ALNYLAM PHARMACEUTICALS, INC.
Form 10-K
February 20, 2014
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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, 2013

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. ¨

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 þ Accelerated filer ¨ 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 28, 2013, was $1,915,005,225. For the purpose of the foregoing calculation only, all directors and executive officers of the registrant are assumed to be affiliates of the registrant.

At January 31, 2014, the registrant had 63,916,814 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 2014 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, 2013, 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, 2013

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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, plan, anticipate, estimate, predict, may, could, should, intend, will, target, goal and similar expressions are intended to ide statements, although not 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, was launched in January 2011 and is focused on the development and commercialization of novel RNAi therapeutics as genetic medicines. Our genetic medicine programs are RNAi therapeutics directed towards genetically defined targets for the treatment of diseases with high unmet medical need. As part of this strategy, our goal is to develop product candidates with the following shared characteristics: a genetically defined target and disease expressed in the liver; the potential to have a major impact in high unmet need patient populations; the ability to leverage our existing RNAi platform with clinically proven delivery to the liver; the opportunity to monitor an early biomarker in Phase 1 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. Under our core product strategy, we expect to have six to seven genetic medicine product candidates in clinical development, including at least two programs in Phase 3 and five to six programs with human proof of concept, by the end of 2015. We are currently advancing the following core programs in clinical or pre-clinical development: patisiran (the International Nonproprietary Name for ALN-TTR02), an intravenously delivered RNAi therapeutic targeting transthyretin, or TTR, in development for the treatment of TTR-mediated amyloidosis, or ATTR, in patients with familial amyloidotic polyneuropathy, or FAP; ALN-TTRsc, a subcutaneously delivered RNAi therapeutic targeting TTR in development for the treatment of ATTR in patients with TTR cardiac amyloidosis, including familial amyloidotic cardiomyopathy, or FAC, and senile systemic amyloidosis, or SSA; ALN-AT3, an RNAi therapeutic targeting antithrombin, or AT, in development for the treatment of hemophilia and rare bleeding disorders, or RBD; ALN-CC5, an RNAi therapeutic targeting complement component C5 in development for the treatment of complement-mediated diseases; ALN-AS1, an RNAi therapeutic targeting aminolevulinate synthase-1, or ALAS-1, in development for the treatment of hepatic porphyrias, including acute intermittent porphyria, or AIP; ALN-PCSsc, an RNAi therapeutic targeting proprotein convertase subtilisin/kexin type 9, or PCSK9, in development for the treatment of hypercholesterolemia; ALN-AAT, an RNAi therapeutic targeting alpha-1-antitrypsin, or AAT, in development for the treatment of AAT deficiency liver disease; ALN-TMP, an RNAi therapeutic targeting transmembrane

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protease, serine 6, or TMPRSS6, in development for the treatment of beta-thalassemia and iron-overload disorders; ALN-ANG, an RNAi therapeutic targeting angioprotein-like 3, or ANGPTL3, in development for the treatment of genetic forms of mixed hyperlipidemia and severe hypertriglyceridemia; and other yet to be disclosed programs. Our strategy is to retain development and commercial rights for our current and future genetic medicine pipeline in North America and Western Europe, while forming alliances with leading, innovative companies for the development and commercialization of these products in the rest of world, or ROW. In early 2014, we formed an alliance with Genzyme Corporation, a Sanofi company, or Genzyme, to develop and commercialize our current Alnylam 5x15 and future genetic medicine pipeline principally in territories outside of North America and Western Europe, subject to certain broader rights.

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, 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 BioScience Co., Ltd., or Ascletis, Monsanto Company, or Monsanto, Genzyme and The Medicines Company, or MDCO. 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 approximately 15% of Regulus outstanding common stock. Through an internal effort we refer to as Alnylam Biotherapeutics, we have evaluated the application of RNAi technology to improve the manufacturing processes for biologics. We have also evaluated the utility of 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.

Recent Developments

Acquisition of Sirna Therapeutics

On January 10, 2014, we entered into a stock purchase agreement with Sirna Therapeutics, Inc., or Sirna, Merck Sharp & Dohme Corp., or Merck, and, for limited purposes, Merck & Co., Inc., pursuant to which we will purchase from Merck all of Merck s right, title and interest in and to all of the outstanding shares of common stock of Sirna. Sirna possesses intellectual property and RNAi assets including pre-clinical therapeutic candidates, chemistry, and siRNA-conjugate and other delivery technologies that we intend to integrate into our platform for delivery of RNAi therapeutics. We will not acquire any employees, manufacturing or other facilities, developed processes or clinical-stage assets as part of the acquisition of Sirna.

In consideration for the Sirna common stock, we will (i) pay Merck $25.0 million in cash and (ii) issue to Merck 2,520,044 shares of our common stock, having a value of $150.0 million as calculated under the terms of

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the stock purchase agreement on the date of execution. Following the closing of this transaction, Merck will beneficially own approximately 4% of our outstanding common stock.

In addition, Merck is eligible to receive the following consideration from us: (i) up to an aggregate of $10.0 million upon the achievement by us or our related parties of specified regulatory milestones for RNAi products covered by Sirna intellectual property, and (ii) up to an aggregate of $105.0 million upon the achievement by us or our related parties of specified development and regulatory ($40.0 million) and commercial ($65.0 million) milestones associated with the clinical development progress of certain pre-clinical candidates discovered by Sirna, together with low single-digit royalties for our products and single-digit royalties for Sirna products, in each case based on annual worldwide net sales, if any, by us and our related parties of any such products.

Under the stock purchase agreement, Merck also agreed not to dispose of (i) any shares of our common stock beneficially owned for a period of six months following the closing date, referred to as the Initial Lock-Up, subject to certain limited exceptions, and (ii) 50% of the shares of our common stock beneficially owned for a period of six additional months following the termination of the Initial Lock-Up, referred to as the Subsequent Lock-Up. During and following the expiration of the Subsequent Lock-Up, Merck will be permitted to sell such shares of our common stock subject to certain limitations, including certain volume and manner of sale restrictions.

The stock purchase agreement contains customary representations, warranties, and covenants of the parties thereto. Subject to customary closing conditions, including the expiration or early termination of the applicable pre-merger waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, the transaction is expected to close during the first quarter of 2014.

Genzyme Collaboration

On January 11, 2014, we entered into a global, strategic collaboration with Genzyme to discover, develop and commercialize RNAi therapeutics as genetic medicines to treat orphan diseases. The 2014 Genzyme collaboration is governed by a master collaboration agreement, including the license terms appended thereto, which will become effective upon closing of the equity transaction, described below. Once effective, the master agreement will supersede and replace the previous collaboration between us and Genzyme entered into in October 2012 to develop and commercialize RNAi therapeutics targeting TTR for the treatment of ATTR, which original Genzyme agreement is described under the heading Strategic Alliances in our annual report on Form 10-K for the year ended December 31, 2012.

The 2014 Genzyme collaboration is structured as an exclusive relationship for the worldwide development and commercialization of RNAi therapeutics in the field of genetic medicines, which includes our current and future genetic medicine programs that reach human proof-of-principal study completion, or Human POP, by the end of 2019, subject to extension to the end of 2021 in various circumstances. We will retain product rights in North America and Western Europe, while Genzyme will obtain exclusive rights to develop and commercialize collaboration products in the ROW, referred to as the Genzyme Territory, together with certain broader co-development/co-promote or worldwide rights for certain products. Genzyme s rights are structured as an opt-in that is triggered upon achievement of Human POP. We will maintain development control for all programs prior to Genzyme s opt-in and maintain development and commercialization control after Genzyme s opt-in for all programs in our territory.

Upon the effective date of the 2014 Genzyme collaboration, Genzyme will opt-in to patisiran for the Genzyme Territory, and we will retain full product rights in North America and Western Europe. We and Genzyme have also agreed to expand our current collaboration on ALN-TTRsc, where we and Genzyme will co-develop and co-promote ALN-TTRsc in North America and Western Europe. We will maintain development and commercialization control with ALN-TTRsc and Genzyme will develop and commercialize the product in the Genzyme Territory.

In addition to its regional rights for our current and future genetic medicine programs in the Genzyme Territory, Genzyme will have the right to either (i) co-develop and co-promote ALN-AT3 for the treatment of

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hemophilia and other RBDs in our territory, with us maintaining development and commercialization control, or (ii) obtain a global license to ALN-AS1 for the treatment of hepatic porphyrias. Genzyme will exercise this selection right upon Human POP for the ALN-AT3 and ALN-AS1 programs. Finally, Genzyme will have the right for a global license to a single, future genetic medicine program that is not one of our currently defined genetic medicine programs. We will retain global rights to any RNAi therapeutic genetic medicine program that does not reach Human POP by the end of 2019, subject to certain limited exceptions. Under the terms of the master agreement, we will retain full rights to all current and future RNAi therapeutic programs outside of the field of genetic medicines, including the right to form new collaborations.

In consideration for the rights granted to Genzyme under the master agreement and pursuant to the terms of a stock purchase agreement, we agreed to sell to Genzyme 8,766,338 shares of our common stock and Genzyme agreed to pay to us $700.0 million in aggregate cash consideration. Following the closing of the stock purchase, Genzyme will beneficially own approximately 12% of our outstanding common stock. The stock purchase agreement contains customary representations, warranties and covenants of each of the parties thereto. Subject to customary closing conditions, including the expiration or early termination of the applicable pre-merger waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, the stock purchase is expected to close during the first quarter of 2014.

A description of our 2014 Genzyme collaboration and the related stock purchase agreement 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 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. Further, certain diseases may be caused by

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the mutation in one copy of the genetic material, a single allele, in which case a specific siRNA could target the disease-causing mutation leaving the normal allele intact.

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, like antisense therapeutics, which are not catalytic and therefore require higher levels of drug to achieve mRNA silencing. 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. Further, siRNA lead candidates can be designed to be active across a broad range of species, greatly simplifying the translation of animal model data to human disease applications. In addition, certain chemical modifications can be applied to confer drug-like properties to siRNAs, making them stable when administered into the bloodstream. Finally, approaches for delivery of RNAi therapeutics have now been engineered to enable a consistent level of target gene silencing in specific organs, such as genes expressed in the liver. There also appears to be a highly correlated level of target knockdown observed in animal studies as compared with results in human clinical trials, ensuring what we believe to be a highly reliable translation of RNAi therapeutics from pre-clinical research into clinical studies. For these reasons, we believe RNAi therapeutics represent a highly modular and reproducible approach for drug discovery and development.

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

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-siRNA 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 1 clinical trials for ALN-TTR01 and ALN-PCS02, Phase 1 and Phase 2 clinical trials for patisiran, as well as in biopsy results from our Phase 1 clinical trial for ALN-VSP. During 2013, we reported results from our Phase 1 clinical trial of ALN-TTRsc, representing the first human data to be presented for our proprietary GalNAc-siRNA conjugate delivery platform, enabling subcutaneous dosing of RNAi therapeutics with a wide therapeutic index, and demonstrating human translation for our GalNAc platform. In addition, 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.

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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. We believe the acquisition of Sirna, when consummated, will complement and extend our own progress and continued focus on RNAi therapeutics, including with siRNA-conjugate technologies. 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

Under our core product strategy, we expect to have six to seven genetic medicine product candidates in clinical development, including at least two programs in Phase 3 and five to six programs with human proof of concept, by the end of 2015. We are currently advancing the following core programs in clinical or pre-clinical development: patisiran for the treatment of ATTR in patients with FAP; ALN-TTRsc for the treatment of ATTR in patients with TTR cardiac amyloidosis, including FAC and SSA; ALN-AT3 for the treatment of hemophilia and RBD; ALN-CC5 for the treatment of complement-mediated diseases; ALN-AS1 for the treatment of hepatic porphyrias, including AIP; ALN-PCSsc for the treatment of hypercholesterolemia; ALN-AAT for the treatment of AAT deficiency liver disease; ALN-TMP for the treatment of beta-thalassemia and iron-overload disorders; ALN-ANG for the treatment of genetic forms of mixed hyperlipidemia and severe hypertriglyceridemia; and other yet to be disclosed programs. Our strategy is to retain development and commercial rights for our current and future genetic medicine pipeline in North America and Western Europe, while forming alliances with leading, innovative companies for the development and commercialization of these products in the ROW. In early 2014, we formed an alliance with Genzyme to develop and commercialize our current and future genetic medicine pipeline principally in territories outside of North America and Western Europe, subject to certain broader rights.

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 that have entered clinical development, ALN-RSV01 for the treatment of respiratory syncytial virus, or 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 Huntington s disease, or HD.

The following is a summary of our product development programs and our partner-based clinical development programs as of January 31, 2014:

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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 $113.0 million in 2013, $86.6 million in 2012 and $99.3 million in 2011.

Core Product Development Programs

Our core genetic medicine 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 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 in the liver and is normally a carrier for 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 damaging 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 FAP and/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 for early stage disease 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. In addition, a Phase 2/3 clinical trial of diflunisal, a commercially available non-steroidal anti-inflammatory agent, has been conducted in patients with FAP. The mean survival for FAC patients is approximately 2.5 years following diagnosis, and there are no approved therapies. SSA is a non-hereditary form of TTR cardiac amyloidosis caused by idiopathic deposition of wild-type TTR; its prevalence is generally unknown, but is associated with advanced age. Although limited treatment options are available, there remains a significant need for novel therapeutics to treat patients with TTR amyloid polyneuropathy and/or cardiomyopathy.

Patisiran (ALN-TTR02). Patisiran is our most advanced product candidate in clinical development. In July 2012, we reported positive clinical results from our patisiran Phase 1 clinical trial, which was conducted in the United Kingdom as a randomized, single-blind, placebo-controlled, single-ascending dose study, which enrolled 17 healthy volunteer subjects. The primary objective of the study was to evaluate the safety and tolerability of a single dose of patisiran. Secondary objectives of this study included the characterization of pharmacokinetics of patisiran and the assessment of clinical activity as measured by effects on serum TTR levels through at least day 56 following a single dose. Patisiran was found to be generally well tolerated in this Phase 1 clinical trial, consistent with our broader clinical experience with LNP-formulated siRNAs.

In November 2013, we reported the achievement of positive clinical results from our Phase 2 clinical trial of patisiran. The Phase 2 clinical trial with patisiran in ATTR polyneuropathy patients (n=29) was an open-label, multi-center, multi-dose, dose-escalation trial to evaluate the safety and tolerability of two doses of patisiran and to demonstrate clinical activity based on serial measurement of circulating serum levels of wild-type and mutant TTR. Patients received two doses of patisiran in 5 cohorts with doses ranging from 0.01 to 0.30 mg/kg, using either a once-every-four-week or once-every-three-week dosing regimen. The international study included ten sites in Portugal, France, Sweden, Germany, Spain, Brazil and the U.S. The data from 28 patients enrolled and analyzed showed that multiple doses of patisiran resulted in rapid, dose-dependent and durable knockdown of serum TTR levels. As compared with the lowest dose group of 0.01 mg/kg, there was a statistically significant knockdown of serum TTR at doses of 0.15 mg/kg ($p<0.05$) and 0.30 mg/kg ($p<0.001$). The study results support further evaluation of patisiran at the 0.30 mg/kg dose administered once every three weeks. With this dose and regimen, mean TTR knockdown at nadir of 83.8% and 86.7% was observed following the first and second doses, respectively, with maximum TTR knockdown of up to 96.0%.

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A number of additional analyses were performed in this clinical trial. First, a proprietary mass spectrometry method was used to measure serum levels of wild-type and mutant V30M proteins. These results showed one-to-one correspondence in knockdown of mutant and wild-type TTR (r^2=0.95, p<0.001), with essentially superimposable pharmacodynamic effects toward both protein species. Of interest, patients on TTR stabilizer therapy (specifically tafamidis or diflunisal) showed significantly increased baseline levels of serum TTR; regardless, patisiran administration resulted in a similar degree of TTR knockdown in these patients. These results confirm the absence of any interference by TTR stabilizer drugs with the pharmacologic activity of patisiran, and also demonstrate that RNAi-mediated knockdown of TTR is achieved independent of baseline TTR serum levels. Finally, and as expected, serum TTR knockdown was highly correlated with a reduction in circulating levels of retinol binding protein (RBP) (r^2=0.89, p<0.001) and vitamin A (r^2=0.90, p<0.001).

Multiple doses of patisiran were found to be generally well tolerated in this clinical trial. The majority of the adverse events were mild or moderate. There were no abnormalities seen in liver function tests, renal function or hematologic parameters. There were two serious adverse events, including an episode of self-limiting cellulitis of the arm that occurred as a result of drug extravasation at the infusion site in a patient with poor intravenous access. In addition, an episode of nausea and vomiting occurred in a patient with autonomic involvement due to disease; this patient discontinued the study after one dose. The most common adverse event reported was a mild or moderate infusion-related reaction, or IRR, which occurred in 10.3% (3/29) of patients overall; this adverse event was managed with a prolonged intravenous infusion and was not associated with any patient discontinuations. Notably, no IRRs were reported among 12 patients who received 0.30 mg/kg once every three weeks, nine of whom received their infusion with a proprietary micro-dosing regimen administered over 70 minutes.

During 2013, we also initiated a Phase 2 open-label extension, or OLE, study with patisiran. Eligible patients treated in the Phase 2 clinical trial are being enrolled in the OLE study, where they will receive patisiran at a dose of 0.30 mg/kg every three weeks for up to two years. The primary objective of this study is to evaluate the long-term safety and tolerability of patisiran administration. In addition, the study will measure a number of clinical endpoints every six months. This includes measurement of a modified composite Neuropathy Impairment Score, termed mNIS+7, which is an evaluation of muscle weakness, sensory and autonomic function, and nerve conductance across a 304-point scale, where neuropathy progression leads to an increased score over time. A number of additional clinical endpoints will be assessed, including: quality of life; timed ten-meter walk test to evaluate mobility; modified body mass index, or BMI, as a measure of nutritional status; level of disability; and nerve fiber density in skin biopsies. In addition, serum TTR levels will be measured.

In November 2013, we also announced the initiation of our APOLLO Phase 3 clinical trial of patisiran. The APOLLO Phase 3 clinical trial is a randomized, double-blind, placebo-controlled, global study designed to evaluate the efficacy and safety of patisiran in ATTR patients with FAP. The primary endpoint of the study is the difference in the change in mNIS+7 between patisiran and placebo at 18 months. Secondary endpoints include: the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) score; NIS-weakness; modified BMI; timed ten-meter walk; and the COMPASS-31 autonomic symptom score. The trial is designed to enroll up to 200 FAP patients with a baseline NIS in the range of ten to 100, which represents patients with Stage 1 or Stage 2 disease. Patients will be randomized two-to-one, patisiran-to-placebo, with patisiran administered at 0.30 mg/kg once every three weeks for 18 months. The study was designed with 90% power to conservatively detect as little as a 37.5% difference in change in mNIS+7 between treatment groups, with a two-sided alpha of 0.05. The placebo mNIS+7 progression rate was derived from an Alnylam analysis of natural history data from 283 FAP patients. Prior to the initiation of the APOLLO study, we obtained protocol assistance for the patisiran Phase 3 clinical trial from the European Medicines Agency, or EMA, and completed our End-of-Phase 2 meeting with the U.S. Food and Drug Administration, or FDA. All patients completing the APOLLO Phase 3 clinical trial will be eligible to enroll in a Phase 3 OLE study.

The Committee for Orphan Medicinal Products, or COMP, of the EMA has designated patisiran as an orphan medicinal product for the treatment of FAP. Orphan Drug Designation, or ODD, by the European Commission, or 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

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product approval, ODD 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, FDA provided ODD to patisiran as a therapeutic for the treatment of FAP. The FDA s ODD 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 November 2013, the FDA granted Fast Track designation to patisiran for the treatment of FAP. According to the FDA, Fast Track is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and to fill an unmet medical need. The purpose is to get important new drugs to the patient earlier.

ALN-TTRsc. In addition to patisirian, we are also advancing ALN-TTRsc, which utilizes our proprietary GalNAc-siRNA conjugate delivery technology enabling subcutaneous dose administration, with a wide therapeutic index. In September 2013, we reported interim results from our Phase 1 clinical trial of ALN-TTRsc conducted in the United Kingdom. The Phase 1 clinical trial was a randomized, double-blind, placebo-controlled, single- and multi-dose, dose-escalation trial, enrolling up to 40 healthy volunteer subjects. The primary objective of this study was to evaluate the safety and tolerability of single and multiple doses of subcutaneously administered ALN-TTRsc. Secondary objectives included assessment of clinical activity of the ALN-TTRsc as measured by serum TTR levels. In an initial single-ascending dose phase of the study, subjects (n=16) received subcutaneous doses of placebo or ALN-TTRsc from 1.25 to 10.0 mg/kg. In the multiple-ascending dose phase of the study, subjects (n=12) received ten subcutaneous doses of placebo or ALN-TTRsc from 2.5 to 10.0 mg/kg. As reported in September 2013, interim data from the 28 subjects enrolled and analyzed in this study as of that date showed that single- and multi-dose administration of ALN-TTRsc resulted in rapid, dose-dependent, consistent and durable knockdown of serum TTR levels. In the multi-dose cohorts (n=12), there was a statistically significant knockdown of serum TTR at doses of 2.5 mg/kg ($p<0.01$), 5.0 mg/kg ($p<0.001$) and 10.0 mg/kg ($p<0.001$) as compared to placebo. At a dose of 5.0 mg/kg, ALN-TTRsc administration resulted in an up to 93.3% knockdown of serum TTR and a mean TTR knockdown of 87.5% at nadir. At a dose of 10.0 mg/kg, ALN-TTRsc administration led to an up to 94.0% knockdown of serum TTR and a mean TTR knockdown of 92.4% at nadir. Analysis of the TTR knockdown in humans as compared to results obtained in non-human primates, or NHPs, showed a closely correlated, essentially one-to-one relationship on a mg/kg basis ($r^2=0.83$, $p<0.001$). We believe these results confirm human translation for our GalNAc-siRNA conjugate platform, which is also being employed in the majority of our other pre-clinical and clinical genetic medicine programs.

In this study, as reported in September 2013, single and multiple doses of ALN-TTRsc were found to be generally well tolerated. There were no significant adverse events associated with drug at doses through 10.0 mg/kg. All adverse events were deemed mild or moderate in severity. Injection site reactions were observed in a minority of subjects receiving ALN-TTRsc (24%) or placebo (14%). These were reported as being clinically mild and consisted of transient erythema associated in a minority of cases with edema and/or pain. In all cases, these reactions were self-limiting and resolved within approximately two hours of onset. There were no study discontinuations, flu-like symptoms, or changes in cytokines, C-reactive protein, liver function tests, renal function or hematologic parameters.

In December 2013, we initiated a pilot Phase 2 clinical trial with ALN-TTRsc. The Phase 2 clinical trial is an open-label, multi-dose study of ALN-TTRsc, designed to enroll approximately 15 TTR cardiac amyloidosis patients with FAC or SSA. The primary objective of the study is to evaluate the general tolerability of ALN-TTRsc. Patients will receive five daily doses followed by five weekly doses of five mg/kg, with follow-up through Day 90. Secondary objectives include assessment of clinical activity as measured by knockdown of serum TTR levels and additional tests, such as cardiac imaging (including echocardiography and cardiac MRI), circulating cardiac biomarkers (NT-proBNP and troponins T and I), six-minute walk test, New York Heart Association classification, and measures of heart failure symptoms and quality of life (Kansas City Cardiomyopathy Questionnaire and EQ-5D QOL). Patients completing the Phase 2 clinical trial will be eligible to participate in an OLE study for further assessment of general tolerability and clinical activity with long-term dosing.

In October 2012, 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 to develop and commercialize

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RNAi therapeutics targeting TTR, including patisiran and ALN-TTRsc, for the treatment of ATTR and other human diseases. In early 2014, this relationship was extended as a significantly broader alliance to advance RNAi therapeutics as genetic medicines. Under the 2014 Genzyme collaboration, we will lead development and commercialization of patisiran in North America and Western Europe while Genzyme will develop and commercialize the product in the Genzyme Territory. In addition, under this new collaboration, we and Genzyme have agreed to co-develop and co-commercialize ALN-TTRsc in North America and Western Europe, with Genzyme developing and commercializing the product in the Genzyme Territory. This broadened relationship on ALN-TTRsc is aimed at expanding and accelerating the product s potential global value. The 2014 Genzyme collaboration is described below under the heading Strategic Alliances.

ALN-AT3 Hemophilia and Rare Bleeding Disorders (RBD)

ALN-AT3 is an RNAi therapeutic targeting AT, a genetically defined target, for the treatment of hemophilia and RBD. Hemophilias are hereditary disorders caused by genetic deficiencies of various blood clotting factors, resulting in recurrent bleeds into joints, muscles and other major internal organs. Hemophilia A, or HA, is defined by loss-of-function mutations in Factor VIII, and there are greater than 40,000 registered HA patients in the United States and EU. Hemophilia B, or HB, defined by loss-of-function mutations in Factor IX, affects greater than 9,500 registered patients in the United States and EU. RBD are defined by congenital deficiencies of other blood coagulation factors including Factors II, V, VII, X and XI. Based on our analysis of the available patient and market data, we estimate that there are approximately 1,000 RBD patients worldwide with a severe bleeding phenotype. Standard treatment for hemophilia patients involves replacement of the missing clotting factor either as prophylaxis or on-demand therapy. As many as one-third of people with severe HA will develop an antibody to their replacement factor, a very serious complication. These inhibitor patients become refractory to standard replacement therapy. There exists a small subset of hemophilia patients who have co-inherited a prothrombotic mutation, such as Factor V Leiden, antithrombin deficiency, protein C deficiency and prothrombin G20210A. People with hemophilia who have co-inherited these prothrombotic mutations are characterized as having milder disease, with a later onset of disease, lower risk of bleeding and reduced requirements for Factor VIII or Factor IX treatment as part of their disease management. There remains a significant need for novel therapeutics to treat people with hemophilia and RBD.

ALN-AT3 is a novel therapeutic approach aimed at re-balancing the coagulation cascade and normalizing hemostasis in severe HA and HB patients, including patients with inhibitors against their replacement factor. The program aims to reproduce the human genetic findings of a milder clinical disease in people with hemophilia who have co-inherited prothrombotic mutations. In January 2014, we initiated a Phase 1 clinical trial with ALN-AT3. The Phase 1 clinical trial is being conducted in the U.K. as a single- and multi-dose, dose-escalation study consisting of two parts. Part A is a randomized, single-blind, placebo-controlled, single-dose, dose-escalation study, enrolling up to 24 healthy volunteer subjects. The primary objective of this part of the study is to evaluate the safety and tolerability of a single low subcutaneous dose of ALN-AT3, with the potential secondarily to show changes in AT plasma levels at sub-pharmacologic doses. Part B of the study will be an open-label, multi-dose, dose-escalation study enrolling up to 18 people with moderate to severe HA or HB. The primary objective of this part of the study is to evaluate the safety and tolerability of multiple doses of subcutaneously administered ALN-AT3 in hemophilia subjects. Secondary objectives include assessment of clinical activity as determined by knockdown of circulating AT levels and increase in thrombin generation at pharmacologic doses of ALN-AT3. Thrombin generation is known to be a biomarker for bleeding frequency and severity in people with hemophilia.

Pre-clinical studies showed that ALN-AT3 achieves rapid, dose-dependent and durable knockdown of AT in rodents and NHPs. In NHPs, weekly subcutaneous doses as low as 0.125 mg/kg led to a 50% knockdown of AT, while weekly doses of 0.50 mg/kg led to approximately 90% knockdown. In addition, ALN-AT3 administration was found to normalize thrombin generation and improve hemostasis in hemophilia mice and fully correct thrombin generation in a NHP hemophilia inhibitor model. Additional pre-clinical results showing that repeat administration of ALN-AT3 was well tolerated in HA mice, with no adverse findings up to dose levels 200 times greater than those required to achieve 50% AT knockdown. Results from these studies also demonstrated that ALN-AT3 administration achieved complete correction in HA mice of the activated Partial Thromboplastin Time (aPTT), an *ex vivo* measure of blood coagulation that is significantly prolonged in hemophilia.

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Under the 2014 Genzyme collaboration, Genzyme will have the right to opt-in to the ALN-AT3 program after completion of Human POP to *either* co-develop and co-promote ALN-AT3 with us in North America and Western Europe, with Genzyme developing and commercializing in the Genzyme Territory (subject to its development decision regarding ALN-AS1), *or* to develop and commercialize the product in the Genzyme Territory. In both circumstances, we will lead and control development and commercialization in North America and Western Europe.

ALN-CC5 Complement-Mediated Diseases

ALN-CC5 is an RNAi therapeutic targeting the C5 component of the complement pathway for the treatment of complement-mediated diseases. The complement system plays a central role in immunity as a protective mechanism for host defense, but its dysregulation results in life-threatening complications in a broad range of human diseases including paroxysmal nocturnal hemoglobinuria, or PNH, atypical hemolytic-uremic syndrome, or aHUS, myasthenia gravis and neuromyelitis optica, amongst many others. Complement component C5, which is predominantly expressed in liver cells, is a genetically and clinically validated target; loss of function human mutations are associated with an attenuated immune response against certain infections. Intravenous anti-C5 monoclonal antibody therapy (eculizumab) has demonstrated clinical activity and tolerability in a number of complement-mediated diseases. It is approved for the treatment PNH and aHUS in the United States, Europe and other countries. A subcutaneously administered RNAi therapeutic that silences C5 represents a novel approach to the treatment of complement-mediated diseases, with a potentially competitive profile compared with intravenously administered anti-C5 monoclonal antibody therapy.

ALN-CC5 utilizes Alnylam s proprietary GalNAc-siRNA conjugate delivery platform enabling subcutaneous dose administration. In December 2013, we presented pre-clinical data showing robust, dose-dependent and durable knockdown of serum C5 in NHPs. Multiple doses of ALN-CC5 at 2.5 or 5.0 mg/kg led to rapid and dose-dependent knockdown of serum C5 of up to 97.8%, with mean knockdown at nadir of 97.5% ($p<0.001$) at the top dose. Knockdown of C5 was durable, with greater than 90% knockdown sustained for up to three weeks after the final dose. Further, subcutaneous administration resulted in a consistent greater than 80% knockdown of C5 during the treatment period. The results are consistent with published literature that shows an hepatic origin for the vast majority of circulating C5, and confirms that the serum component of locally produced C5 is minimal at best. In addition, multi-dose administration of ALN-CC5 resulted in robust and durable inhibition of serum hemolytic activity, a measure of complement activity in the blood. At the top dose of 5.0 mg/kg, an up to 94% inhibition of hemolytic activity was observed, with a mean nadir reduction of 92% ($p<0.01$). Inhibition of hemolytic activity was sustained for at least two weeks after the final dose. Further, inhibition of hemolytic activity was shown to be highly correlated with serum levels of C5 ($r^2=0.93$, $p<10^{-15}$). Importantly, a greater than 80% inhibition in hemolytic activity has been previously validated in studies of eculizumab in patients with PNH as being associated with clinical benefit. The essentially complete knockdown of C5 was well tolerated in NHPs, as evidenced by no changes in hematology, serum chemistry or coagulation parameters at 24 hours after the last dose. We are continuing to optimize our C5-targeted siRNA lead candidate, and expect to identify our final development candidate for ALN-CC5 in early 2014.

Under the 2014 Genzyme collaboration, Genzyme will have the right to opt-in to the ALN-CC5 program after completion of Human POP to develop and commercialize the product in the Genzyme Territory. We will lead and control development and commercialization in North America and Western Europe.

ALN-AS1 Hepatic Porphyrias

ALN-AS1 is an RNAi therapeutic targeting ALAS-1 for the treatment of hepatic porphyrias, including 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 heme 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

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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 treated with intravenous heme analogues that have a slow onset and can result in severe thrombophlebitis and iron overload. 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 subcutaneously administered RNAi therepautic targeting ALAS-1. Inhibition of ALAS-1 is known to reduce the accumulation of heme precursors that are believed to cause the clinical manifestations of AIP. ALN-AS1 has the potential to be a therapy for the treatment of hepatic porphyrias, including acute attacks, as well as a potential prophylactic approach for the prevention of recurrent attacks. In October 2013, we announced that we have identified a development candidate for advancement and presented data from pre-clinical models of the human disease showing that multi-dose administration of a GalNAc-siRNA targeting ALAS-1 results in a rapid, dose-dependent and long-lasting knockdown of ALAS-1 mRNA and complete inhibition of the toxic intermediates that mediate the symptoms and pathology of AIP. We have initiated IND-enabling studies, with the goal of filing an IND application or IND equivalent for ALN-AS1.

Under the 2014 Genzyme collaboration, Genzyme will have the right to opt-in to the ALN-AS1 program after completion of Human POP to *either* obtain a global license to ALN-AS1 for the treatment of hepatic porphyrias (subject to its development decision regarding ALN-AT3), *or* to develop and commercialize the product in the Genzyme Territory. In the latter case, we will lead and control development and commercialization in North America and Western Europe.

ALN-PCS Hypercholesterolemia

ALN-PCS is an 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 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. Hypercholesterolemia is a condition characterized by very high levels of cholesterol in the blood which is known to increase the risk of coronary artery disease, the leading cause of death in the United States. 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, diabetes, 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 February 2013, we and MDCO entered into a license and collaboration agreement pursuant to which we granted to MDCO 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 MDCO is included below under the heading Strategic Alliances.

In April 2012, we reported clinical data from our Phase 1 clinical trial of ALN-PCS02. ALN-PCS02 employs the same LNP formulation used for patisiran. The Phase 1 clinical trial was conducted in the United Kingdom as a randomized, single-blind, placebo-controlled, single-ascending dose study in healthy volunteer

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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-PCS02 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 ($p<0.05$). ALN-PCS02 was found to be generally 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-PCS02, 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 a GalNAc-siRNA conjugate targeting PCSK9 that enables subcutaneous dose administration. In October 2013, we and MDCO announced that we have identified a lead development candidate for the collaboration, ALN-PCSsc, that is a subcutaneously administered RNAi therapeutic. Specifically, pre-clinical studies in NHPs performed in the absence of concomitant statin therapy showed that this new development candidate led to an up to 95% knockdown of plasma PCSK9, with mean PCSK9 knockdown at nadir of 87% ($p<0.0001$ compared with pre-dose values according to ANOVA models) and an up to 67% lowering of LDL-C, with mean LDL-C lowering at nadir of 62% ($p<0.0001$ compared with pre-dose values). The level of LDL-C reduction was achieved in the absence of statin co-administration. Knockdown of PCSK9 and lowering of LDL-C was rapid and durable, with effects lasting greater than 50 days after the final dose, supportive of the potential for once-monthly dosing and potentially a highly competitive target product profile. We are advancing ALN-PCSsc to file an IND application or IND equivalent and will lead the program through the completion of Phase 1. MDCO is responsible for leading and funding development from Phase 2 forward and for commercializing the product if development is successful.

Additional Genetic Medicine Programs

In addition to the programs described above, we are also advancing other early stage genetic medicine programs. These programs include: ALN-AAT, an RNAi therapeutic targeting AAT in development for the treatment of AAT deficiency liver disease; ALN-TMP, an RNAi therapeutic targeting TMPRSS6 in development for the treatment of beta-thalassemia and iron-overload disorders; ALN-ANG, an RNAi therapeutic targeting ANGPTL3 in development for the treatment of genetic forms of mixed hyperlipidemia and severe hypertriglyceridemia; and other yet to be disclosed programs. We expect to identify one to two new development candidates by the end of 2014.

Partner-Based Product Development Programs

While focusing our core efforts on advancing our genetic medicine 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-RSV01 Respiratory Syncytial Virus (RSV) Infection

ALN-RSV01 is an RNAi therapeutic for the treatment of RSV infection. We have conducted numerous clinical trials of ALN-RSV01, including an international multi-center, randomized, double-blind, placebo-

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controlled Phase 2b clinical trial with ALN-RSV01 for the treatment of RSV infection in lung transplant patients. In September 2012, we reported complete results from our Phase 2b clinical trial. During 2012, we met with the FDA and European regulatory authorities regarding the results of the ALN-RSV01 Phase 2b clinical trial and obtained preliminary guidance on the design of a potential Phase 3 clinical trial.

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. We do not intend to advance the ALN-RSV01 program into a Phase 3 clinical trial unless we are able to identify a partner outside the Kyowa Hakko Kirin territory.

ALN-VSP Liver Cancer

ALN-VSP is a systemically delivered RNAi therapeutic for the treatment of advanced solid tumors with liver involvement. In January 2013, we published complete study results from our Phase 1 clinical trial for ALN-VSP. The ALN-VSP Phase 1 clinical trial was a multi-center, open-label, dose-escalation study in patients with advanced solid tumors with liver involvement who failed to respond to or had progressed after standard treatment.

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. 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. We do not intend to advance the ALN-VSP program into a Phase 2 clinical trial unless we are able to identify a partner outside of the Ascletis territory.

Other Partner-Based Programs

In addition to ALN-RSV01 and ALN-VSP, 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.

Additional Discovery Programs

In addition to our core development efforts on genetic medicine programs 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 that we can partner with third parties.

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 the treatment of 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 alliances that create significant value for ourselves and our collaborators in the advancement of RNAi therapeutics as a new class of innovative medicines. Specifically, our goal is to retain development and commercial rights for our current and future genetic medicine pipeline in North America and Western Europe, while forming alliances with leading, innovative companies for the development and commercialization of these products in the ROW. In early 2014, we formed an alliance with Genzyme to develop and commercialize our current and future genetic medicine pipeline principally in territories outside of North America and Western Europe, subject to certain broader rights. This broad collaboration will replace our 2012 alliance with Genzyme, has been approved by the boards of both companies, and is subject to customary closing conditions and clearances under the Hart-Scott Rodino Antitrust Improvements Act.

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With respect to programs that are outside of our core focus on genetic medicines, for example, in the fields of metabolic and infectious disease and in oncology, we intend to seek regional or global alliances. For example, in 2012, we formed a regional alliance with 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 MDCO 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. 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. Currently, we own approximately 15% of Regulus outstanding common stock. Through an internal effort we refer to as Alnylam Biotherapeutics, we have evaluated the application of RNAi technology to improve the manufacturing processes for biologics. We have also evaluated the utility of 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.

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, 2014, we had granted such licenses, on both an exclusive and non-exclusive basis, to approximately 20 companies.

Since delivery of RNAi therapeutics remains an important 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 Acuitas Therapeutics Inc. (formerly AlCana Technologies, Inc.), or Acuitas, 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, and Whitehead Institute for Biomedical Research, or Whitehead, 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.

Product Alliances.

Genzyme. On January 11, 2014, we entered into a global, strategic collaboration with Genzyme to discover, develop and commercialize RNAi therapeutics as genetic medicines to treat orphan diseases. The 2014 Genzyme collaboration is governed by a master collaboration agreement, including the license terms appended thereto, which will become effective upon closing of the equity transaction, described below. Once effective, the master agreement will supersede and replace the previous collaboration between us and Genzyme entered into in October 2012 to develop and commercialize RNAi therapeutics targeting TTR for the treatment of ATTR, which original Genzyme agreement is described under the heading Strategic Alliances in our annual report on Form 10-K for the year ended December 31, 2012.

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The 2014 Genzyme collaboration is structured as an exclusive relationship for the worldwide development and commercialization of RNAi therapeutics in the field of genetic medicines, which includes our current and future genetic medicine programs that reach Human POP by the end of 2019, subject to extension to the end of 2021 in various circumstances. We will retain product rights in North America and Western Europe, while Genzyme will obtain exclusive rights to develop and commercialize collaboration products in the Genzyme Territory, together with certain broader co-development/co-promote or worldwide rights for certain products. Genzyme s rights are structured as an opt-in that is triggered upon achievement of Human POP. We will maintain development control for all programs prior to Genzyme s opt-in and maintain development and commercialization control after Genzyme s opt-in for all programs in our territory.

Upon the effective date of the 2014 Genzyme collaboration, Genzyme will opt-in to patisiran for the Genzyme Territory, and we will retain full product rights in North America and Western Europe. We and Genzyme have also agreed to expand our current collaboration on ALN-TTRsc, where we and Genzyme will co-develop and co-promote ALN-TTRsc in North America and Western Europe. We will maintain development and commercialization control with ALN-TTRsc and Genzyme will develop and commercialize the product in the Genzyme Territory.

In addition to its regional rights for our current and future genetic medicine programs in the Genzyme Territory, Genzyme will have the right to either (i) co-develop and co-promote ALN-AT3 for the treatment of hemophilia and other RBDs in our territory, with us maintaining development and commercialization control, or (ii) obtain a global license to ALN-AS1 for the treatment of hepatic porphyrias. Genzyme will exercise this selection right upon Human POP for the ALN-AT3 and ALN-AS1 programs. Finally, Genzyme will have the right for a global license to a single, future genetic medicine program that is not one of our currently defined genetic medicine programs. We will retain global rights to any RNAi therapeutic genetic medicine program that does not reach Human POP by the end of 2019, subject to certain limited exceptions. Under the terms of the master agreement, we will retain full rights to all current and future RNAi therapeutic programs outside of the field of genetic medicines, including the right to form new collaborations.

In consideration for the rights granted to Genzyme under the master agreement, Genzyme is required to make payments to us for each collaboration product upon the achievement of specified development, regulatory and commercial milestones for each (i) regional (e.g., patisiran) and co-developed/co-promoted (e.g., ALN-TTRsc) collaboration product totaling up to $75.0 million and (ii) global collaboration product up to $200.0 million, and to pay tiered double-digit royalties up to twenty percent for each regional and global collaboration product based on annual net sales, if any, of each collaboration product by Genzyme, its affiliates and sublicensees. In the case of co-developed/co-promoted collaboration products, the parties will share profits equally and we w