MIT, Cancer Research Technology Limited, or CRT, Whitehead Institute for Biomedical Research, or Whitehead, The University of Texas Southwestern Medical

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Center, or UTSW, as well as a number of other entities, to obtain rights to intellectual property in the field of RNAi. Finally, we have sought, and may seek in the future, funding for the development of our proprietary RNAi therapeutics pipeline from the government and foundations.

Strategic Alliances

We have formed, and intend to continue to form, strategic alliances to gain access to the financial, technical, clinical and commercial resources necessary to develop and market RNAi therapeutics. We expect these alliances to provide us with financial support in the form of upfront cash payments, license fees, equity investments, research and development funding, milestone payments and/or royalties or profit sharing based on sales of RNAi therapeutics.

Platform Alliances.

Roche/Arrowhead. In July 2007, we and, for limited purposes, Alnylam Europe AG, or Alnylam Europe, entered into a license and collaboration agreement with Roche. Under the license and collaboration agreement, which became effective in August 2007, we granted Roche a non-exclusive license to our intellectual property, including delivery-related intellectual property existing as of the date of the license and collaboration agreement, to develop and commercialize therapeutic products that function through RNAi, subject to our existing contractual obligations to third parties. In November 2010, Roche announced the discontinuation of certain activities in research and early development, including its RNAi research efforts. In October 2011, Arrowhead announced its acquisition of RNA therapeutics assets from Roche, including the license and collaboration agreement. As a result of the assignment, Arrowhead owns all of the rights and obligations of Roche under the license and collaboration agreement. The license is initially limited to four therapeutic areas, and may be expanded to include additional therapeutic areas upon payment to us by Arrowhead of an additional $50.0 million for each additional therapeutic area, if any.

In consideration for the rights we granted under the license and collaboration agreement, Roche paid us $273.5 million in upfront cash payments. In addition, in exchange for our contributions under the collaboration agreement, for each RNAi therapeutic product developed by Arrowhead, its affiliates or sublicensees under the collaboration agreement, we are entitled to receive milestone payments upon achievement of specified development, regulatory and commercialization events, totaling up to an aggregate of $100.0 million per therapeutic target, together with a single-digit percentage royalty payment based on worldwide annual net sales, if any. The potential future milestone payments for each therapeutic target include up to $17.5 million for the achievement of specified development milestones, up to $62.5 million for the achievement of specified regulatory milestones and up to $20.0 million for the achievement of specified commercialization milestones. We could potentially earn the next development milestone payment of $1.0 million under the license and collaboration agreement based upon the initiation of the first Phase I clinical trial by Arrowhead for an RNAi therapeutic product. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any milestone or royalty payments from Arrowhead.

The term of the license and collaboration agreement generally ends upon the later of ten years from the first commercial sale of a licensed product and the expiration of the last-to-expire patent covering a licensed product. We estimate that our fundamental RNAi patents covered under the license and collaboration agreement will expire both in and outside the United States generally between 2016 and 2025, subject to any potential patent term extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available. Arrowhead may terminate the license and collaboration agreement, on a licensed product-by-licensed product, licensed patent-by-licensed patent, and country-by-country basis, upon 180-days prior written notice to us, but is required to continue to make milestone and royalty payments to us if any royalties were payable on net sales of a terminated licensed product during the previous 12 months. The license and collaboration agreement may also be terminated by either party in the event the other party fails to cure a material breach under the license and collaboration agreement.

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Takeda. In May 2008, we entered into a license and collaboration agreement with Takeda to pursue the development and commercialization of RNAi therapeutics. Under the Takeda agreement, we granted to Takeda a non-exclusive, worldwide, royalty-bearing license to our intellectual property, including delivery-related intellectual property, controlled by us as of the date of the Takeda agreement or during the five years thereafter, to develop, manufacture, use and commercialize RNAi therapeutics, subject to our existing contractual obligations to third parties. The license initially is limited to the fields of oncology and metabolic disease and may be expanded at Takeda s option to include other therapeutic areas, subject to specified conditions. Under the Takeda agreement, Takeda will be our exclusive platform partner in the Asian territory, as defined in the agreement, through May 2013.

In consideration for the rights granted to Takeda under the Takeda agreement, Takeda agreed to pay us $150.0 million in upfront and near-term technology transfer payments. In addition, we have the option, exercisable until the start of Phase III development, to opt-in under a 50-50 profit sharing agreement to the development and commercialization in the United States of up to four Takeda licensed products, and would be entitled to opt-in rights for two additional products for each additional field expansion, if any, elected by Takeda under the Takeda agreement. In June 2008, Takeda paid us an upfront payment of $100.0 million and agreed to pay us an additional $50.0 million upon achievement of specified technology transfer milestones. We have received payment of the entire $50.0 million of technology transfer milestones. If Takeda elects to expand its license to additional therapeutic areas, Takeda will be required to pay us $50.0 million for each additional field selected, if any. In addition, for each RNAi therapeutic product developed by Takeda, its affiliates and sublicensees, we are entitled to receive specified development, regulatory and commercialization milestone payments, totaling up to $171.0 million per product, together with a double-digit percentage royalty payment based on worldwide annual net sales, if any. The potential future milestone payments per product include up to $26.0 million for the achievement of specified development milestones, up to $40.0 million for the achievement of specified regulatory milestones and up to $105.0 million for the achievement of specified commercialization milestones. We could potentially earn the next milestone payment of $2.0 million under the Takeda agreement based upon the achievement of a specified pre-clinical event by Takeda for an RNAi therapeutic product. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any additional milestone payments or any royalty payments from Takeda.

Takeda also has the option, subject to certain conditions, to collaborate with us on the research and development of RNAi drug delivery technology for targets agreed to by the parties. In addition, through May 2013, Takeda has a right of first negotiation for the development and commercialization of our RNAi therapeutic products in the Asian territory, excluding our ALN-RSV, ALN-TTR and ALN-PCS programs. In addition to the 50-50 profit sharing option, we have a similar right of first negotiation to participate with Takeda in the development and commercialization of licensed products in the United States. The collaboration is governed by a joint technology transfer committee, a joint research collaboration committee and a joint delivery collaboration committee, each of which is comprised of an equal number of representatives from each party.

The term of the Takeda agreement generally ends upon the later of (i) the expiration of our last-to-expire patent covering a licensed product and (ii) the last-to-expire term of a profit sharing agreement in the event we elect to enter into such an agreement. We estimate that our fundamental RNAi patents covered under the Takeda agreement will expire both in and outside the United States generally between 2016 and 2025, subject to any potential patent term extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available. The Takeda agreement may be terminated by either party in the event the other party fails to cure a material breach under the agreement. In addition, Takeda may terminate the agreement on a licensed product-by-licensed product or country-by-country basis upon 180-days prior written notice to us, provided, however, that Takeda is required to continue to make royalty payments to us for the duration of the royalty term with respect to a licensed product.

Monsanto. In August 2012, we and Monsanto entered into a license and collaboration agreement, pursuant to which we granted to Monsanto a worldwide, exclusive, royalty bearing right and license, including the right to grant sublicenses, to our RNAi platform technology and intellectual property controlled by us as of the date of the Monsanto agreement or during the 30 months thereafter, in the field of agriculture. The Monsanto

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agreement also includes the transfer of technology from us to Monsanto and a collaborative research project. Under the Monsanto agreement, Monsanto will be our exclusive collaborator in the agriculture field for a ten-year period.

In consideration for the rights granted to Monsanto under the Monsanto agreement, Monsanto paid us $29.2 million in upfront cash payments. Monsanto is also required to make near-term milestone payments to us upon the achievement of specified technology transfer and patent-related milestones. We are also entitled to receive additional funding for collaborative research efforts. In the aggregate, we can earn up to $5.0 million in potential future milestone payments and research funding under the Monsanto alliance. In December 2012, we received $1.5 million of the $5.0 million in potential milestone payments from Monsanto based upon the achievement of a specified patent-related event. In addition, Monsanto is required to pay to us a percentage of specified fees from certain sublicense agreements Monsanto may enter into that include access to our intellectual property, as well as low single-digit royalty payments on worldwide, net sales by Monsanto, its affiliates and sublicensees of certain licensed products, as defined in the Monsanto agreement, if any. We could potentially earn the next milestone payment of $2.5 million under the Monsanto agreement based upon the completion of technology transfer activities. Due to the uncertainty of the application of RNAi technology in the field of agriculture, we may not receive any additional milestone payments or any royalty payments from Monsanto.

The term of the Monsanto agreement generally ends upon the expiration of the last-to-expire patent licensed under the agreement. We estimate that our fundamental RNAi patents licensed under the Monsanto agreement will expire both in and outside the United States generally between 2016 and 2025, subject to any potential patent term extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available. After August 27, 2013, Monsanto may terminate the Monsanto agreement in its entirety upon 30-days prior written notice to us, provided, however, that Monsanto is required to continue to make royalty payments to us if any royalties were payable on net sales of a licensed product during the previous 24 months. The Monsanto agreement may also be terminated by either party in the event the other party fails to cure a material breach under the Monsanto agreement.

Under the terms of the Monsanto agreement, in the event that during the exclusivity period we cease to own or otherwise exclusively control certain licensed patent rights in the agriculture field, for any reason other than Monsanto s breach of the Monsanto agreement or its negligence or willful misconduct, resulting in the loss of exclusivity with respect to Monsanto s rights to such patent rights, and such loss of exclusivity has a material adverse effect on the licensed products, then we would be required to pay Monsanto up to $5.0 million as liquidated damages, and Monsanto s royalty obligations to us under the Monsanto agreement would be reduced or, under certain circumstances, terminated. We have the right to cure any such loss of patent rights under the Monsanto agreement.

Discovery and Development Alliances.

Isis. In April 2009, we and Isis amended and restated our existing strategic collaboration and license agreement, originally entered into in March 2004, to extend the broad cross-licensing arrangement regarding double-stranded RNAi that was established in 2004, pursuant to which Isis granted us licenses to its current and future patents and patent applications relating to chemistry and to RNA-targeting mechanisms for the research, development or commercialization of double-stranded RNA, or dsRNA, products. We have the right to use Isis technologies in our development programs or in coll