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 collaborations and Isis agreed not to grant licenses under these patents to any other organization for the discovery, development and commercialization of dsRNA products designed to work through an RNAi mechanism, except in the context of a collaboration in which Isis plays an active role. We granted Isis non-exclusive licenses to our current and future patents and patent applications relating to RNA-targeting mechanisms and to chemistry for research use. We also granted Isis the non-exclusive right to develop and commercialize dsRNA products developed using RNAi technology against a limited number of targets. In addition, we granted Isis non-exclusive rights to research, develop and commercialize single-stranded RNA products. In August 2012, we and Isis amended the amended and restated Isis agreement to provide for the discovery, development and commercialization of dsRNA products by us or our sublicensees in the field of agriculture.

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We agreed to pay Isis milestone payments, totaling up to approximately $3.4 million, upon the occurrence of specified development and regulatory events, and royalties on sales, if any, for each product that we or a collaborator develops using Isis intellectual property. In addition, we agreed to pay to Isis a percentage of specified fees from strategic collaborations we may enter into that include access to Isis intellectual property. Isis agreed to pay us, per therapeutic target, a license fee of $0.5 million, and milestone payments totaling approximately $3.4 million, payable upon the occurrence of specified development and regulatory events, and royalties on sales, if any, for each product developed by Isis or a collaborator that utilizes our intellectual property. Isis has the right to elect up to ten non-exclusive target licenses under the agreement and has the right to purchase one additional non-exclusive target per year during the term of the collaboration. 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 under this alliance.

As part of the amended and restated Isis agreement, we and Isis established a collaborative effort focused on single-stranded RNAi, or ssRNAi, technology, and we obtained from Isis a co-exclusive, worldwide license to research, develop and commercialize ssRNAi products. We paid Isis $11.0 million in license fees upon signing the agreement in connection with the ssRNAi research program. In addition, we were obligated to fund research activities conducted by both us and Isis at a minimum of $3.0 million a year for three years. In November 2010, we exercised our right to terminate the ssRNAi collaborative effort, and all licenses to ssRNAi products granted by Isis to us, and any obligation thereunder requiring us to provide further research funding or pay additional license fees, milestone payments, royalties or sublicense payments to Isis for such ssRNAi products, also terminated. The termination of this collaborative effort did not affect the remainder of the amended and restated Isis agreement, including our licenses to Isis current and future patents and patent applications relating to dsRNAs, which remains in effect.

The term of the Isis agreement generally ends upon the expiration of the last-to-expire patent licensed thereunder, whether such patent is a patent licensed by us to Isis, or vice versa. As the license will include additional patents, if any, filed to cover future inventions, if any, the date of expiration cannot be determined at this time.

Novartis. In the second half of 2005, we entered into a series of transactions with Novartis, which included a stock purchase agreement, an investor rights agreement and a research collaboration and license agreement. In October 2010, the research program under the collaboration and license agreement was substantially completed in accordance with the terms of such agreement, subject to certain surviving rights and obligations of the parties.

In consideration for the rights granted to Novartis under the collaboration and license agreement, Novartis made an upfront payment of $10.0 million to us in October 2005, partly to reimburse prior costs incurred by us to develop *in vivo* RNAi technology. We also received research funding and development milestone payments from Novartis.

In September 2010, Novartis exercised its right under the collaboration and license agreement to select 31 designated gene targets, for which Novartis has exclusive rights to discover, develop and commercialize RNAi therapeutic products using our intellectual property and technology, including delivery-related intellectual property and related technology. Under the terms of the collaboration and license agreement, for any RNAi therapeutic products Novartis develops against these targets, we are entitled to receive milestone payments upon achievement of certain specified development and annual net sales events, up to an aggregate of $75.0 million per therapeutic product, as well as royalties on annual net sales of any such 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 Novartis. Novartis right of first offer with respect to an exclusive license for additional targets has terminated. At January 31, 2013, Novartis owned 6.5% of our outstanding common stock.

Product Alliances.

Medtronic. In July 2007, we entered into an amended and restated collaboration agreement with Medtronic to pursue the development of therapeutic products for the treatment of neurodegenerative disorders which can be addressed by the delivery of siRNAs to the human nervous system through implantable infusion

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systems. We are responsible for supplying the siRNA component and Medtronic is responsible for supplying the device component of any product resulting from the collaboration.

With respect to the initial product development program focused on our RNAi therapeutic candidate, ALN-HTT for HD, through July 2012, each party was funding 50% of the development efforts for the United States, subject to the funding reimbursement received from CHDI described below. In connection with our January 2012 strategic corporate restructuring, we determined to align our resources to focus on our lead programs. In April 2012, as part of this alignment of resources, we exercised our option under the Medtronic agreement to opt-out of the 50-50 expense/profit share arrangement of the ALN-HTT drug-device development program and to move to a royalty and milestone licensing structure. Medtronic has the right to continue development of the ALN-HTT program and has assumed responsibility for future development plans. We are transitioning the program to Medtronic, and intend to continue to supply ALN-HTT for the program, as well as provide technical support to Medtronic, as requested. If Medtronic continues the program, we would be compensated for the supply of ALN-HTT, and would be entitled to certain development milestone payments, as well as royalties on annual net sales, if any.

In addition, we and Medtronic may jointly agree to collaborate on additional product development programs for the treatment of other neurodegenerative diseases under the amended and restated collaboration agreement, which remains in effect.

The amended and restated collaboration agreement expires, on a product-by-product and country-by-country basis, upon expiration of the royalty term for the applicable product. The royalty term is the longer of a specified number of years from the first commercial sale of the applicable product and the expiration of the last-to-expire of specified patent rights. Royalties are paid at a lower level during any part of a royalty term in which specified patent coverage does not exist. Either party may terminate the amended and restated collaboration agreement on 60 days prior written notice if the other party materially breaches the agreement in specified ways and fails to cure the breach within the 60-day notice period. Either party may also terminate the agreement in the event that specified pre-clinical testing does not yield results meeting specified success criteria.

In November 2010, we, Medtronic and CHDI formed a collaboration in connection with the ALN-HTT program for HD. CHDI is a not-for-profit virtual biotech company that is exclusively dedicated to rapidly discovering and developing therapies that slow the progression of HD. Under this collaboration, CHDI agreed to initially fund approximately 50% of the costs of the ALN-HTT program up to the point at which an IND or comparable foreign regulatory application could be filed. We and Medtronic agreed to repay CHDI for this funding, with interest, in the event that a product is ultimately commercialized from the funded research. CHDI is not entitled to receive milestone or royalty payments independent of our and Medtronic s repayment obligations, nor does it have any other rights to any product developed through the funded research. In connection with our opt-out under the Medtronic agreement, in May 2012, CHDI notified us and Medtronic that it would cease further funding of the program pursuant to the terms of the CHDI agreement. We continue to be obligated to repay CHDI for our pro-rata share of funding received through the effective date of our opt-out under the Medtronic agreement, with interest, in the event that a product is ultimately commercialized from the funded research.

Kyowa Hakko Kirin. In June 2008, we entered into a license and collaboration agreement with Kyowa Hakko Kirin, under which we granted Kyowa Hakko Kirin an exclusive license to our intellectual property in Japan and other markets in Asia for the development and commercialization of an RNAi therapeutic for the treatment of RSV infection. The Kyowa Hakko Kirin agreement covers ALN-RSV01, as well as additional RSV-specific RNAi therapeutic compounds that comprise the ALN-RSV program. We retain all development and commercialization rights worldwide outside of the licensed territory.

Under the terms of the Kyowa Hakko Kirin agreement, in June 2008, Kyowa Hakko Kirin paid us an upfront cash payment of $15.0 million. In addition, Kyowa Hakko Kirin is required to make payments to us upon achievement of specified development and sales milestones totaling up to $78.0 million, and royalty payments based on annual net sales, if any, of RNAi therapeutics for the treatment of RSV by Kyowa Hakko Kirin, its affiliates and sublicensees in the licensed territory. Due to the uncertainty of pharmaceutical development and the

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high historical failure rates generally associated with drug development, we may not receive any milestone or royalty payments from Kyowa Hakko Kirin.

Under the agreement, Kyowa Hakko Kirin is responsible, at its expense, for all development activities under the development plan that are reasonably necessary for the regulatory approval and commercialization of an RNAi therapeutic for the treatment of RSV in Japan and the rest of the licensed territory. We are responsible for supply of the product to Kyowa Hakko Kirin under a supply agreement unless Kyowa Hakko Kirin elects, prior to the first commercial sale of the product in the licensed territory, to manufacture the product itself or arrange for a third party to manufacture the product.

The term of the Kyowa Hakko Kirin agreement generally ends on a country-by-country basis upon the later of (1) the expiration of our last-to-expire patent covering a licensed product and (2) the tenth anniversary of the first commercial sale in the country of sale. We estimate that our principal patents covered under the Kyowa Hakko Kirin agreement will expire both in and outside the United States generally between 2016 and 2025. These patent rights are subject to any potential patent term extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available. Additional patent filings relating to the collaboration may be made in the future. The Kyowa Hakko Kirin agreement may be terminated by either party in the event the other party fails to cure a material breach under the agreement. In addition, Kyowa Hakko Kirin may terminate the agreement without cause upon 180 days prior written notice to us, subject to certain conditions.

Genzyme. 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, known as the Genzyme territory, to develop and commercialize RNAi therapeutics targeting TTR for the treatment of ATTR and other human diseases. The Genzyme agreement covers ALN-TTR02 and ALN-TTRsc, and may in the future cover additional TTR-specific RNAi therapeutic compounds that comprise our TTR program, which we refer to together as Licensed Products, subject, in the case of improvement products, as defined in the Genzyme agreement, to specified additional terms and conditions. We retain all development and commercialization rights worldwide outside of the Genzyme territory.

In consideration for the rights granted to Genzyme under the Genzyme agreement, Genzyme paid us an upfront cash payment of $22.5 million. Upon achievement of certain milestones, we will be entitled to receive milestone payments, up to an aggregate of $50.0 million, including up to $25.0 million in specified development milestones and $25.0 million in specified regulatory milestones. In addition, we will be entitled to tiered royalties expected to yield an effective royalty rate percentage ranging from the mid-teens to mid-twenties based on annual net sales, if any, of Licensed Products in the Genzyme territory by Genzyme, its affiliates and sublicensees. We could potentially earn the next development milestone payment of $7.0 million under the Genzyme agreement based upon the completion of a successful Phase II ALN-TTR clinical trial, as defined in the Genzyme agreement. 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 Genzyme.

Under the Genzyme agreement, the parties will collaborate in the development of Licensed Products, with Genzyme assuming primary responsibility for the development and commercialization of Licensed Products in the Genzyme territory and us retaining primary responsibility for the development and commercialization of Licensed Products in the rest of the world. The collaboration between Genzyme and us is governed by a joint steering committee that will be comprised of an equal number of representatives from each party. Under the agreement, Genzyme is establishing a development plan for the ALN-TTR program relating to the development activities to be undertaken in the Genzyme territory. Genzyme is responsible, at its expense, for all development activities under the development plan that are reasonably necessary for the regulatory approval and commercialization of an RNAi therapeutic for the treatment of ATTR in the Genzyme territory. We and Genzyme intend to enter into a supply agreement to provide for supply of Licensed Products to Genzyme for clinical trials, and, at Genzyme s request, commercial sales. Genzyme may elect, at any time during the term of the Genzyme agreement, to manufacture Licensed Products itself or arrange for a third party to manufacture the product.

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Genzyme also has a right of first negotiation in the event that we desire to grant any third party rights to develop and/or commercialize a Licensed Product for the treatment of ATTR or other human diseases outside of the Genzyme territory.

We have agreed to indemnify Genzyme for legal costs and other losses or amounts required to be paid by Genzyme, if any, in connection with or related to certain of our ongoing litigation matters. Unless terminated earlier in accordance with the terms of the agreement, the Genzyme agreement expires on a Licensed Product-by-Licensed Product and country-by-country basis upon the latest to occur of (1) the expiration of the last valid claim of our patents or joint patents covering a Licensed Product, (2) the expiration of the regulatory exclusivity, as defined in the Genzyme agreement, and (3) twenty-five years from first commercial sale of such Licensed Product in such country. We estimate that our fundamental RNAi patents covering ALN-TTR compounds under the Genzyme agreement will expire both in and outside of the United States generally between 2016 and 2021. We also estimate that our patents covering ALN-TTR compounds under the Genzyme agreement in the United States and elsewhere will expire in 2032. These patent rights are subject to potential patent term extensions and/or supplemental protection certificates extending such terms in countries where such extensions may become available. In addition, more patent filings relating to the collaboration may be made in the future. Either party may terminate the Genzyme agreement in the event the other party fails to cure a material breach or in the event that development ends after a specified time period without regulatory approval of a Licensed Product. We may terminate the agreement upon patent-related challenges by Genzyme. Genzyme has the right to terminate the agreement without cause at any time upon six months prior written notice. Genzyme may also terminate the agreement upon forty-five days prior written notice if Genzyme determines that specified success criteria have not been met following the completion of a Phase II clinical trial.

During the period from the effective date of the Genzyme agreement until the first commercial sale of a Licensed Product in a country in the Genzyme territory, and thereafter during any period during which Genzyme is paying us any royalties on net sales of any Licensed Product in such country, neither party will, alone or with an affiliate or agreed upon third party, develop or commercialize in such country, any product for the treatment of ATTR, other than a Licensed Product or an agreed complementary product, without the prior written agreement of the other party.

The Genzyme agreement originally provided that if development of a Licensed Product was terminated by us or Genzyme under certain limited circumstances, Genzyme would have the right to terminate the Genzyme agreement and we would be required to refund amounts paid by Genzyme to us under the agreement prior to such termination. On February 19, 2013, we and Genzyme agreed to amend the Genzyme agreement to remove this provision.

The Medicines Company. 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 PCSK9, including ALN-PCS02 and ALN-PCSsc, for the treatment of hypercholesterolemia and other human diseases. 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. 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 MedCo.

Under the MedCo agreement, we and MedCo will collaborate in the further development of licensed products. We will retain responsibility for the development of licensed products until Phase I completion, as defined in the MedCo agreement, at our cost, up to an agreed upon initial development cost cap. MedCo will assume all other responsibility for the development and commercialization of licensed products, at its sole cost. Initially the collaboration will include the development of both ALN-PCS02 and ALN-PSCsc in parallel, provided that we and MedCo intend to select one of ALN-PCS02 or ALN-PSCsc for ongoing development at a

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specified development stage, in accordance with the terms of the MedCo agreement. The collaboration between us and MedCo will be governed by a joint steering committee that will be comprised of an equal number of representatives from each party.

We will be solely responsible for obtaining supply of finished product reasonably required for the conduct of our obligations under the initial development plan through Phase I completion, and supplying MedCo with finished product reasonably required for the first Phase II clinical trial of a licensed product conducted by MedCo, at our expense, provided such costs do not exceed the development costs cap, subject to certain exceptions. After such time, MedCo will have the sole right and responsibility to manufacture and supply licensed product for development and commercialization under the MedCo development plan, subject to the terms of the MedCo agreement. We and MedCo intend to enter into a supply and technical transfer agreement to provide for supply of licensed products to MedCo within a specified time following the effective date of the MedCo agreement.

Unless terminated earlier in accordance with the terms of the agreement, the MedCo agreement expires on a licensed product-by-licensed product and country-by-country basis upon expiration of the last royalty term for any licensed product in any country, where a royalty term is defined as the latest to occur of (1) the expiration of the last valid claim of patent rights covering a licensed product, (2) the expiration of the Regulatory Exclusivity, as defined in the MedCo agreement, and (3) the twelfth anniversary of the first commercial sale of the licensed product in such country. We estimate that our fundamental RNAi patents covering licensed products under the MedCo agreement will expire both in and outside of the United States generally between 2015 and 2023. We also estimate that our ALN-PCS product-specific patents covering licensed products under the MedCo agreement in the United States and elsewhere will expire at the end of 2033. These patent rights are subject to potential patent term extensions and/or supplemental protection certificates extending such terms in countries where such extensions may become available. In addition, more patent filings relating to the collaboration may be made in the future.

Either party may terminate the MedCo agreement in the event the other party fails to cure a material breach or upon patent-related challenges by the other party. We may terminate the agreement in the event that a lead licensed product has not been designated by the joint steering committee within a designated time period. In addition, MedCo has the right to terminate the agreement without cause at any time upon four months prior written notice.

During the term of the MedCo agreement, neither party will, alone or with an affiliate or third party, research, develop or commercialize, or grant a license to any third party to research, develop or commercialize, in any country, any product directed to the PCSK9 gene, other than a licensed product, without the prior written agreement of the other party, subject to the terms of the MedCo agreement.

Cubist. In January 2009, we entered into a license and collaboration agreement with Cubist to develop and commercialize therapeutic products based on certain of our RNAi technology for the treatment of RSV. Licensed products initially included ALN-RSV01, as well as several other second-generation RNAi-based RSV inhibitors. In November 2009, we and Cubist entered into an amendment to our license and collaboration agreement, which provided that we and Cubist would focus our collaboration and joint development efforts on ALN-RSV02, a second-generation compound, intended for use in pediatric patients. In December 2010, we and Cubist jointly made a portfolio decision to put the development of ALN-RSV02 on hold. Pursuant to the terms of the amendment, we continued to develop ALN-RSV01 for adult transplant patients at our sole discretion and expense and Cubist had the right to opt into collaborating with us on ALN-RSV01, subject to specified 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 the license and collaboration agreement effective as of February 6, 2013. As of the effective date, the parties have no further rights and obligations under the license and collaboration agreement, notwithstanding anything to the contrary in the agreement. We intend to seek another partner to advance the ALN-RSV01 program into a Phase III clinical trial.

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Intellectual Property Licenses

In December 2002, we entered into a co-exclusive license with Max Planck Innovation for the worldwide rights to use and sublicense certain patented technology to develop and commercialize therapeutic products and related applications. We also obtained the rights to use, without the right to sublicense, the technology for all diagnostic uses other than for the purposes of therapeutic monitoring. We were also given the right to acquire the remaining 50% exclusive rights, which right we exercised upon our acquisition of Ribopharma AG in July 2003. In June 2005, we entered into an amendment to our agreement with Max Planck Innovation that secured our exclusivity to use and sublicense certain patented technology to develop and commercialize therapeutic products and related applications.

We are not obligated to pay any development or sales milestone payments to Max Planck Innovation, however, we will be required to pay Max Planck Innovation future single-digit royalties on net sales of all therapeutic and prophylactic products developed with the technology, if any.

Our agreements with Max Planck Innovation generally remain in effect until the expiration of the last-to-expire patent licensed thereunder. We estimate that the principal issued patents covered under the Max Planck Innovation agreements will expire both in and outside the United States during 2021, subject to any potential patent term extensions, restoration and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available. We may terminate the agreements without cause with six months prior notice to Max Planck Innovation, and Max Planck Innovation may terminate the agreements in the event that we materially breach our obligations thereunder. Max Planck Innovation also has the right to terminate the agreements in the event that we, independently or through a third party, attack the validity of any of the licensed patents.

Delivery-Related Licenses and Collaborations

We are working internally and with third-party collaborators with the goal of developing new technologies to achieve effective and safe delivery of RNAi therapeutics to a broad spectrum of organ and tissue types. In connection with these efforts, we have entered into a number of agreements to evaluate and gain access to certain delivery technologies. In some instances, we are providing or have previously provided funding to support the advancement of these delivery technologies. During 2012, we continued to make advances relating to the delivery of RNAi therapeutics, both internally and together with our collaborators.

Arrowhead. In January 2012, we and Arrowhead entered into collaboration and joint licensing agreements, pursuant to which we received a license from Arrowhead to utilize their dynamic polyconjugate, or DPC, delivery technology for an RNAi therapeutic product. Arrowhead is eligible to receive from us milestone payments and royalties, if any, on sales of product resulting from the license. In addition, we granted Arrowhead a license under our intellectual property that enables the discovery, development and commercialization of an RNAi therapeutic targeting the hepatitis B virus, or HBV. We are eligible to receive from Arrowhead milestone payments and royalties, if any, on sales of any product resulting from the license.

MIT. In November 2011, we extended for an additional three years, through May 2015, the term of our agreement with the David H. Koch Institute for Integrative Cancer Research at MIT, under which we are sponsoring an exclusive research program focused on the discovery of new materials and formulations for the delivery of RNAi therapeutics. We and MIT have published data describing advancements in the discovery and development of LNPs based on novel lipidoid formulations for the systemic delivery of RNAi therapeutics. Lipidoids are lipid-like materials discovered for the delivery of RNAi therapeutics, and were originally described by us and our collaborators at MIT. Lipidoid formulations represent one of several approaches we are pursuing for systemic delivery of RNAi therapeutics under our research agreement with MIT.

Tekmira. In November 2012, we, TPC and Protiva agreed to restructure our existing contractual relationship. In connection with this restructuring, the parties entered into a cross-license agreement, and agreed to terminate certain prior agreements, including: the May 2008 amended and restated license and collaboration

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between us and TPC, the May 2008 amended and restated cross-license agreement between us and Protiva, and the January 2009 manufacturing agreement between us and TPC.

Under the 2012 cross-license agreement, the parties have consolidated certain intellectual property related to LNP technology for the systemic delivery of RNAi therapeutics. Specifically, certain patents and patent applications, including the MC3 lipid family, were assigned by us to TPC. We retain rights to use this intellectual property for the research, development and commercialization of RNAi therapeutic products, including the rights to sublicense this intellectual property on a product-by-product basis. Tekmira has also granted us a worldwide license to its LNP technology for the research, development and commercialization of LNP-based RNAi therapeutics, which license shall be exclusive for up to eight targets designated by us, and otherwise shall be non-exclusive. We have the right to sublicense on a product-by-product basis.

In addition, we elected to buy out our manufacturing obligations to TPC with respect to our LNP-based pipeline programs. Pursuant to the terms of the 2012 cross-license agreement, we made a one-time payment of $30.0 million to TPC for the termination of, and our release from, all of our obligations under the manufacturing agreement, including without limitation the obligations to obtain materials and/or services from TPC. We also have the right to manufacture and have manufactured our LNP-based RNAi therapeutics, which right may be sublicensed to our collaborators.

Further, as part of this restructuring, we elected to buy-down certain future potential milestone and royalty payments due to Tekmira for certain of our RNAi therapeutics, formulated using LNP technology. Specifically, pursuant to the cross-license agreement, we made a one-time payment of $35.0 million to TPC, which amount constituted payment for the termination of the 2008 license agreements with TPC and Protiva and the parties rights and obligations thereunder, as well as the buy-down of certain milestone payments and the significant reduction of royalty rates for ALN-VSP, ALN-PCS and ALN-TTR. Under the 2012 cross-license agreement, we will be obligated to pay TPC an aggregate of $10.0 million in contingent milestone payments related to advancement of ALN-VSP and ALN-TTR, which now represent the only potential milestones due to Tekmira for ALN-VSP, ALN-PCS and ALN-TTR LNP-based RNAi therapeutics. Specifically, we will be obligated to pay TPC a $5.0 million milestone payment upon each of (i) the initiation of a Phase III clinical trial of an LNP-based ALN-TTR therapeutic product, and (ii) the manufacture of ALN-VSP clinical trial material for use in China.

Consistent with the prior license agreements, under the 2012 cross-license agreement, we are obligated to pay TPC up to an aggregate of $16.0 million in milestone payments for any future RNAi therapeutic formulated using Tekmira LNP technology, excluding ALN-VSP, ALN-PCS and ALN-TTR, together with low single-digit royalty payments on annual product sales, if any.

Under the 2012 cross-license Agreement, Tekmira maintains the three exclusive and five non-exclusive licenses previously granted by us under the prior license agreements to research, develop and commercialize RNAi therapeutics directed to up to eight gene targets. In addition, we granted Tekmira a non-exclusive license for two additional gene targets, on the same terms and conditions as the prior non-exclusive licenses. Tekmira also acquired from AlCana its existing options for three additional non-exclusive licenses, which have been included under the 2012 cross-license agreement. Tekmira may sublicense these rights on a product-by-product basis. We waived our right under the prior license agreements to opt-in to the Tekmira research program directed to polo-like kinase 1, or PLK1. Under the 2012 cross-license agreement, we are eligible to receive from Tekmira up to an aggregate of $8.5 million in milestone payments for RNAi therapeutics directed to nine of the targets for which we have granted licenses to Tekmira, together with single-digit royalties on annual product sales, if any, of RNAi therapeutic products directed to all thirteen of the targets for which we have granted licenses to Tekmira. 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 Tekmira.

The term of the 2012 cross-license agreement generally ends upon the expiration of the last-to-expire royalty term. Royalties are payable on a product-by-product and country-by-country basis commencing on the first commercial sale of a product in a country and continuing during any period in which (a) in the case of us, a valid claim within the Tekmira Royalty-Bearing Patents (as defined in the 2012 cross-license agreement) covers our applicable product in such country of sale, or (b) in the case of Tekmira products, a valid claim within our

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patents covers the applicable Tekmira product in such country of sale. We estimate that our fundamental RNAi patents covered under the 2012 cross-license agreement will expire both in and outside the United States generally between 2019 and 2021, and that the Tekmira LNP patents covered under the 2012 cross-license agreement will expire both in and outside the United States generally between 2020 and 2030, subject in each case to any potential patent term extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available. Either party may terminate a license it granted to the other in the event that the other party fails to cure a material breach of its obligations relating to that license. Furthermore, either party may terminate the 2012 cross-license agreement in the event the other party fails to cure a material breach of an obligation under the agreement. In addition, either party may terminate the 2012 cross-license agreement upon patent-related challenges by the other party.

UBC and AlCana. In July 2009, we entered into a research agreement with UBC and AlCana that was focused on the discovery of novel lipids, such as the MC3 lipid, employed in second-generation LNP formulations for the systemic delivery of RNAi therapeutics. Pursuant to the terms of the research agreement, we funded collaborative research through July 2012, which was conducted by our scientists, together with scientists at UBC and AlCana. Under the research agreement, UBC and AlCana are eligible to receive up to an aggregate of $1.3 million in milestone payments from us for each licensed product (as defined in the research agreement) directed to a particular target (as defined in the research agreement), together with single-digit royalty payments on annual product sales, if any.

Concurrent with the execution of the research agreement, we also entered into a supplemental agreement with TPC, Protiva, UBC and AlCana, which contains additional terms regarding the intellectual property rights arising out of the research agreement. In connection with 2012 cross-license agreement with Tekmira described above, we and Tekmira agreed to supersede the rights and obligations under the supplemental agreement as between ourselves, with the rights and obligations set forth in the 2012 cross-license agreement.

Other Opportunities. We are pursuing additional approaches for delivery that include other lipid-based formulations, mimetic lipoprotein particles and siRNA conjugation strategies, among others. In addition, we have other RNAi therapeutic delivery collaborations and intend to continue to collaborate with academic and corporate third parties, as well as government entities, to evaluate and gain access to different delivery technologies.

microRNA Therapeutics

Regulus. In September 2007, we and Isis established Regulus, a company focused on the discovery, development and commercialization of microRNA therapeutics. Regulus leverages our and Isis technologies, know-how and intellectual property relating to microRNA therapeutics.

Regulus, which initially was established as a limited liability company, converted to a C corporation as of January 2, 2009 and changed its name to Regulus Therapeutics Inc. In consideration for our and Isis initial interests in Regulus, we and Isis each granted Regulus exclusive licenses to our intellectual property for certain microRNA therapeutics as well as certain patents in the microRNA field. Regulus operates as an independent company with a separate board of directors, scientific advisory board and management team, some of whom have options to purchase common stock of Regulus. Members of the board of directors of Regulus who are our employees or Isis employees have not been eligible to receive options to purchase Regulus common stock. In October 2012, Regulus completed an underwritten initial public offering, raising $50.9 million in gross proceeds, including proceeds from the exercise by the underwriters of the over-allotment option. Currently, we own approximately 17% of Regulus outstanding common stock.

Regulus is exploring therapeutic opportunities that arise from microRNA dysregulation. Since microRNAs are believed to regulate broad networks of genes and biological pathways, microRNA therapeutics define a new and potentially high-impact strategy to target multiple nodes on disease pathways. microRNAs are small non-coding RNAs that regulate the expression of other genes. More than 500 microRNAs have been identified to date in humans, each of which is believed to interact with a specific set of genes that control key aspects of cell biology. Since microRNAs may act as master regulators of the genome and are often found to be dysregulated in disease, microRNAs potentially represent an exciting new platform for drug discovery and development. Regulus

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is advancing microRNA therapeutics in several areas including oncology, fibrosis, hepatitis C virus, or HCV, and metabolic diseases.

Regulus has entered into a number of strategic alliances with leading pharmaceutical companies, including GSK, Sanofi, Biogen Idec and AstraZeneca. Each of Alnylam and Isis is entitled to receive specified sublicense income in connection with certain collaborative agreements entered into by Regulus, as well as royalties on net sales, if any, of certain products developed by Regulus or its collaborators, in each case subject to the terms and conditions of the license and collaboration agreement among Regulus, Isis and Alnylam.

Alnylam Biotherapeutics

Since 2009, we have advanced our efforts regarding the application of RNAi technologies to improve the manufacturing processes for biologics, including recombinant proteins and monoclonal antibodies. These applications of RNAi technology, which we are advancing in an internal effort we refer to as Alnylam Biotherapeutics, have the potential to create new business opportunities. In particular, we are advancing RNAi technologies to improve the quantity and quality of biologics manufacturing processes using mammalian cell culture, such as Chinese hamster ovary, or CHO, cells. This RNAi technology potentially could be applied to the improvement of manufacturing processes for existing marketed drugs, new drugs in development and for the emerging biosimilars market. We have developed proprietary delivery lipids that enable the efficient delivery of siRNAs into CHO cells when grown in suspension culture, as well as other cell systems that are used for the manufacture of biologics. Studies have demonstrated that silencing certain target genes involved in certain CHO cell apoptotic and metabolic pathways resulted in improved cell viability as compared with untreated cells. Additional studies demonstrated the ability to target a viral infection of CHO cells and alter glycosylation pathways. We have formed several collaborations around our Alnylam Biotherapeutics initiative with leading biotechnology and pharmaceutical companies and may seek additional collaborations with established biologic manufacturers, selling licenses, products and services.

VaxiRNA

We are also applying RNAi technology to improve the manufacturing processes for vaccines in an effort called VaxiRNA. The VaxiRNA platform stems from work we have performed as part of our Alnylam Biotherapeutics efforts. With VaxiRNA, we are using siRNAs that silence specific genes in vaccine production systems, such as cells or chicken eggs, which limit or prevent the efficient growth of viruses used in the manufacture of vaccine products. New innovations in vaccine manufacturing are needed to enable the scale and speed of global immunization for a number of pathogens. In October 2011, we formed a VaxiRNA collaboration with GSK for influenza vaccine production. Under the terms of the agreement, GSK has agreed to provide research funding and certain success-based milestone payments to us. If successfully applied in the manufacture of commercial product, we will also have the right to receive payments on unit product sales, if any. In addition, GSK has obtained an option for VaxiRNA applications toward two additional vaccine products. In 2012, we received a $3.2 million development milestone payment from GSK under this agreement related to progress in our collaboration.

Licenses

To further enable the field and monetize our intellectual property rights, we have established our InterfeRx program and our research reagents and services licensing program.

InterfeRx Program. Our InterfeRx program consists of the licensing of our intellectual property to others for the development and commercialization of RNAi therapeutic products relating to specific targets outside our direct strategic focus. We expect to receive license fees, annual maintenance fees, milestone payments and royalties on sales of any resulting RNAi therapeutic products. Generally, we do not expect to collaborate with our InterfeRx licensees in the development of RNAi therapeutic products, but may do so in certain circumstances. To date, we have granted InterfeRx licenses to several companies, including Quark Pharmaceuticals, Inc., or Quark, Calando Pharmaceuticals, Inc., or Calando, and Tekmira. In general, these licenses allow the licensees to

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discover, develop and commercialize RNAi therapeutics for a limited number of targets in return for upfront, milestone, license maintenance and/or royalty payments to us. In some cases, we also retained a right to negotiate the ability to co-promote and/or co-commercialize the licensed product, and in one case, we included the rights to discover, develop and commercialize RNAi therapeutics utilizing expressed RNAi (i.e., RNAi mediated by siRNAs generated from DNA constructs introduced into cells). In addition, Sylentis, S.A.U., or Sylentis, and Benitec Ltd., or Benitec, each have an option to take an InterfeRx license, subject to certain conditions. We have granted InterfeRx licenses or options relating to approximately 23 gene targets and, as of January 31, 2013, 11 of these targets have been selected by InterfeRx partners.

Research Reagents and Services. We have granted approximately 14 licenses to our intellectual property for the development and commercialization of research reagents and services, and intend to enter into additional licenses on an ongoing basis. Our target licensees are vendors that provide siRNAs and related products and services for use in biological research. We offer these licenses in return for an initial license fee, annual renewal fees and royalties from sales of siRNA research reagents and services. No single research reagent or research services license is material to our business.

Patents and Proprietary Rights

We have devoted considerable effort and resources to establish what we believe to be a strong intellectual property position relevant to RNAi therapeutic products and delivery technologies. In this regard, we have amassed a portfolio of patents, patent applications and other intellectual property covering:

- fundamental aspects of the structure and uses of siRNAs, including their use as therapeutics, and RNAi-related mechanisms;
- chemical modifications to siRNAs that improve their suitability for therapeutic and other uses;
- siRNAs directed to specific targets as treatments for particular diseases;
- delivery technologies, such as in the field of cationic liposomes; and
- all aspects of our specific development candidates.

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. Our intellectual property estate for RNAi therapeutics includes over 1,800 active cases and over 700 granted or issued patents, of which over 300 are issued or granted in the United States, the EU, including by the European Patent Office, or EPO, and Japan. 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.

Intellectual Property Related to Fundamental Aspects and Uses of siRNA and RNAi-related Mechanisms

In this category, we include United States and foreign patents and patent applications that claim key aspects of siRNA architecture and RNAi-related mechanisms. Specifically included are patents and patent applications covering targeted cleavage of mRNA directed by RNA-like oligonucleotides and dsRNAs of particular lengths and particular structural features, such as blunt and/or overhanging ends. Our strategy has been to secure exclusive rights where possible and appropriate to key patents and patent applications that we believe cover fundamental aspects of RNAi. The following table lists patents and/or patent applications to which we have secured rights that we regard as being fundamental for the use of siRNAs as therapeutics.

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Licensor/Owner	Subject Matter	First Priority Date	Inventors	Status	Expiration Date*	Alnylam Rights
Isis	Inactivation of target mRNA	6/6/1996 (EP) and 6/6/1997 (U.S.)	S. Crooke	U.S. 5,898,031, U.S. 6,107,094, U.S. 7,432,250 & U.S. 7,695,902 EP 0928290 Additional applications pending in the U.S. and several foreign jurisdictions	6/6/2016 6/6/2017	Exclusive rights for therapeutic purposes related to siRNAs**
Carnegie Institution of Washington	Double-stranded RNAs to induce RNAi	12/23/1997	A. Fire, C. Mello	U.S. 6,506,559, U.S. 7,560,438 & U.S. 7,538,095 Additional applications pending in the U.S. and several foreign jurisdictions	12/18/2018	Non-exclusive rights for therapeutic purposes
Medical College of Georgia Research Institute, Inc.	Methods for inhibiting gene expression using double-stranded RNA	1/28/1999	Y. Li, M. Farrell, M. Kirby	AU 776150 (Australia) Additional applications pending in the U.S., Europe and Canada	1/28/2020	Exclusive rights
Alnylam	Small double-stranded RNAs as therapeutic products	1/30/1999	R. Kreutzer, S. Limmer	EP 1214945 (opposed), EP 1550719 (revoked/under appeal), CA 2359180 (Canada), AU 778474 (Australia), ZA 2001/5909 (South Africa), DE 20023125 U1, DE 10066235 & DE 10080167 (Germany) Additional applications pending in the U.S. and several foreign jurisdictions	1/29/2020	Owned
Alnylam	Medicament for inhibiting the expression of a target gene and medicament for treating a tumor disease	1/9/2001	R. Kreutzer, S. Limmer, H-P.Vornlocher, P. Hadwiger, A. Geick, M. Ocker, C. Herold, D. Schuppan	EP 1349927 (opposed and maintained in amended form)	1/9/2022	Owned
Alnylam	Method for inhibiting the expression of a target gene	1/9/2001	R. Kreutzer, S. Limmer,	EP 1352061 (opposed, maintained and under appeal)	1/9/2022	Owned

			P. Hadwiger			
Alnylam	Composition and methods for inhibiting a target nucleic acid with double-stranded RNA	4/21/1999	C. Pachuk, C. Satishchandran	AU 781598 (Australia) Additional applications pending in the U.S. and several foreign jurisdictions	4/19/2020	Owned
Cancer Research Technology Limited	RNAi uses in mammalian oocytes, preimplantation embryos and somatic cells	11/19/1999	M. Zernicka-Goetz, F. Wianny, M.J. Evans, D.M. Glover	EP 1230375 (revoked/under appeal), SG 89569 (Singapore), AU 774285 (Australia) Additional applications pending in the U.S. and several foreign jurisdictions	11/17/2020	Exclusive rights for therapeutic purposes
Massachusetts Institute of Technology, Whitehead Institute for Biomedical Research, Max Planck Gesellschaft, University of Massachusetts ***	Mediation of RNAi by small RNAs 21-23 base pairs long	3/30/2000	D.P. Bartel, P.A. Sharp, T. Tuschl, P.D. Zamore	U.S. 12/897,744 (allowed) & U.S. 12/897,754 (allowed) EP 1309726 (opposed and maintained in amended form/under appeal), AU 2001249622 (Australia), NZ 522045 (New Zealand), KR 08724437 & KR 10-0909681 (Korea) Additional applications pending in the U.S. and several foreign jurisdictions	3/30/2021	Non-exclusive rights for therapeutic purposes***

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Licensor/Owner	Subject Matter	First Priority Date	Inventors	Status	Expiration Date*	Alnylam Rights
Massachusetts Institute of Technology, Whitehead Institute, University of Massachusetts, Max Planck Gesellschaft (U.S.)**** Max Planck Gesellschaft (ex-U.S.), European Molecular Biology Laboratory (ex-U.S.)*****	Synthetic and chemically modified siRNAs as therapeutic products	12/1/2000 (EP), 4/24/2004 and 4/27/2004	T. Tuschl, S. Elbashir, W. Lendeckel, M. Wilm#, R. Lührmann# #EMBL inventors	U.S. 7,056,704, U.S. 7,078,196, U.S. 8,329,463, U.S. 8,372,968 & U.S. 8,362,231 EP 1407044 (opposed and maintained in amended form/under appeal), EP 1873259, AU 2002235744 (Australia), ZA 2003/3929 (South Africa), SG 96891 (Singapore), NZ 52588 (New Zealand), JP 4 095 895 (opposed and maintained in amended form/under appeal), JP 4 494 392 (Japan), RU 2322500 (Russia), CN 1568373 (China) Additional applications pending in the U.S. and several foreign jurisdictions	11/29/2021	Exclusive rights for therapeutic purposes****
Alnylam	Methods for inhibiting a target nucleic acid via the introduction of a vector encoding a double-stranded RNA	1/31/2001	T. Giordano, C. Pachuk, C. Satishchandran	AU 785395 (Australia) Additional applications pending in the U.S., Australia and Canada	1/31/2021	Owned
Cold Spring Harbor Laboratory	RNAi uses in mammalian cells	3/16/2001	D. Beach, G. Hannon	Pending in the U.S. and several foreign jurisdictions	03/16/2021	Non-exclusive rights for therapeutic purposes
Stanford University	RNAi uses *in vivo* in mammalian liver	7/23/2001	M.A. Kay, A.P. McCaffrey	AU 2002326410 (Australia) Additional applications pending in the U.S. and several foreign jurisdictions	7/23/2021	Exclusive rights for therapeutic purposes

* For applications filed after June 7, 1995, the patent term generally is 20 years from the earliest application filing date. However, under the Drug Price Competition and Patent Term Extension Act of 1984, known as the Hatch-Waxman Act, we may be able to apply for patent term extensions for our U.S. patents. We cannot predict whether or not any patent term extensions will be granted or the length of any patent term extension that might be granted.

** We hold co-exclusive therapeutic rights with Isis. However, Isis has agreed not to license such rights to any third party, except in the context of a collaboration in which Isis plays an active role.

*** We hold exclusive rights to the interest owned by three co-owners. The University of Massachusetts, or UMass, has licensed its interest separately to third parties.

**** We hold exclusive rights to the interest owned by all co-owners in the U.S., subject to the right of UMass to sublicense the U.S. Tuschl II patent family to Merck & Co., Inc., or Merck.

***** European Molecular Biology Laboratory, or EMBL, has a limited ownership interest in certain ex-US cases in this family with no rights to control or otherwise affect patent prosecution.

We believe that we have a strong portfolio of broad rights to fundamental RNAi patents and patent applications. Many of these rights are exclusive, which we believe prevents potential competitors from commercializing products in the field of RNAi without taking a license from us. In securing these rights, we have focused on obtaining the strongest rights for those intellectual property assets we believe will be most important in providing competitive advantage with respect to RNAi therapeutic products.

We believe that the Crooke patent series, issued in several countries around the world, covers the use of modified oligonucleotides to achieve enzyme-mediated cleavage of a target mRNA. We have obtained rights to the Crooke patents for use with dsRNA products, through a license agreement with Isis. Under the terms of our amended and restated Isis agreement, Isis agreed not to grant licenses under these patents to any other organization for dsRNA products designed to work through an RNAi mechanism, except in the context of a collaboration in which Isis plays an active role.

Through our acquisition of Ribopharma AG, now known as Alnylam Europe, we own the entire Kreutzer-Limmer patent portfolio, which includes pending applications in the United States and many countries worldwide. The first patent to issue in the Kreutzer-Limmer series (EP 1144623) was granted in Europe in 2002, and specifically covered the use of small dsRNAs as therapeutics. This patent was revoked on appeal. The second

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European Kreutzer-Limmer patent (EP 1214945) to issue in the series was granted in Europe in 2005. This patent covers methods using, medicaments comprising and uses of dsRNA structures of 15 to 49 successive nucleotide pairs in length. In January 2009, the Opposition Division of the EPO ruled in favor of the opposing parties in an opposition proceeding related to the second Kreutzer-Limmer patent. We appealed this decision, and in May 2010, the Board of Appeals of the EPO ruled in our favor, rejecting the Opposition Division s ruling that the second Kreutzer-Limmer patent was invalid. The patent was sent back to the Opposition Division to address the remaining grounds asserted by the opponents. In December 2008, the EPO granted a third patent in the Kreutzer-Limmer series (EP 1550719). This patent covers therapeutic dsRNAs which are 15 to 21 consecutive nucleotide pairs in length. The third Kreutzer-Limmer patent was opposed and revoked in July 2012. We have appealed this decision. We have also received grants for patents in the Kreutzer-Limmer series in several other countries, as reflected in the table above. The decision with respect to EP 1144623 will only affect the granted or pending claims of other members of the Kreutzer-Limmer patent series to the extent the same issue arises in the formal examination or post-grant review proceedings of the other members of the series. In the event this happens, we believe that the ruling in the EP 1144623 proceeding would be controlling. In March 2010, the EPO issued a further patent designating Kreutzer and Limmer (among others) as inventors (EP 1349927). This patent covers methods and medicaments having dsRNAs that are less than 25 nucleotides in length having a 3 nucleotide overhang on the antisense strand which inhibit anti-apoptotic genes in tumor cells. This fourth Kreutzer-Limmer patent had also been opposed and in December 2012, the EPO limited the claims to dsRNAs specific for members of the BCL-2 gene family, a family of anti-apoptotic genes implicated in cancer.

The Glover patent series has resulted in several patent grants, including in Europe (EP 1230375). The European Glover patent was revoked in July 2008 during opposition proceedings and our appeal of this decision is pending. Broad claims from this patent cover dsRNAs of any length or structure as mediators of RNAi in mammalian systems. We have an exclusive license to the Glover patent for therapeutic uses from Cancer Research Technology Limited.

The Tuschl patent applications filed by Whitehead, MIT, UMass and Max Planck Gesellschaft zur Foerderung der Wissenschaften e.V. on the invention by Dr. Tuschl and his colleagues, which we call the Tuschl I patent series, cover compositions and methods important for RNAi discovery. While none of the applications in this family have been granted in the United States, the EPO granted patent EP 1309726, which has been opposed. This patent consists of 19 claims broadly covering *in vitro* RNAi methods, including methods of reducing the expression of a gene, including those of mammalian or viral origin, with dsRNAs between 21 and 23 nucleotides in length. In addition, the patent also includes claims covering methods of examining the function of a gene, as well as the use of both unmodified and chemically modified dsRNAs. This patent was opposed and claims in the main request were maintained. This ruling is under appeal. The Tuschl I series has also been granted in New Zealand (NZ 522045) and Korea (KR 08724437 and 10-0909681). We are the exclusive licensee of the ownership interests of the Max Planck Society, MIT and Whitehead in the Tuschl I patent series for RNAi therapeutics.

The Tuschl patent applications filed by Max Planck Gesellschaft zur Foerderung der Wissenschaften e.V. on the invention by Dr. Tuschl and his colleagues, which we call the Tuschl II patent series, cover what we believe are key structural features of siRNAs. Specifically, the Tuschl II patents and patent applications include claims directed to synthetic siRNAs and the use of chemical modifications to stabilize siRNAs. In June 2006, the United States Patent and Trademark Office, or USPTO, issued U.S. Patent No. 7,056,704 and in July 2006, the USPTO issued U.S. Patent No. 7,078,196, each covering methods of making dsRNAs having a 3 overhang structure. In December 2012, the USPTO granted U.S. Patent No. 8,329,463 with claims directed to *in vitro* methods of use of dsRNA of 19 to 23 nucleotides with a 3 overhang of from one to three nucleotides. In January 2013, the USPTO granted U.S. Patent No. 8,362,231 with claims directed to dsRNA compositions consisting of 19 to 23 nucleotides with a 3 overhang of from 1 to 3 nucleotides that contains at least one nucleotide analogue, and in February, 2013, the USPTO granted U.S. Patent No. 8,372,968 with claims directed to dsRNA compositions consisting of 19 to 25 nucleotides with a 3 overhang of from one to five nucleotides. In September 2007, the EPO granted broad claims for the Tuschl II patent in Europe (EP 1407044). Five parties filed Notices of Opposition in the EPO against EP 1407044. In December 2010, the Opposition Division of the EPO ruled in our favor maintaining the patent in amended form. All of the opponents have appealed the decision of the Opposition

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Division. The Japanese Patent Office has granted the Tuschl II patent in Japan (JP 4 095 895 and JP 4 494 392) and the Chinese Patent Office has granted the Tuschl II patent in China (CN 1568373). JP 4 095 895 was the subject of an Invalidation Trial which was requested by a Japanese company. The Japanese court ruled that claims directed to dsRNA of 19 to 23 nucleotides with a 3 overhang of from 1 to 3 nucleotides be maintained with the additional feature that the 3 overhang is stabilized against degradation. We have appealed the inclusion of this additional feature. We have also received grants for patents in the Tuschl II series in several other countries, as reflected in the table above. We have obtained an exclusive license to claims in the Tuschl II patent series uniquely covering the use of RNAi for therapeutic purposes.

The Fire and Mello patent owned by the Carnegie Institution covers the use of dsRNAs to induce RNAi. The Carnegie Institution has made this patent broadly available for licensing and we, like many companies, have taken a non-exclusive license to the patent for therapeutic purposes. We believe, however, that the claims of the Fire and Mello patent do not cover the structural features of dsRNAs that are important for the biological activity of siRNAs in mammalian cells. We believe that these specific features are the subjects of the Crooke, Kreutzer-Limmer, Glover and Tuschl II patents and patent applications for which we have secured exclusive rights.

The other pending patent applications listed in the table above either provide further coverage for structural features of siRNAs or relate to the use of siRNAs in mammalian cells. For some of these, we have exclusive rights, and for others, we have non-exclusive rights. In addition, in December 2008, we acquired the intellectual property assets of Nucleonics, Inc., a privately held biotechnology company. This acquisition included over 100 active patent filings, including 15 patents that have been granted worldwide, of which five have been granted in the United States and Europe. With this acquisition, we obtained patents and patent applications with early priority dates, notably the Li & Kirby, Pachuk I and Giordano patent families, that cover broad structural features of RNAi therapeutics, thus extending the breadth of our fundamental intellectual property.

Intellectual Property Related to Chemical Modifications

Our amended and restated collaboration and license agreement with Isis provides us with rights to practice the inventions covered by over 200 issued patents worldwide, as well as rights based on future chemistry patent applications through April 2014 for use with dsRNA products. These patents will expire both in and outside the United States generally between 2011 and 2029, subject to any potential patent term extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available. These inventions cover chemical modifications we may wish to incorporate into dsRNA therapeutic products designed to work through an RNAi mechanism. Under the terms of our amended and restated license agreement, Isis agreed not to grant licenses under these patents to any other organization for dsRNA products designed to work through an RNAi mechanism, except in the context of a collaboration in which Isis plays an active role.

In addition to licensing these intellectual property rights from Isis, we are also working to develop our own proprietary chemical modifications that may be incorporated into siRNAs to endow them with drug-like properties. We have filed a large number of patent applications relating to these novel and proprietary chemical modifications.

With the combination of the technology we have licensed from Isis, U.S. Patent No. 7,078,196, a patent in the Tuschl II patent series, and our own patent application filings, we possess issued claims that cover methods of making siRNAs that incorporate any of various chemical modifications, including the use of phosphorothioates, 2 -O-methyl, and/or 2 -fluoro modifications. These modifications are believed to be important for achieving drug-like properties for RNAi therapeutics. We hold exclusive worldwide rights to these claims for RNAi therapeutics.

Intellectual Property Related to the Delivery of siRNAs to Cells

We are pursuing internal research and collaborative approaches regarding the delivery of siRNAs to mammalian cells. These approaches include exploring technology that may allow delivery of siRNAs to cells through the use of cationic lipids, cholesterol and carbohydrate conjugation, peptide and antibody-based targeting, and polymer conjugations. Our collaborative efforts include working with academic and corporate

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third parties to examine specific embodiments of these various approaches to delivery of siRNAs to appropriate cell tissue, and in-licensing of the most promising technology. For example, we have obtained an exclusive license from UBC and Tekmira in the field of RNAi therapeutics to intellectual property covering cationic liposomes and their use to deliver nucleic acid to cells. The issued United States patents and foreign counterparts, including the Semple (U.S. Patent No 6,858,225) and Wheeler (U.S. Patent Nos. 5,976,567 and 6,815,432) patents, cover compositions, methods of making and methods of using cationic liposomes to deliver agents, such as nucleic acid molecules, to cells. These patents will expire both in and outside the United States on October 30, 2017, January 6, 2015 and June 7, 2015, respectively, subject to any potential patent term extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available.

In addition, in April 2012, the USPTO granted U.S. Patent No. 8,158,601, which includes 30 claims covering composition of matter and formulations of the MC3 lipid, as well as methods of using these compositions and formulations. The patent lists inventors who are, or were, our employees as well as employees of AlCana. MC3 is being utilized in our ALN-TTR02 and ALN-PCS development programs and may potentially be utilized in other development programs. We assigned this patent, amongst other patents and patent applications relating to lipids and LNP technology, to Tekmira in connection with our November 2012 restructuring and cross-license agreement. We retain rights to use this intellectual property for the research, development and commercialization of RNAi therapeutic products, including the rights to sublicense this intellectual property on a product-by-product basis. A description of our 2012 restructuring and cross-license agreement with Tekmira is set forth above under Strategic Alliances Delivery-Related Licenses and Collaborations Tekmira.

Intellectual Property Related to siRNAs Directed to Specific Targets

We have filed a number of patent applications claiming specific siRNAs directed to various gene targets that correlate to specific diseases. While there may be a significant number of competing applications filed by other organizations claiming siRNAs to treat the same gene target, we were among the first companies to focus and file on RNAi therapeutics, and thus, we believe that a number of our patent applications may predate competing applications that others may have filed. Reflecting this, in August 2005, the EPO granted a broad patent, which we call the Kreutzer-Limmer II patent, with 103 allowed claims on therapeutic compositions, methods and uses comprising siRNAs that are complementary to mRNA sequences in over 125 disease target genes. In July 2009, the EPO ruled in our favor in an opposition proceeding related to the Kreutzer-Limmer II patent. The decision has been appealed by the opponents. The Kreutzer-Limmer II patent will expire on January 9, 2022, subject to any potential patent term extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available. Some of these claimed gene targets are being pursued by our development and pre-clinical programs, such as those expressed by viral pathogens including RSV and influenza virus. In addition, the claimed targets include oncogenes, cytokines, cell adhesion receptors, angiogenesis targets, apoptosis and cell cycle targets, and additional viral disease targets, such as hepatitis C virus and HIV. The Kreutzer-Limmer II patent series is pending in the United States and many foreign countries. Moreover, a patent in the Tuschl II patent series, U.S. Patent No. 7,078,196, claims methods of preparing siRNAs that mediate cleavage of an mRNA in mammalian cells and, therefore, covers methods of making siRNAs directed toward any and all target genes. We hold exclusive worldwide rights to these claims for RNAi therapeutics.

In addition, during 2011, the USPTO declared an interference between our issued patent covering ALN-VSP, our RNAi therapeutic undergoing clinical testing for the treatment of liver cancers, and a pending third-party application assigned to Protiva. In connection with the settlement of all outstanding litigation with Tekmira in November of 2012, the interference was settled and the Protiva application was assigned to us. A description of our settlement with Tekmira is set forth in Part I, Item 3, Legal Proceedings, of this annual report on Form 10-K.

With respect to specific siRNAs, we believe that patent coverage will result from demonstrating that particular compositions exert suitable biological and therapeutic effects. Accordingly, we are focused on achieving such demonstrations for siRNAs in key therapeutic programs.

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Intellectual Property Related to Our Development Candidates

As our development pipeline matures, we have made and plan to continue to make patent filings that claim all aspects of our development candidates, including dose, method of administration and manufacture.

Intellectual Property Challenges

As the field of RNAi therapeutics is maturing, patent applications are being fully processed by national patent offices around the world. There is uncertainty about which patents will issue, and, if they do, as to when, to whom, and with what claims. It is likely that there will be significant litigation and other proceedings, such as interference, reexamination and opposition proceedings, in various patent offices relating to patent rights in the RNAi field. For example, as noted above, various third parties have initiated oppositions to patents in our Kreutzer-Limmer and Tuschl II series in the EPO, as well as in other jurisdictions. We expect that additional oppositions will be filed in the EPO and elsewhere, and other challenges will be raised relating to other patents and patent applications in our portfolio. In many cases, the possibility of appeal exists for either us or our opponents, and it may be years before final, unappealable rulings are made with respect to these patents in certain jurisdictions. 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. A description of ongoing legal matters relating to certain aspects of our intellectual property portfolio is set forth in Part I, Item 3, Legal Proceedings, of this annual report on Form 10-K.

Competition

The pharmaceutical marketplace is extremely competitive, with hundreds of companies competing to discover, develop and market new drugs. We face a broad spectrum of current and potential competitors, ranging from very large, global pharmaceutical companies with significant resources, to other biotechnology companies with resources and expertise comparable to our own and to smaller biotechnology companies with fewer resources and expertise than we have. We believe that for most or all of our drug development programs, there will be one or more competing programs under development at other companies. In many cases, the companies with competing programs will have access to greater resources and expertise than we do and may be more advanced in those programs.

The competition we face can be grouped into three broad categories:

- other companies working to develop RNAi and microRNA therapeutic products;
- companies developing technology known as antisense, which, like RNAi, attempts to silence the activity of specific genes by targeting the mRNAs copied from them; and
- marketed products and development programs for therapeutics that treat the same diseases for which we may also be developing treatments.

We are aware of several other companies that are working to develop RNAi therapeutic products. Some of these companies are seeking, as we are, to develop chemically synthesized siRNAs as drugs. Others are following a gene therapy approach, with the goal of treating patients not with synthetic siRNAs but with synthetic, exogenously-introduced genes designed to produce siRNA-like molecules within cells.

Companies working on chemically synthesized siRNAs include Merck, through its subsidiary Sirna Therapeutics, Inc., or Sirna, Novartis, Takeda, Kyowa Hakko Kirin, Marina Biotech, Inc., Arrowhead and its subsidiary, Calando, Quark, Silence Therapeutics plc, Tekmira, Sylentis and Dicerna Pharmaceuticals, Inc. Many of these companies have licensed our intellectual property. Benitec is working on gene therapy approaches to RNAi therapeutics.

Companies working on microRNA therapeutics include Rosetta Genomics, Santaris Pharma A/S, or Santaris, miRagen Therapeutics, Inc., Mirna Therapeutics, Inc. and Asuragen, Inc.

Antisense technology uses short, single-stranded, DNA-like molecules to block mRNAs encoding specific proteins. While we believe that RNAi drugs may potentially have significant advantages over antisense

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oligonucleotides, or ASOs, including greater potency and specificity, others are developing ASO drugs that are currently at a more advanced stage of development than RNAi drugs. For example, Isis has developed an ASO drug, Vitravene®, which was approved by the FDA in 1998, but is no longer available in the U.S. Isis also has several ASO product candidates in clinical development, including mipomersen, which is a lipid-lowering drug being developed by Isis in collaboration with Genzyme. In December 2012, the Committee for Medicinal Products for Human Use, or CHMP, recommended against approval of the drug in Europe for familial hypercholesterolemia. In January 2013, the FDA approved mipomersen for the treatment of patients with homozygous familial hypercholesterolemia, or HoFH. In addition, a number of other companies have product candidates in various stages of pre-clinical and clinical development. Included in these companies are Santaris and AVI BioPharma, Inc. Because of their later stage of development, ASOs, rather than siRNAs, may become the preferred technology for drugs that target mRNAs in order to turn off the activity of specific genes.

The competitive landscape continues to expand and we expect that additional companies will initiate programs focused on the development of RNAi therapeutic products using the approaches described above as well as potentially new approaches that may result in the more rapid development of RNAi therapeutics or more effective technologies for RNAi drug development or delivery.

Competing Drugs for Our RNAi Therapeutics in Clinical Development

TTR-Mediated Amyloidosis (ATTR). Until recently, liver transplantation was the only available treatment option for FAP. Only a subset of FAP patients with early stage disease qualify for this costly and invasive procedure and, even following liver transplantation, the disease continues to progress for many patients, presumably due to normal TTR being deposited into preexisting fibrils. Moreover, there is a shortage of donors to provide healthy livers for transplantation. In November 2011, Pfizer received marketing approval from the EC for tafamidis for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. Tafamidis has orphan drug status in the EU for the treatment of FAP associated with ATTR. Tafamidis is intended to stabilize wild-type and variant TTR, to prevent dissociation of the TTR protein and thereby inhibit the formation of TTR oligomers and amyloid fibrils. The only currently available treatments for FAC are aimed at relief of symptoms, such as diuretics, or water pills, to treat the swelling of the ankles, one of the symptoms of FAC.

There are a few drugs in clinical development for the treatment of ATTR. Researchers at Boston University, in collaboration with the National Institute of Neurological Disorders and Stroke, are currently conducting a Phase II/III clinical trial for diflunisal for the treatment of FAP. Diflunisal is a commercially available non-steroidal anti-inflammatory agent that has been found to stabilize TTR *in vitro*. In addition, Isis, together with its partner GSK, is developing ISIS-TTR_{Rx}, an ASO designed to treat patients with FAP. Isis has completed a Phase I clinical trial evaluating the safety and activity of six subcutaneous doses of ISIS-TTR_{Rx} over four weeks in healthy volunteers. Isis reported that in this clinical trial, ISIS-TTR_{Rx} produced significant reductions of approximately 80% in TTR protein at the highest dose studied, and reported that ISIS-TTR_{Rx} was generally well tolerated with no significant adverse events, although Isis has also reported the occurrence of injection site reactions and flu-like symptoms for ISIS-TTR_{Rx}. Isis has announced that ISIS-TTR_{Rx} was granted fast track designation by the FDA for the treatment of patients with FAP, and that it is planning to initiate a Phase II/III clinical trial in the first quarter of 2013.

Hypercholesterolemia. The current standard of care for patients with hypercholesterolemia includes the use of several agents. Front line therapy consists of HMG CoA reductase inhibitors, commonly known as statins, which block production of cholesterol by the liver and increase clearance of LDL-c from the bloodstream. These include atorvastatin, simvastatin, rosuvastatin and pravastatin. A different class of compounds, which includes ezetimibe and ezetimibe/simvastatin, function by blocking cholesterol uptake from the diet and are utilized on their own or in combination with statins. Aegerion Pharmaceuticals, Inc. is developing lomitapide, an microsomal triglyceride protein, or MTP, inhibitor for the treatment of dyslipidemia. In December 2012, the FDA approved lomitapide for use in patients with homozygous familial hypercholesterolemia.

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With regard to future therapies in clinical development, mipomersen is a lipid-lowering drug targeting apolipoprotein B-100 being developed by Isis in collaboration with Genzyme. In July 2011, Genzyme submitted a marketing authorization application for mipomersen in Europe. In December 2012, the CHMP recommended against approval of the drug in Europe for familial hypercholesterolemia. In January 2013, the FDA approved mipomersen for the treatment of patients with HoFH.

Isis and Genzyme have evaluated mipomersen in four positive Phase III clinical trials in which its primary endpoints were met. In all four Phase III clinical trials, treatment with mipomersen lowered LDL-c and had a beneficial impact on other atherogenic lipids. A weekly injectable therapeutic, mipomersen is being developed primarily for patients at significant cardiovascular risk who are unable to achieve target cholesterol lowering levels with statins alone or who are intolerant of statins. In addition, several anti-PCSK9 antibodies have advanced into clinical development, including REGN727/SAR236553, which is being developed by Regeneron Pharmaceuticals, Inc., or Regeneron, in collaboration with Sanofi. Data reported from one REGN727/SAR236553 Phase II clinical trial in patients with severe hypercholesterolemia have demonstrated mean reductions in LDL-c from baseline ranging from approximately 30% to greater than 65% depending on the dosing regimen of REGN727/SAR236553 compared to a mean reduction of 10% with placebo ($p<0.05$ for all dose groups). Regeneron announced the launch of ODYSSEY OUTCOMES, an 18,000 patient Phase III clinical trial designed to test the efficacy and safety of REGN727 added to maximal doses of statins in reducing cardiovascular morbidity and mortality in patients with recent acute coronary syndrome, a population at high risk of cardiovascular events despite best contemporary therapy. Amgen Inc., Eli Lilly and Company and Pfizer also have anti-PCSK9 antibodies in clinical development and we are aware of several additional similar compounds in advanced pre-clinical development.

RSV. The only product currently approved for the treatment of RSV infection is ribavirin, which is marketed by Valeant. This is approved only for treatment of hospitalized infants and young children with severe lower respiratory tract infections due to RSV. While it is also used to treat RSV infection in lung transplant patients, no randomized controlled trials of ribavirin have been conducted in the lung transplant patient population. Ribavirin has been reported to have limited efficacy and limited anti-viral activity against RSV. Moreover, administration of inhaled ribavarin is complicated and requires elaborate environmental reclamation devices because of potential harmful effects on health care personnel exposed to the drug.

Other current RSV therapies consist of primarily treating the symptoms or preventing the viral infection in premature infants by using the prophylactic drug palivizumab, which is marketed by MedImmune, LLC, the worldwide biologics unit for AstraZeneca PLC. Palivizumab is a neutralizing monoclonal antibody that prevents the virus from infecting the cell by blocking the RSV F protein. Palivizumab is injected intramuscularly to premature infants once a month during the RSV season to prevent infection. MedImmune has also initiated a Phase I/IIa clinical trial of a live, attenuated intranasal vaccine in development to help prevent severe RSV infections and has several ongoing Phase I clinical trials to evaluate a second live, attenuated intranasal vaccine in development to help prevent severe lower respiratory tract disease caused by RSV or parainfluenza virus 3.

Liver Cancer. There are a variety of surgical procedures, chemotherapeutics, radiation and other approaches that are used in the management of both primary and secondary liver cancer. However, for the majority of patients the prognosis remains poor with fatal outcomes within several months of diagnosis. In November 2007, the United States Food and Drug Administration, or FDA approved sorafenib for the treatment of un-resectable liver cancer. Sorafenib is the product of Onyx Pharmaceuticals, Inc., developed in collaboration with Bayer Pharmaceuticals Corporation.

There are also a large number of drugs in various stages of clinical development as cancer therapeutics, although the efficacy and safety of these newer drugs are difficult to ascertain at this point of development.

Other Competition

Finally, for many of the diseases that are the subject of our RNAi therapeutics pre-clinical development and discovery programs, there are already drugs on the market or in development. However, notwithstanding the availability of these drugs or drug candidates, we believe there currently exists sufficient unmet medical need to warrant the advancement of RNAi therapeutic programs.

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Regulatory Matters

The research, testing, manufacture and marketing of drug products and their delivery systems are extensively regulated in the United States and the rest of the world. In the United States, drugs are subject to rigorous regulation by the FDA. The Federal Food, Drug, and Cosmetic Act and other federal and state statutes and regulations govern, among other things, the research, development, testing, approval, manufacture, storage, record keeping, reporting, packaging, labeling, promotion and advertising, marketing and distribution of pharmaceutical products. Failure to comply with the applicable regulatory requirements may subject a company to a variety of administrative or judicially-imposed sanctions and the inability to obtain or maintain required approvals to test or market drug products. These sanctions could include, among other things, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, clinical holds, injunctions, fines, civil penalties or criminal prosecution.

The steps ordinarily required before a new pharmaceutical product may be marketed in the United States include non-clinical laboratory tests, animal tests and formulation studies, the submission to the FDA of an IND, which must become effective prior to commencement of clinical testing, approval by an independent review board, or IRB, at each clinical site before each trial may be initiated, completion of adequate and well-controlled clinical trials to establish that the drug product is safe and effective for the indication for which FDA approval is sought, submission to the FDA of an NDA, review and recommendation by an advisory committee of independent experts (particularly for new chemical entities), satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with current good manufacturing practice, or cGMP, requirements, satisfactory completion of an FDA inspection of the major investigational sites to ensure data integrity and assess compliance with good clinical practices, or GCP, requirements, and FDA review and approval of the NDA. Satisfaction of FDA pre-market approval requirements typically takes several years, but may vary substantially depending upon the complexity of the product and the nature of the disease. Government regulation may delay or prevent marketing of potential products for a considerable period of time and impose costly procedures on a company s activities. Success in early stage clinical trials does not necessarily assure success in later stage clinical trials. Data obtained from clinical activities, including the data derived from our clinical trials for ALN-TTR01, ALN-TTR02, ALN-TTRsc, ALN-PCS, ALN-RSV01 and ALN-VSP, is not always conclusive and may be subject to alternative interpretations that could delay, limit or even prevent regulatory approval. Even if a product receives regulatory approval, later discovery of previously unknown problems with a product, including new safety risks, may result in restrictions on the product or even complete withdrawal of the product from the market.

Non-clinical tests include laboratory evaluation of product chemistry and formulation, as well as animal testing to assess the potential safety and efficacy of the product. The conduct of the non-clinical tests and formulation of compounds for testing must comply with federal regulations and requirements. The results of non-clinical testing are submitted to the FDA as part of an IND, together with manufacturing information, analytical and stability data, a proposed clinical trial protocol and other information.

A 30-day waiting period after the filing of an IND is required prior to such application becoming effective and the commencement of clinical testing in humans. If the FDA has not commented on, or questioned, the application during this 30-day waiting period, clinical trials may begin. If the FDA has comments or questions, these must be resolved to the satisfaction of the FDA prior to commencement of clinical trials. The IND review process can result in substantial delay and expense. We, an IRB, or the FDA may, at any time, suspend, terminate or impose a clinical hold on ongoing clinical trials. If the FDA imposes a clinical hold, clinical trials cannot commence or recommence without FDA authorization and then only under terms authorized by the FDA.

Clinical trials involve the administration of an investigational new drug to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted in compliance with federal regulations and requirements, including GCPs, under protocols detailing, among other things, the objectives of the trial and the safety and effectiveness criteria to be evaluated. Each protocol involving testing on human subjects in the United States must be submitted to the FDA as part of the IND. In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it

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commences at that institution, and the IRB must conduct continuing review. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations.

Clinical trials to support NDAs for marketing approval are typically conducted in three sequential phases, which may overlap or be combined. In Phase I, the initial introduction of the drug into healthy human subjects or patients, the drug is tested to primarily assess safety, tolerability, pharmacokinetics, pharmacological actions and metabolism associated with increasing doses. Phase II usually involves trials in a limited patient population, to assess the optimum dosage, identify possible adverse effects and safety risks, and provide preliminary support for the efficacy of the drug in the indication being studied.

If a compound demonstrates evidence of effectiveness and an acceptable safety profile in Phase II clinical trials, Phase III clinical trials may be undertaken to further evaluate clinical efficacy and to further test for safety in an expanded patient population, typically at geographically dispersed clinical trial sites, to establish the overall benefit-risk relationship of the drug and to provide adequate information for the labeling of the drug. Phase I, Phase II or Phase III testing of any drug candidates may not be completed successfully within any specified time period, if at all. The FDA closely monitors the progress of each of the three phases of clinical trials that are conducted in the United States. The FDA may, at its discretion, reevaluate, alter, suspend or terminate the testing based upon the data accumulated to that point and the FDA s assessment of the risk/benefit ratio to the subject. The FDA, an IRB, or a clinical trial sponsor may suspend or terminate clinical trials at any time for various reasons, including a finding that the subjects or patients are being exposed to an unacceptable health risk. The FDA can also request that additional clinical trials be conducted as a condition to product approval. Finally, sponsors are required to publicly disseminate information about ongoing and completed clinical trials on a government website administered by the National Institutes of Health, or NIH, and are subject to civil monetary penalties and other civil and criminal sanctions for failing to meet these obligations. After successful completion of the required clinical testing, generally an NDA is prepared and submitted to the FDA.

We believe that any RNAi product candidate we develop, whether for the treatment of ATTR, hemophilia and RBD, AIP, hypercholesterolemia, hemoglobinopathies, including beta-thalassemia, RSV, liver cancers, HD or the various indications targeted in our pre-clinical discovery programs, will be regulated as a new drug by the FDA. FDA approval of an NDA is required before marketing of a new drug may begin in the United States. The NDA must include the results of extensive pre-clinical, clinical and other testing, as described above, a compilation of data relating to the product s pharmacology, chemistry, manufacture and controls, proposed labeling and other information. In addition, an NDA for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must contain data assessing the safety and efficacy for the claimed indication in all relevant pediatric subpopulations, and support dosing and administration for each pediatric subpopulation for which the drug is shown to be safe and effective. In some circumstances, the FDA may grant deferrals for the submission of some or all pediatric data, or full or partial waivers. The cost of preparing and submitting an NDA is substantial. Under federal law, NDAs are subject to substantial application user fees and the sponsor of an approved NDA is also subject to annual product and establishment user fees.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission before accepting them for filing to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. Once the submission is accepted for filing, the FDA begins an in-depth review of the NDA. The FDA has agreed to specified performance goals regarding the timing of its review of NDAs, although the FDA does not always meet these goals. The review process is often significantly extended by FDA requests for additional information or clarification regarding information already provided in the submission. The FDA may also refer applications for novel drug products or drug products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. The FDA normally also will conduct a pre-approval inspection to ensure the manufacturing facility, methods and controls are adequate to preserve the drug s identity, strength, quality, purity and stability, and are in compliance with regulations governing cGMPs. In addition, the FDA often will conduct

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a bioresearch monitoring inspection of the clinical trial sites involved in conducting pivotal studies to ensure data integrity and compliance with applicable GCP requirements.

If the FDA evaluation of the NDA and the inspections of manufacturing facilities and clinical trial sites are favorable, the FDA may issue an approval letter, which authorizes commercial marketing of the drug with specific prescribing information for a specific indication. As a condition of NDA approval, the FDA may require post-approval testing, including Phase IV trials, and surveillance to monitor the drug s safety or efficacy and may impose other conditions, including labeling restrictions, which can materially impact the potential market and profitability of the drug. In addition, the FDA may impose distribution and use restrictions and other limitations on labeling and communication activities with respect to an approved drug product through a Risk Evaluation and Mitigation Strategy, or REMS, plan. Once granted, product approvals may be further limited or withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

While we believe that any RNAi therapeutic we develop will be regulated as a new drug under the Federal Food, Drug, and Cosmetic Act, the FDA may decide to regulate certain RNAi therapeutic products as biologics under the Public Health Service Act. Biologics must have a biologics license application, or BLA, approved prior to commercialization. Like NDAs, BLAs are subject to user fees. To obtain BLA approval, an applicant must provide non-clinical and clinical evidence and other information to demonstrate that the biologic product is safe, pure and potent, and like NDAs, must complete clinical trials that are typically conducted in three sequential phases (Phase I, II and III). Additionally, the applicant must demonstrate that the facilities in which the product is manufactured, processed, packaged or held meet standards, including cGMPs and any additional standards in the license designed to ensure its continued safety, purity and potency. Biologics establishments are subject to pre-approval inspections. The review process for BLAs is also time consuming and uncertain, and BLA approval may be conditioned on post-approval testing and surveillance and subject to distribution and use restrictions, or other limitations, through a REMS plan. Once granted, BLA approvals may be suspended or revoked under certain circumstances, such as if the product fails to conform to the standards established in the license.

Once an NDA or BLA is approved, a product will be subject to certain post-approval requirements, including requirements for adverse event reporting, submission of periodic reports, recordkeeping, product sampling and distribution. Additionally, the FDA also strictly regulates the promotional claims that may be made about prescription drug products and biologics. In particular, the FDA generally prohibits pharmaceutical companies from promoting their drugs or biologics for uses that are not approved by the FDA as reflected in the product s approved labeling, although recent court decisions suggest that such promotion may be protected speech under the First Amendment in certain circumstances. In addition, the FDA requires substantiation of any safety or effectiveness claims, including claims that one product is superior in terms of safety or effectiveness to another. Superiority claims generally must be supported by two adequate and well-controlled head-to-head clinical trials. To the extent that market acceptance of our products may depend on their superiority over existing therapies, any restriction on our ability to advertise or otherwise promote claims of superiority, or requirements to conduct additional expensive clinical trials to provide proof of such claims, could negatively affect the sales of our products or our costs. We must also notify the FDA of any change in an approved product beyond variations already allowed in the approval. Certain changes to the product, its labeling or its manufacturing require prior FDA approval and may require the conduct of further clinical investigations to support the change, which may require the payment of additional, substantial user fees. Such approvals may be expensive and time-consuming and, if not approved, the FDA will not allow the product to be marketed as modified.

If the FDA s evaluation of the NDA or BLA submission or manufacturing facilities is not favorable, the FDA may refuse to approve the NDA or BLA or issue a complete response letter. The complete response letter describes the deficiencies that the FDA has identified in an application and, when possible, recommends actions that the applicant might take to place the application in condition for approval. Such actions may include, among other things, conducting additional safety or efficacy studies after which the sponsor may resubmit the application for further review. Even with the completion of this additional testing or the submission of additional requested information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. With limited exceptions, the FDA may withhold approval of an NDA or BLA regardless of prior advice it may have provided or commitments it may have made to the sponsor.

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Some of our product candidates may need to be administered using specialized drug delivery systems. We may rely on drug delivery systems that are already approved to deliver drugs like ours to similar physiological sites or, in some instances, we may need to modify the design or labeling of the legally available device for delivery of our product candidate. In such an event, the FDA may regulate the product as a combination product or require additional approvals or clearances for the modified device. In addition, to the extent the delivery device is owned by another company, we would need that company s cooperation to implement the necessary changes to the device and to obtain any additional approvals or clearances. Obtaining such additional approvals or clearances, and cooperation of other companies, when necessary, could significantly delay, and increase the cost of obtaining marketing approval, which could reduce the commercial viability of a product candidate. To the extent that we rely on previously unapproved drug delivery systems, we may be subject to additional testing and approval requirements from the FDA above and beyond those described above.

Once an NDA is approved, the product covered thereby becomes a listed drug that can, in turn, be relied upon by potential competitors in support of approval of an abbreviated new drug application, or ANDA, or 505(b)(2) application upon expiration of certain patent and non-patent exclusivity periods, if any. An approved ANDA generally provides for marketing of a drug product that has the same active ingredients in the same strength, dosage form and route of administration as the listed drug and has been shown through appropriate testing (unless waived) to be bioequivalent to the listed drug. There is no requirement, other than the requirement for bioequivalence testing (which may be waived by the FDA), for an ANDA applicant to conduct or submit results of non-clinical or clinical tests to prove the safety or effectiveness of its drug product. Drugs approved in this way are commonly referred to as generic equivalents to the listed drug, are listed as such by the FDA and can often be substituted by pharmacists under prescriptions written for the original listed drug. A 505(b)(2) application is a type of NDA that relies, in part, upon data the applicant does not own and to which it does not have a right of reference. Such applications typically are submitted for changes to previously approved drug products.

Federal law provides for a period of three years of exclusivity following approval of a listed drug that contains a previously approved active ingredient but is approved in, among other things, a new dosage, dosage form, route of administration or combination, or for a new use, if the FDA determines that new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are essential to the approval of the application. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations and, as a general matter, does not prohibit the FDA from approving ANDAs or 505(b)(2) applications for generic versions of the original, unmodified drug product. Federal law also provides a period of up to five years exclusivity following approval of a drug containing no previously approved active moiety, which is the molecule or ion responsible for the action of the drug substance, during which ANDAs and 505(b)(2) applications referencing the protected listed drug cannot be submitted unless the submission accompanies a challenge to a listed patent, in which case the submission may be made four years following the original product approval. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the pre-clinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Additionally, in the event that the sponsor of the listed drug has properly informed the FDA of patents covering its listed drug, applicants submitting an ANDA or 505(b)(2) application referencing the listed drug are required to make one of four patent certifications for each listed patent, except for patents covering methods of use for which the ANDA or 505(b)(2) applicant is not seeking approval. If an applicant certifies its belief that one or more listed patents are invalid, unenforceable, or not infringed (and thereby indicates it is seeking approval prior to patent expiration), it is required to provide notice of its filing to the NDA sponsor and the patent holder within certain time limits. If the patent holder then initiates a suit for patent infringement against the ANDA or 505(b)(2) applicant within 45 days of receipt of the notice, the FDA cannot grant effective approval of the ANDA or 505(b)(2) application until either 30 months have passed or there has been a court decision or settlement order holding or stating that the patents in question are invalid, unenforceable or not infringed. If the patent holder does not initiate a suit for patent infringement within the 45 days, the ANDA or 505(b)(2) application may be approved immediately upon successful completion of FDA review, unless blocked by another

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listed patent or regulatory exclusivity period. If the ANDA or 505(b)(2) applicant certifies that it does not intend to market its generic product before some or all listed patents on the listed drug expire, then the FDA cannot grant effective approval of the ANDA or 505(b)(2) application until those patents expire. The first of the ANDA applicants submitting substantially complete applications certifying that one or more listed patents for a particular product are invalid, unenforceable, or not infringed may qualify for an exclusivity period of 180 days running from when the generic product is first marketed, during which subsequently submitted ANDAs containing similar certifications cannot be granted effective approval. The 180-day generic exclusivity can be forfeited in various ways, including if the first applicant does not market its product within specified statutory timelines. If more than one applicant files a substantially complete ANDA on the same day, each such first applicant will be entitled to share the 180-day exclusivity period, but there will only be one such period, beginning on the date of first marketing by any of the first applicants.

In addition, once a BLA is approved, the product covered thereby becomes a reference product that can, in turn, be relied upon by potential competitors in support of approval of an abbreviated BLA following periods of data and marketing exclusivity. Biological products that are considered to be reference products are granted two overlapping periods of data and marketing exclusivity: a four-year period during which no abbreviated BLA relying upon the reference product may be submitted, and a twelve-year period during which no abbreviated BLA relying upon the reference product may be approved by FDA. For purposes of the Public Health Service Act, a reference product is defined as the single biological product licensed under [a full BLA] against which a biological product is evaluated in an application submitted under [an abbreviated BLA]. We believe that if our products are approved via BLAs, they will be considered to be reference products that are entitled to both four-year and twelve-year exclusivity. The FDA, however, has not issued any regulations or final guidance explaining how it will implement the abbreviated BLA provisions, including the exclusivity provisions for reference products. It is thus possible that the FDA will decide to interpret the provisions in such a way that our products are not considered to be reference products for purposes of the statute or to be entitled to any period of data or marketing exclusivity. Even if our products are considered to be reference products eligible for exclusivity, other companies nevertheless could market competing versions of such biological products if such companies can complete, and FDA permits the submission of and approves, full BLAs with complete human clinical data packages for such products,

Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for this type of disease or condition will be recovered from sales in the United States for that drug. Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA.

If a product that has orphan drug designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications, including a full NDA or BLA, to market the same drug for the same indication, except in very limited circumstances, for seven years. For purposes of small molecule drugs, the FDA defines same drug as a drug that contains the same active moiety and is intended for the same use as the previously approved orphan drug. For purposes of large molecule drugs, the FDA defines same drug as a drug that contains the same principal molecular structural features, but not necessarily all of the same structural features, and is intended for the same use as the drug in question. Notwithstanding the above definitions, a drug that is clinically superior to an orphan drug will not be considered the same drug and thus will not be blocked by orphan drug exclusivity.

A designated orphan drug may not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. In addition, orphan drug exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the drug to meet the needs of patients with the rare disease or condition.

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The FDA also administers a clinical research grants program, whereby researchers may compete for funding to conduct clinical trials to support the approval of drugs, biologics, medical devices and medical foods for rare diseases and conditions. An application for an orphan grant should propose one discrete clinical trial to facilitate FDA approval of the product for a rare disease or condition. The study may address an unapproved new product or an unapproved new use for a product already on the market. The future availability of such grants is subject to uncertainties regarding continued federal funding.

From time to time, legislation is drafted and introduced in Congress that could significantly change the statutory provisions governing the approval, manufacturing and marketing of drug products. In addition, FDA regulations and guidance are often revised or reinterpreted by the agency or reviewing courts in ways that may significantly affect our business and development of our product candidates and any products that we may commercialize. It is impossible to predict whether additional legislative changes will be enacted, or FDA regulations, guidance or interpretations changed, or what the impact of any such changes may be. Federal budget uncertainties or spending reductions may reduce the capabilities of the FDA, extend the duration of required regulatory reviews, and reduce the availability of clinical research grants.

Foreign Regulation of New Drug Compounds

In addition to regulations in the United States, we are subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of our products.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in all or most foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application, or CTA, much like the IND prior to the commencement of human clinical trials. In Europe, for example, a CTA must be submitted to each country s national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the CTA is approved in accordance with a country s requirements, clinical trial development may proceed. Similarly, all clinical trials in Australia require review and approval of clinical trial proposals by an ethics committee, which provides a combined ethical and scientific review process.

The requirements and process governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical trials must be conducted in accordance with GCP, which have their origin in the World Medical Association s Declaration of Helsinki, the applicable regulatory requirements, and guidelines developed by the International Conference on Harmonization, or ICH, for GCP practices in clinical trials.

The approval procedure also varies among countries and can involve requirements for additional testing. The time required may differ from that required for FDA approval and may be longer than that required to obtain FDA approval. Although there are some procedures for unified filings in the EU, in general, each country has its own procedures and requirements, many of which are time consuming and expensive. Thus, there can be substantial delays in obtaining required approvals from foreign regulatory authorities after the relevant applications are filed.

In Europe, marketing authorizations may be submitted under a centralized or decentralized procedure. The centralized procedure is mandatory for the approval of biotechnology and many pharmaceutical products and provides for the grant of a single marketing authorization that is valid in all EU member states. The decentralized procedure is a mutual recognition procedure that is available at the request of the applicant for medicinal products that are not subject to the centralized procedure. We strive to choose the appropriate route of European regulatory filing to accomplish the most rapid regulatory approvals. However, our chosen regulatory strategy may not secure regulatory approvals on a timely basis or at all.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

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Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any drug products for which we obtain regulatory approval. In the United States and markets in other countries, sales of any products for which we may receive regulatory approval for commercial sale will depend in part on the availability of reimbursement from third-party payors. Third-party payors include government health administrative authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payor will provide coverage for a drug product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the drug product. Third-party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drugs for a particular indication. Third-party payors may provide coverage, but place stringent limitations on such coverage, such as requiring alternative treatments to be tried first. These third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. In addition, significant uncertainty exists as to the reimbursement status of newly approved healthcare product candidates. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to incurring the costs required to obtain FDA approvals. Our product candidates may not be considered medically reasonable or necessary or cost-effective. Even if a drug product is covered, a payor s decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

Federal, state and local governments in the United States continue to consider legislation to limit the growth of healthcare costs, including the cost of prescription drugs. Future legislation could limit payments for pharmaceuticals such as the drug candidates that we are developing.

Different pricing and reimbursement schemes exist in other countries. In the EU, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate systems under which products may be marketed only after a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other member states allow companies to set their own prices for medicines, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert competitive pressure that may reduce pricing within a country.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, the emphasis on managed care in the United States has increased and we expect will continue to exert downward pressure on pharmaceutical pricing. Coverage policies, third-party reimbursement rates and pharmaceutical pricing regulations may change at any time. In particular, the Patient Protection and Affordable Care Act, or PPACA, and a related reconciliation bill were enacted in the United States in March 2010, and contain provisions that may reduce the profitability of pharmaceutical products, including, for example, increased rebates for drugs reimbursed by Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries, and annual fees based on pharmaceutical companies share of sales to federal health care programs. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Hazardous Materials

Our research and development processes involve the controlled use of hazardous materials, chemicals and radioactive materials and produce waste products. We are subject to federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposal of hazardous materials and waste products. We do not expect the cost of complying with these laws and regulations to be material.

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Manufacturing

To date, we have manufactured only limited supplies of drug substance for use in IND-enabling toxicology studies in animals at our own facility and have contracted with several third-party contract manufacturing organizations for the supply of drug substance and finished product to meet our testing needs for pre-clinical toxicology and clinical testing. We expect to continue to rely on third-party contract manufacturing organizations for the supply of drug substance and certain drug product, including siRNAs and siRNA conjugates, for our product candidates for the foreseeable future. In November 2012, we elected to buy out our manufacturing obligations to TPC with respect to our LNP-based pipeline programs. Pursuant to the terms of the 2012 cross-license agreement with Tekmira, we made a one-time payment of $30.0 million to Tekmira for the termination of, and our release from, all of our obligations under the manufacturing agreement, including without limitation the obligations to obtain materials and/or services from TPC. We also have the right to manufacture and have manufactured our LNP-based RNAi therapeutics, which right may be sublicensed to our collaborators. During 2012, we established a manufacturing facility and have developed cGMP capabilities and processes for the manufacture of ALN-TTR02 formulated finished drug product for Phase III clinical trials and early commercial use. We expect to manufacture late stage clinical and early stage commercial supply for ALN-TTR02 in our facility. In the future, we may also develop our own capabilities to manufacture drug substance, including siRNAs and siRNA conjugates for human clinical use. Commercial quantities of any drugs that we may seek to develop will have to be manufactured in facilities, and by processes, that comply with FDA regulations and other federal, state and local regulations, as well as comparable foreign regulations.

We believe we have sufficient manufacturing capacity through our third-party contract manufacturers and our internal manufacturing facility to meet our current research and clinical needs. We believe that the supply capacity we have established externally, together with the internal capacity we developed during 2012 to support clinical trials, will be sufficient to meet our anticipated needs. We also believe that with reasonably anticipated benefits from increases in scale and improvements in chemistry, we will be able to manufacture our product candidates at commercially competitive prices.

Scientific Advisors

We seek advice from our scientific advisory board, which consists of a number of leading scientists and physicians, on scientific and medical matters. Our scientific advisory board meets regularly to assess:

- our research and development programs;
- the design and implementation of our clinical programs;
- our patent and publication strategies;
- new technologies relevant to our research and development programs; and
- specific scientific and technical issues relevant to our business.

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The current members of our scientific advisory board are:

Name	Position/Institutional Affiliation
Dennis A. Ausiello, M.D.	Jackson Professor of Clinical Medicine/Harvard Medical School; Chief of Medicine/Massachusetts General Hospital
David P. Bartel, Ph.D.	Member/Whitehead Institute for Biomedical Research; Professor/Massachusetts Institute of Technology; Investigator/Howard Hughes Medical Institute
Robert S. Langer, Ph.D.	Institute Professor/Massachusetts Institute of Technology
Judy Lieberman, M.D., Ph.D.	Senior Investigator/Immune Disease Institute Harvard Medical School; Professor/Harvard Medical School
Paul R. Schimmel, Ph.D.	Ernest and Jean Hahn Professor/Skaggs Institute for Chemical Biology, The Scripps Research Institute
Phillip A. Sharp, Ph.D.	Institute Professor/The Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology
Daniel J. Rader, M.D.	Professor of Medicine and Chief, Division of Translational Medicine and Human Genetics/Perelman School of Medicine, University of Pennsylvania
Markus Stoffel, M.D., Ph.D.	Professor/Institute of Molecular Systems Biology, Swiss Federal Institute of Technology (ETH) Zurich
Thomas H. Tuschl, Ph.D.	Professor/Rockefeller University; Investigator/Howard Hughes Medical Institute
Phillip D. Zamore, Ph.D.	Gretchen Stone Cook Professor/University of Massachusetts Medical School; Co-Director/RNAi Therapeutics Institute, University of Massachusetts Medical School; Investigator/Howard Hughes Medical Institute

Employees

At January 31, 2013, we had 129 employees, 107 of whom were engaged in research and development. None of our employees are represented by a labor union or covered by a collective bargaining agreement, nor have we experienced work stoppages. We believe that relations with our employees are good.

Financial Information About Geographic Areas

See the section entitled Segment Information appearing in Note 2 to our consolidated financial statements for financial information about geographic areas. The Notes to our consolidated financial statements are contained in Part II, Item 8, Financial Statements and Supplementary Data, of this annual report on Form 10-K.

Corporate Information

The company comprises four entities, Alnylam Pharmaceuticals, Inc. and three wholly owned subsidiaries (Alnylam U.S., Inc., Alnylam Europe AG and Alnylam Securities Corporation). Alnylam Pharmaceuticals, Inc. is a Delaware corporation that was formed in May 2003. Alnylam U.S., Inc. is also a Delaware corporation that was formed in June 2002. Alnylam Securities Corporation is a Massachusetts corporation that was formed in December 2006. Alnylam Europe AG, which was incorporated in Germany in June 2000 under the name Ribopharma AG, was acquired by Alnylam Pharmaceuticals, Inc. in July 2003. Our principal executive office is located at 300 Third Street, Cambridge, Massachusetts 02142, and our telephone number is (617) 551-8200.

Investor Information

We maintain an internet website at http://www.alnylam.com. The information on our website is not incorporated by reference into this annual report on Form 10-K and should not be considered to be a part of this annual report on Form 10-K. Our website address is included in this annual report on Form 10-K as an inactive technical reference only. Our reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, including our annual reports on Form 10-K, our quarterly reports on Form 10-Q and our current reports on Form 8-K, and amendments to those reports, are accessible through our website, free of charge, as soon as reasonably practicable after these reports are filed electronically with, or

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otherwise furnished to, the SEC. We also make available on our website the charters of our audit committee, compensation committee, nominating and corporate governance committee, and science and technology committee, as well as our corporate governance guidelines and our code of business conduct and ethics. In addition, we intend to disclose on our web site any amendments to, or waivers from, our code of business conduct and ethics that are required to be disclosed pursuant to the SEC rules.

You may read and copy any materials we file with the SEC at the SEC s Public Reference Room at 100 F Street, NE, Washington, DC 20549. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC also maintains an Internet website that contains reports, proxy and information statements, and other information regarding Alnylam and other issuers that file electronically with the SEC. The SEC s Internet website address is http://www.sec.gov.

Executive Officers of the Registrant

Set forth below is information about our executive officers, as of December 31, 2012.

Name	Age	Position
John M. Maraganore, Ph.D	50	Chief Executive Officer and Director
Barry E. Greene	49	President and Chief Operating Officer
Akshay K. Vaishnaw, M.D., Ph.D.	50	Executive Vice President and Chief Medical Officer
Laurence E. Reid, Ph.D.	49	Senior Vice President and Chief Business Officer
Michael P. Mason	38	Vice President of Finance and Treasurer

John M. Maraganore, Ph.D. has served as our Chief Executive Officer and as a member of our board of directors since December 2002. Dr. Maraganore also served as our President from December 2002 to December 2007. From April 2000 to December 2002, Dr. Maraganore served as Senior Vice President, Strategic Product Development at Millennium Pharmaceuticals, Inc., a biopharmaceutical company. Dr. Maraganore serves as a member of the board of directors of the Biotechnology Industry Organization.

Barry E. Greene has served as our President and Chief Operating Officer since December 2007, as our Chief Operating Officer since he joined us in October 2003, and from February 2004 through December 2005, as our Treasurer. From February 2001 to September 2003, Mr. Greene served as General Manager of Oncology at Millennium Pharmaceuticals, Inc., a biopharmaceutical company. Mr. Greene serves as a member of the board of directors of Acorda Therapeutics, Inc., a biotechnology company.

Akshay K. Vaishnaw, M.D., Ph.D. has served as our Executive Vice President and Chief Medical Officer since June 2012 and prior to that as our Senior Vice President and Chief Medical Officer from June 2011 to June 2012. He served as our Senior Vice President, Clinical Research from December 2008 to June 2011, and prior to that served as our Vice President, Clinical Research from the time he joined us in January 2006. From December 1998 through December 2005, Dr. Vaishnaw held various positions at Biogen Idec Inc. (formerly Biogen, Inc.), a biopharmaceutical company, most recently as Senior Director, Translational Medicine. Dr. Vaishnaw is a Member of the Royal College of Physicians, United Kingdom.

Laurence E. Reid, Ph.D. has served as our Senior Vice President and Chief Business Officer since he joined us in June 2010. From January 2006 through May 2010, Dr. Reid served as the Chief Business Officer at Ensemble Therapeutics, a biotechnology company. Prior to joining Ensemble Therapeutics, Dr. Reid worked as a founder of two start-up companies in the fields of stem cell therapeutics and inflammation. Dr. Reid previously spent ten years at Millennium Pharmaceuticals, Inc., a biopharmaceutical company, from 1993 through 2003, where he served in a range of general management and business development positions, including General Manager of Millennium UK with responsibility for Millennium s European operations, Vice President of Business Development and Strategic Planning for the company s predictive medicine efforts, as well as in pharmaceutical business development and technology acquisition.

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Michael P. Mason has served as our Vice President of Finance and Treasurer since February 2011. From December 2005 to February 2011, Mr. Mason served as our Corporate Controller, and from August 2009 to February 2011, as our Senior Director of Finance. From June 2006 to July 2009, Mr. Mason served as our Director of Finance. From May 2000 through November 2005, Mr. Mason served in several finance and commercial roles at Praecis Pharmaceuticals Incorporated, a public biotechnology company, most recently as Corporate Controller. Prior to Praecis, Mr. Mason worked in the audit practice at KPMG LLP, a national audit, tax and advisory services firm. Mr. Mason has an MBA and is a certified public accountant.

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ITEM 1A. RISK FACTORS

Our business is subject to numerous risks. We caution you that the following important factors, among others, could cause our actual results to differ materially from those expressed in forward-looking statements made by us or on our behalf in filings with the SEC, press releases, communications with investors and oral statements. 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, expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these words. Any or all of our forward-looking statements in this annual report on Form 10-K and in any other public statements we make may turn out to be wrong. They can be affected by inaccurate assumptions we might make or by known or unknown risks and uncertainties. Many factors mentioned in the discussion below will be important in determining future results. Consequently, no forward-looking statement can be guaranteed. Actual future results may vary materially from those anticipated in forward-looking statements. We explicitly disclaim any obligation to update any forward-looking statements to reflect events or circumstances that arise after the date hereof. You are advised, however, to consult any further disclosure we make in our reports filed with the SEC.

Risks Related to Our Business

Risks Related to Being an Early Stage Company

Because we are in early-stage clinical development, there is limited information about our ability to successfully overcome many of the risks and uncertainties encountered by companies in the biopharmaceutical industry.

As a company in the early stages of clinical development, we have limited experience and have not yet demonstrated an ability to successfully overcome many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the biopharmaceutical area. For example, to execute our business plan, we will need to successfully:

- execute product development activities using unproven technologies related to both RNAi and to the delivery of siRNAs to the relevant tissues and cells;
- build and maintain a strong intellectual property portfolio;
- gain regulatory acceptance for the development of our product candidates and market success for any products we commercialize;
- develop and maintain successful strategic alliances; and
- manage our spending as costs and expenses increase due to clinical trials, regulatory approvals and commercialization.

If we are unsuccessful in accomplishing these objectives, we may not be able to develop product candidates, commercialize products, raise capital, expand our business or continue our operations.

The approach we are taking to discover and develop novel RNAi therapeutics is unproven and may never lead to marketable products.

We have concentrated our efforts and therapeutic product research on RNAi technology, and our future success depends on the successful development of this technology and products based on it. Neither we nor any other company has received regulatory approval to market therapeutics utilizing siRNAs, the class of molecule we are trying to develop into drugs. The scientific discoveries that form the basis for our efforts to discover and develop new drugs are relatively new. The scientific evidence to support the feasibility of developing drugs based on these discoveries is both preliminary and limited. Skepticism as to the feasibility of developing RNAi therapeutics has been expressed in scientific literature. For example, there are potential challenges to achieving

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safe RNAi therapeutics based on the so-called off-target effects and activation of the interferon response. In addition, decisions by other companies with respect to their RNAi development efforts may increase skepticism in the marketplace regarding the potential for RNAi therapeutics.

Relatively few product candidates based on these discoveries have ever been tested in animals or humans. siRNAs may not naturally possess the inherent properties typically required of drugs, such as the ability to be stable in the body long enough to reach the tissues in which their effects are required, nor the ability to enter cells within these tissues in order to exert their effects. We currently have only limited data, and no conclusive evidence, to suggest that we can introduce these drug-like properties into siRNAs. We may spend large amounts of money trying to introduce these properties, and may never succeed in doing so. In addition, these compounds may not demonstrate in patients the chemical and pharmacological properties ascribed to them in laboratory studies, and they may interact with human biological systems in unforeseen, ineffective or harmful ways. As a result, we may never succeed in developing a marketable product, we may not become profitable and the value of our common stock will decline.

Further, our focus solely on RNAi technology for developing drugs, as opposed to multiple, more proven technologies for drug development, increases the risks associated with the ownership of our common stock. If we are not successful in developing a product candidate using RNAi technology, we may be required to change the scope and direction of our product development activities. In that case, we may not be able to identify and implement successfully an alternative product development strategy.

Risks Related to Our Financial Results and Need for Financing

We have a history of losses and may never become and remain consistently profitable.

We have experienced significant operating losses since our inception. At December 31, 2012, we had an accumulated deficit of $507.0 million. To date, we have not developed any products nor generated any revenues from the sale of products. Further, we do not expect to generate any such revenues in the foreseeable future. We expect to continue to incur annual net operating losses over the next several years and will require substantial resources over the next several years as we expand our efforts to discover, develop and commercialize RNAi therapeutics. We anticipate that the majority of any revenues we generate over the next several years will be from alliances with pharmaceutical and biotechnology companies or funding from contracts with the government or foundations, but cannot be certain that we will be able to secure or maintain these alliances or contracts, or meet the obligations or achieve any milestones that we may be required to meet or achieve to receive payments. We anticipate that revenues derived from such sources will not be sufficient to make us consistently profitable.

We believe that to become and remain consistently profitable, we must succeed in discovering, developing and commercializing novel drugs with significant market potential. This will require us to be successful in a range of challenging activities, including pre-clinical testing and clinical trial stages of development, obtaining regulatory approval for these novel drugs and manufacturing, marketing and selling them. We may never succeed in these activities, and may never generate revenues that are significant enough to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. If we cannot become and remain consistently profitable, the market price of our common stock could decline. In addition, we may be unable to raise capital, expand our business, develop additional product candidates or continue our operations.

We will require substantial additional funds to complete our research and development activities and if additional funds are not available, we may need to critically limit, significantly scale back or cease our operations.

We have used substantial funds to develop our RNAi technologies and will require substantial funds to conduct further research and development, including pre-clinical testing and clinical trials of our product candidates, and to manufacture and market any products that are approved for commercial sale. Because we cannot be certain of the length of time or activities associated with successful development of our product candidates, we are unable to estimate the actual funds we will require to develop and commercialize them.

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Our future capital requirements and the period for which we expect our existing resources to support our operations may vary from what we expect. We have based our expectations on a number of factors, many of which are difficult to predict or are outside of our control, including:

- our progress in demonstrating that siRNAs can be active as drugs;
- our ability to develop relatively standard procedures for selecting and modifying siRNA product candidates;
- progress in our research and development programs, as well as the magnitude of these programs;
- the timing, receipt and amount of milestone and other payments, if any, from present and future collaborators, if any;
- the timing, receipt and amount of funding under future government or foundation contracts, if any;
- our ability to maintain and establish additional collaborative arrangements and/or new business initiatives;
- the resources, time and costs required to initiate and complete our pre-clinical and clinical trials, obtain regulatory approvals, and obtain and maintain licenses to third-party intellectual property;
- our ability to manufacture, or contract with third-parties for the manufacture of, our product candidates for clinical testing and commercial sale;
- the resources, time and cost required for the preparation, filing, prosecution, maintenance and enforcement of patent claims;
- our ability to achieve the anticipated cost reductions as a result of, and to successfully manage the potential impact of, our January 2012 strategic corporate restructuring and workforce reduction on our culture, collaborative relationships and business operations;
- the costs associated with legal activities, including litigation, arising in the course of our business activities and our ability to prevail in any such legal disputes;
- progress in the research and development programs of Regulus; and
- the timing, receipt and amount of sales and royalties, if any, from our potential products.

If our estimates and predictions relating to these factors are incorrect, we may need to modify our operating plan.

Even if our estimates are correct, we will be required to seek additional funding in the future and intend to do so through either collaborative arrangements, public or private equity offerings or debt financings, or a combination of one or more of these funding sources. Additional funds may not be available to us on acceptable terms or at all.

In addition, the terms of any financing may adversely affect the holdings or the rights of our stockholders. For example, if we raise additional funds by issuing equity securities, under our shelf registration statement or otherwise, further dilution to our stockholders will result. In addition, as a condition to providing additional funds to us, future investors may demand, and may be granted, rights superior to those of existing stockholders. Debt financing, if available, may involve restrictive covenants that could limit our flexibility in conducting future business activities and, in the event of insolvency, would be paid before holders of equity securities received any distribution of corporate assets.

If we are unable to obtain funding on a timely basis, we may be required to significantly delay or curtail one or more of our research or development programs or undergo additional reductions in our workforce or other corporate restructuring activities. We also could be required to seek funds through arrangements with collaborators or others that may require us to relinquish rights to some of our technologies, product candidates or products that we would otherwise pursue on our own.

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If the estimates we make, or the assumptions on which we rely, in preparing our consolidated financial statements prove inaccurate, our actual results may vary from those reflected in our projections and accruals.

Our consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America, or GAAP. The preparation of these consolidated financial statements requires us to make estimates and judgments that affect the reported amounts of our assets, liabilities, revenues and expenses, the amounts of charges accrued by us and related disclosure of contingent assets and liabilities. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances. We cannot assure you, however, that our estimates, or the assumptions underlying them, will be correct.

The investment of our cash, cash equivalents and fixed income marketable securities is subject to risks which may cause losses and affect the liquidity of these investments.

At December 31, 2012, we had $226.2 million in cash, cash equivalents and fixed income marketable securities. We historically have invested these amounts in corporate bonds, commercial paper, securities issued by the U.S. government obligations, certificates of deposit and money market funds meeting the criteria of our investment policy, which is focused on the preservation of our capital. These investments are subject to general credit, liquidity, market and interest rate risks, including the impact of U.S. sub-prime mortgage defaults that have affected various sectors of the financial markets and caused credit and liquidity issues. We may realize losses in the fair value of these investments or a complete loss of these investments, which would have a negative effect on our consolidated financial statements. In addition, should our investments cease paying or reduce the amount of interest paid to us, our interest income would suffer. The market risks associated with our investment portfolio may have an adverse effect on our results of operations, liquidity and financial condition.

Risks Related to Our Dependence on Third Parties

Our license and collaboration agreements with pharmaceutical companies are important to our business. If these pharmaceutical companies do not successfully develop drugs pursuant to these agreements or we develop drugs targeting the same diseases as our non-exclusive licensees, our business could be adversely affected.

In July 2007, we entered into a license and collaboration agreement with Roche. Under the license and collaboration agreement we granted Roche a non-exclusive license to our intellectual property 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 their RNAi research efforts. In October 2011, Arrowhead announced its acquisition of RNA therapeutics assets from Roche, including our license and collaboration agreement with Roche. As a result of the assignment, Arrowhead now has all of the rights and obligations of Roche under that agreement. The license is 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 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 and sales events, totaling up to an aggregate of $100.0 million per therapeutic target, together with royalty payments based on worldwide annual net sales, if any. Our receipt of milestone payments under this agreement is dependent upon Arrowhead s ability to successfully develop and commercialize RNAi therapeutic products.

In May 2008, we entered into a similar license and collaboration agreement with Takeda, which is limited to two therapeutic areas, and which may be expanded to include additional therapeutic areas, upon payment to us by Takeda of an additional $50.0 million for each additional therapeutic area, if any. For each RNAi therapeutic product developed by Takeda, its affiliates and sublicensees, we are entitled to receive specified development and commercialization milestone payments, totaling up to $171.0 million per product, together with royalty

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payments based on worldwide annual net sales, if any. In addition, we agreed that we will not grant any other party rights to develop RNAi therapeutics in the Asian territory through May 2013.

In September 2010, Novartis exercised its right under our collaboration and license agreement to select 31 designated gene targets, for which Novartis has exclusive rights to discover, develop and commercialize RNAi therapeutic products using our intellectual property and technology. Under the terms of the collaboration and license agreement, for any RNAi therapeutic products Novartis develops against these targets, we are entitled to receive milestone payments upon achievement of certain specified development and annual net sales events, up to an aggregate of $75.0 million per therapeutic product, as well as royalties on annual net sales of any such product.

If Takeda, Novartis or Arrowhead fails to successfully develop products using our technology, we may not receive any milestone or royalty payments under our agreements with them. In addition, even if Takeda is not successful in its efforts, we are limited in our ability to form alliances with other parties in the Asian territory until May 2013. We also have the option under the Takeda agreement, 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 collaboration agreement. If Takeda fails to successfully develop products, we may not realize any economic benefit from these opt-in rights. Finally, Takeda could become a competitor of ours in the development of RNAi-based drugs targeting the same diseases that we choose to target. Takeda has significantly greater financial resources than we do and far more experience in developing and marketing drugs, which could put us at a competitive disadvantage if we were to compete with them in the development of RNAi-based drugs targeting the same disease.

We may not be able to execute our business strategy if we are unable to enter into alliances with other companies that can provide business and scientific capabilities and funds for the development and commercialization of our product candidates. If we are unsuccessful in forming or maintaining these alliances on terms favorable to us, our business may not succeed.

We do not have any capability for sales, marketing or distribution and have limited capabilities for drug development. In addition, we believe that other companies are expending substantial resources in developing safe and effective means of delivering siRNAs to relevant cell and tissue types. Accordingly, we have entered into alliances with other companies and collaborators that we believe can provide such capabilities, and we intend to enter into additional such alliances in the future. 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. In February 2013, we entered into a global alliance 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. In such alliances, we expect our current, and may expect our future, collaborators to provide substantial capabilities in delivery of RNAi therapeutics to the relevant cell or tissue type, clinical development, regulatory affairs, and/or marketing, sales and distribution. For example, under our agreements with MIT, Tekmira, UBC and AlCana, and Arrowhead, among others, we have access to certain existing delivery technologies and/or are developing additional delivery capabilities. In addition, under certain of our other alliances, we may expect our collaborators to develop, market and/or sell certain of our product candidates. We may have limited or no control over the development, sales, marketing and distribution activities of these third parties. Our future revenues may depend heavily on the success of the efforts of these third parties. For example, we will rely entirely on (i) Kyowa Hakko Kirin for development and commercialization of any RNAi products for the treatment of RSV in Asia; (ii) Ascletis for development and commercialization of any RNAi products for the treatment of liver cancer in China and certain other territories and (iii) Genzyme for the development and commercialization of ALN-TTR in Japan and the Asia-Pacific region. If Kyowa Hakko Kirin, Ascletis and/or Genzyme are not successful in their commercialization efforts, our future revenues from RNAi therapeutics for these indications may be adversely affected.

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We may not be successful in entering into such alliances on terms favorable to us due to various factors, including our ability to successfully demonstrate proof of concept for our technology in man, our ability to demonstrate the safety and efficacy of our specific drug candidates, our ability to manufacture or have manufactured RNAi therapeutics, the strength of our intellectual property and/or concerns around challenges to our intellectual property. Even if we do succeed in securing any such alliances, we may not be able to maintain them if, for example, development or approval of a product candidate is delayed, challenges are raised as to the validity or scope of our intellectual property or sales of an approved drug are lower than we expected. In addition, under our collaboration agreements with Monsanto and Genzyme, we may be required to pay liquidated damages or repay upfront payments and may lose royalty and other rights. In the case of the Monsanto agreement, if we cease to own or otherwise exclusively control certain licensed patent rights in the agriculture field, 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 (as defined in the agreement), we would be required to pay Monsanto up to $5.0 million in liquidated damages, and Monsanto s royalty obligations to us would be reduced or, under certain circumstances, terminated.

Furthermore, any delay in entering into collaboration agreements would likely either delay the development and commercialization of our certain of our product candidates and reduce their competitiveness even if they reach the market, or prevent the development of certain product candidates. Any such delay related to our collaborations could adversely affect our business.

For certain product candidates that we may develop, we have formed collaborations to fund all or part of the costs of drug development and commercialization, such as our collaborations with Takeda, Medtronic and MedCo. We may not, however, be able to enter into additional collaborations for ALN-TMP, ALN-VSP or ALN-RSV, and the terms of any collaboration agreement we do secure may not be favorable to us. If we are not successful in our efforts to enter into future collaboration arrangements with respect to one or more of these product candidates, we may not have sufficient funds to develop that or any other product candidate internally, or to bring any product candidates to market. If we do not have sufficient funds to develop and bring our product candidates to market, we will not be able to generate sales revenues from these product candidates, and this will substantially harm our business.

If any collaborator terminates or fails to perform its obligations under agreements with us, the development and commercialization of our product candidates could be delayed or terminated.

Our dependence on collaborators for capabilities and funding means that our business could be adversely affected if any collaborator terminates its collaboration agreement with us or fails to perform its obligations under that agreement. Our current or future collaborations, if any, may not be scientifically or commercially successful. Disputes may arise in the future with respect to the ownership of rights to technology or products developed with collaborators, which could have an adverse effect on our ability to develop and commercialize any affected product candidate.

Our current collaborations allow, and we expect that any future collaborations will allow, either party to terminate the collaboration for a material breach by the other party. Our agreement with Kyowa Hakko Kirin for the development and commercialization of RSV therapeutics for the treatment of RSV infection in Japan and other major markets in Asia may be terminated by Kyowa Hakko Kirin without cause upon 180-days prior written notice to us, subject to certain conditions, and our agreement with MedCo relating to the development and commercialization of ALN-PCS worldwide may be terminated by MedCo at any time upon four months prior written notice. If we were to lose a commercialization collaborator, we would have to attract a new collaborator or develop internal sales, distribution and marketing capabilities, which would require us to invest significant amounts of financial and management resources.

In addition, if we have a dispute with a collaborator over the ownership of technology or other matters, or if a collaborator terminates its collaboration with us, for breach or otherwise, or determines not to pursue the research and development of RNAi therapeutics, it could delay our development of product candidates, result in the need for additional company resources to develop product candidates, make it more difficult for us to attract new collaborators and could adversely affect how we are perceived in the business and financial communities.

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For example, in March 2011, Tekmira filed a civil complaint against us claiming, among other things. misappropriation of its confidential and proprietary information and trade secrets. As a result of the litigation, which was settled in November 2012, we were required to expend resources and management attention that would otherwise have been engaged in other activities. Moreover, a collaborator, or in the event of a change in control of a collaborator or the assignment of a collaboration agreement to a third-party, the successor entity or assignee, could determine that it is in its interests to:

- pursue alternative technologies or develop alternative products, either on its own or jointly with others, that may be competitive with the products on which it is collaborating with us or which could affect its commitment to the collaboration with us;
- pursue higher-priority programs or change the focus of its development programs, which could affect the collaborator s commitment to us; or
- if it has marketing rights, choose to devote fewer resources to the marketing of our product candidates, if any are approved for marketing, than it does for product candidates developed without us.

If any of these occur, the development and commercialization of one or more product candidates could be delayed, curtailed or terminated because we may not have sufficient financial resources or capabilities to continue such development and commercialization on our own.

We rely on third parties to conduct our clinical trials, and if they fail to fulfill their obligations, our development plans may be adversely affected.

We rely on independent clinical investigators, contract research organizations and other third-party service providers to assist us in managing, monitoring and otherwise carrying out our clinical trials. We have contracted, and we plan to continue to contract with certain third-parties to provide certain services, including site selection, enrollment, monitoring and data management services. Although we depend heavily on these parties, we do not control them and therefore, we cannot be assured that these third-parties will adequately perform all of their contractual obligations to us. If our third-party service providers cannot adequately and timely fulfill their obligations to us, or if the quality and accuracy of our clinical trial data is compromised due to failure by such third-party to adhere to our protocols or regulatory requirements or if such third-parties otherwise fail to meet deadlines, our development plans may be delayed or terminated.

We have very limited manufacturing experience or resources and we must incur significant costs to develop this expertise and/or rely on third parties to manufacture our products.

We have very limited manufacturing experience. Some of our product candidates utilize specialized formulations, such as liposomes or LNP-based formulations, whose scale-up and manufacturing could be very difficult. We also have very limited experience in such scale-up and manufacturing, requiring us to depend on a limited number of third parties, who might not be able to deliver in a timely manner, or at all. In order to develop products, apply for regulatory approvals and commercialize our products, we will need to develop, contract for, or otherwise arrange for the necessary manufacturing capabilities. Our internal manufacturing capabilities are limited to small-scale production of material for use in *in vitro* and *in vivo* experiments that is not required to be produced under current good manufacturing practice, or cGMP, standards. During 2012, we developed cGMP capabilities and processes for the manufacture of ALN-TTR02 for Phase III clinical use and early commercial supply. We may manufacture clinical trial materials ourselves or we may rely on others to manufacture the materials we will require for any clinical trials that we initiate. There are a limited number of manufacturers that supply synthetic siRNAs. We currently rely on several contract manufacturers for our supply of synthetic siRNAs. There are risks inherent in pharmaceutical manufacturing that could affect the ability of our contract manufacturers to meet our delivery time requirements or provide adequate amounts of material to meet our needs. Included in these risks are synthesis and purification failures and contamination during the manufacturing process, which could result in unusable product and cause delays in our development process, as well as additional expense to us. To fulfill our siRNA requirements, we may also need to secure alternative suppliers of synthetic siRNAs.

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In addition to the manufacture of the synthetic siRNAs, we may have additional manufacturing requirements related to the technology required to deliver the siRNA to the relevant cell or tissue type, such as LNPs or conjugates. In some cases, the delivery technology we utilize is highly specialized or proprietary, and for technical and legal reasons, we may have access to only one or a limited number of potential manufacturers for such delivery technology. Failure by manufacturers to properly formulate our siRNAs for delivery could result in unusable product. Furthermore, a breach by such manufacturers of their contractual obligations or a dispute with such manufacturers would cause delays in our discovery and development process, as well as additional expense to us. Given the limited number of suppliers for our delivery technology and other materials, we have developed cGMP capabilities and processes for the manufacture of ALN-TTR02 for Phase III clinical use and early commercial supply, and in the future, we may also develop our own capabilities to manufacture drug substance, including siRNAs and siRNA conjugates for human clinical use. In developing these manufacturing capabilities by building our own manufacturing facility, we have incurred substantial expenditures. Also, we will likely need to hire and train employees to staff our new facility.

The manufacturing process for any products that we may develop is subject to FDA and foreign regulatory authority approval process and we will need to contract with manufacturers who can meet all applicable FDA and foreign regulatory authority requirements on an ongoing basis. In addition, if we receive the necessary regulatory approval for any product candidate, we also expect to rely on third parties, including our commercial collaborators, to produce materials required for commercial supply. We may experience difficulty in obtaining adequate manufacturing capacity for our needs. If we are unable to obtain or maintain contract manufacturing for these product candidates, or to do so on commercially reasonable terms, we may not be able to successfully develop and commercialize our products.

To the extent that we have existing, or enter into future, manufacturing arrangements with third parties, we depend, and will depend in the future, on these third parties to perform their obligations in a timely manner and consistent with contractual and regulatory requirements, including those related to quality control and quality assurance. The failure of a third-party manufacturer to perform its obligations as expected, or, to the extent we manufacture all or a portion of our product candidates ourselves, our failure to execute on our manufacturing requirements could adversely affect our business in a number of ways, including:

- we or our current or future collaborators may not be able to initiate or continue clinical trials of products that are under development;
- we or our current or future collaborators may be delayed in submitting regulatory applications, or receiving regulatory approvals, for our product candidates;
- we may lose the cooperation of our collaborators;
- our products could be the subject of inspections by regulatory authorities;
- we may be required to cease distribution or recall some or all batches of our products; and
- ultimately, we may not be able to meet commercial demands for our products.

If any third-party manufacturer with whom we contract fails to perform its obligations, we may be forced to manufacture the materials ourselves, for which we may not have the capabilities or resources, or enter into an agreement with a different third-party manufacturer, which we may not be able to do on reasonable terms, if at all. In some cases, the technical skills required to manufacture our products or product candidates may be unique or proprietary to the original manufacturer and we may have difficulty, or there may be contractual restrictions prohibiting us from, transferring such skills to a back-up or alternate supplier, or we may be unable to transfer such skills at all. In addition, if we are required to change manufacturers for any reason, we will be required to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. The delays associated with the verification of a new manufacturer could negatively affect our ability to develop product candidates in a timely manner or within budget. Furthermore, a manufacturer may possess technology related to the manufacture of our product candidate that such manufacturer owns independently. This would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have another third-party manufacture our products or product candidates.

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We have no sales, marketing or distribution experience and would have to invest significant financial and management resources to establish these capabilities.

We have no sales, marketing or distribution experience. We currently expect to rely heavily on third parties to launch and market certain of our product candidates, if approved. However, if we elect to develop internal sales, distribution and marketing capabilities as part of our core product strategy, we will need to invest significant financial and management resources. For core products where we decide to perform sales, marketing and distribution functions ourselves, we could face a number of additional risks, including:

- we may not be able to attract and build a significant marketing or sales force;
- the cost of establishing a marketing or sales force may not be justifiable in light of the revenues generated by any particular product; and
- our direct sales and marketing efforts may not be successful.

If we are unable to develop our own sales, marketing and distribution capabilities, we will not be able to successfully commercialize our core products without reliance on third parties.

The current credit and financial market conditions may exacerbate certain risks affecting our business.

Due to the tightening of global credit, there may be a disruption or delay in the performance of our third-party contractors, suppliers or collaborators. We rely on third parties for several important aspects of our business, including significant portions of our manufacturing needs, development of product candidates and conduct of clinical trials. If such third parties are unable to satisfy their commitments to us, our business could be adversely affected.

Risks Related to Managing Our Operations

If we are unable to attract and retain qualified key management and scientists, staff, consultants and advisors, our ability to implement our business plan may be adversely affected.

We are highly dependent upon our senior management and scientific staff. The loss of the service of any of the members of our senior management, including Dr. John Maraganore, our Chief Executive Officer, may significantly delay or prevent the achievement of product development and other business objectives. Our employment agreements with our key personnel are terminable without notice. We do not carry key man life insurance on any of our employees.

We face intense competition for qualified individuals from numerous pharmaceutical and biotechnology companies, universities, governmental entities and other research institutions, many of which have substantially greater resources with which to reward qualified individuals than we do. In addition, as a result of our September 2010 and January 2012 corporate restructurings and workforce reductions, we may face additional challenges in retaining our existing employees and recruiting new employees to join our company as our business needs change. We may be unable to attract and retain suitably qualified individuals, and our failure to do so could have an adverse effect on our ability to implement our future business plan.

Our corporate restructuring and workforce reduction plan may not result in anticipated savings, could result in total costs and expenses that are greater than expected and could disrupt our business.

In January 2012, we announced a corporate restructuring and workforce reduction plan pursuant to which we reduced our workforce by approximately 33%. We took these actions in order to reduce costs, streamline operations and improve our cost structure. The workforce reduction was substantially completed at the end of the first quarter of 2012. As a result of the reduction in workforce, in the first quarter of 2012, we recorded a restructuring charge of $3.9 million and during the remainder of 2012, paid substantially all of the costs related to this restructuring. The restructuring charges were based on a number of assumptions. Actual results may differ materially and additional charges not currently expected may be incurred in connection with, or as a result of,

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these reductions. In addition, we may not realize, in full or in part, the anticipated benefits, savings and improvements in our cost structure from our restructuring efforts due to unforeseen difficulties, delays or unexpected costs. If we are unable to achieve the anticipated benefits, savings or improvements in our cost structure in the expected time frame or other unforeseen events occur, our business and results of operations may be adversely affected.

Our restructuring plan has been and may continue to be disruptive to our operations. For example, cost savings measures may distract management from our core business, harm our reputation, yield unanticipated consequences, such as attrition beyond planned reductions in workforce, or increased difficulties in our day-to-day operations, and may adversely affect employee morale. Our workforce reductions could also harm our ability to attract and retain qualified management, scientific, manufacturing and sales and marketing personnel who are critical to our business. Any failure to attract or retain qualified personnel could prevent us from successfully developing and commercializing our products and product candidates in the future.

We may have difficulty expanding our operations successfully as we seek to evolve from a company primarily involved in discovery and pre-clinical testing into one that develops and commercializes drugs.

Despite our January 2012 workforce reduction in connection with our strategic corporate restructuring, we expect that as we seek to increase the number of product candidates we are developing we will need to expand our operations in the future. This growth may place a strain on our administrative and operational infrastructure. If product candidates we develop enter and advance through clinical trials, we will need to expand our development, regulatory, manufacturing, marketing and sales capabilities or contract with other organizations to provide these capabilities for us. As our operations expand due to our development progress, we expect that we will need to manage additional relationships with various collaborators, suppliers and other organizations. Our ability to manage our operations and future growth will require us to continue to improve our operational, financial and management controls, reporting systems and procedures. We may not be able to implement improvements to our management information and control systems in an efficient or timely manner and may discover deficiencies in existing systems and controls.

Our business and operations could suffer in the event of system failures.

Despite the implementation of security measures, our internal computer systems and those of our contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war, and telecommunication and electrical failures. Such events could cause interruption of our operations. For example, the loss of pre-clinical trial data or data from completed or ongoing clinical trials for our product candidates could result in delays in our regulatory filings and development efforts and significantly increase our costs. To the extent that any disruption or security breach were to result in a loss of or damage to our data, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the development of our product candidates could be delayed.

Risks Related to Our Industry

Risks Related to Development, Clinical Testing and Regulatory Approval of Our Product Candidates

Any product candidates we develop may fail in development or be delayed to a point where they do not become commercially viable.

Before obtaining regulatory approval for the commercial distribution of our product candidates, we must conduct, at our own expense, extensive pre-clinical tests and clinical trials to demonstrate the safety and efficacy in humans of our product candidates. Pre-clinical and clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome, and the historical failure rate for product candidates is high. We currently have several programs in clinical development, including ALN-RSV01 and ALN-TTR02 in Phase II clinical trials and ALN-TTRsc, ALN-PCS and ALN-VSP in Phase I clinical development. However, we may not be able to further advance these or any other product candidate through clinical trials.

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If we enter into clinical trials, the results from pre-clinical testing or early clinical trials of a product candidate may not predict the results that will be obtained in subsequent human clinical trials of that product candidate or any other product candidate. For example, ALN-VSP, ALN-PCS, ALN-TTR02 and ALN-TTRsc employ novel delivery formulations that have yet to be extensively evaluated in human clinical trials and proven safe and effective. We, the FDA or other applicable regulatory authorities, or an institutional review board, or IRB, or similar foreign review board or committee, may suspend clinical trials of a product candidate at any time for various reasons, including if we or they believe the subjects or patients participating in such trials are being exposed to unacceptable health risks. Among other reasons, adverse side effects of a product candidate on subjects or patients in a clinical trial could result in the FDA or foreign regulatory authorities suspending or terminating the trial and refusing to approve a particular product candidate for any or all indications of use.

Clinical trials of a new product candidate require the enrollment of a sufficient number of patients, including patients who are suffering from the disease the product candidate is intended to treat and who meet other eligibility criteria. Rates of patient enrollment are affected by many factors, including the size of the patient population, the age and condition of the patients, the stage and severity of disease, the nature of the protocol, the proximity of patients to clinical sites, the availability of effective treatments for the relevant disease, the seasonality of infections and the eligibility criteria for the clinical trial. For example, we may experience difficulty enrolling our clinical trials, including, but not limited to, our ALN-TTR02 trial, due to the availability of existing approved treatments. Although our RNAi therapeutics have been generally safe and well tolerated in our clinical trials to date, in our ALN-VSP clinical trial, one patient with advanced pancreatic neuroendocrine cancer with extensive involvement of the liver developed hepatic failure five days following the second dose of ALN-VSP and subsequently died; this was deemed possibly related to the study drug. In addition, in our ALN-VSP and ALN-TTR01 Phase I clinical trials, we have reported an incidence of acute infusion reactions occurring in 15-20% of patients. These were graded as mild or moderate in severity and readily responded to slowing of the infusion rate; all patients completed dosing without further incident. The frequency of acute infusion reactions in our ALN-PCS and ALN-TTR02 Phase I clinical trials has been less than three percent. In our ALN-PCS clinical trial, we reported the occurrence of a mild, transient rash that was observed in sixteen subjects, including four who received placebo; the incidence of this finding was the same in both placebo and drug treatment arms. In addition, our Phase II clinical trial of ALN-TTR02 trial targets a small population of patients suffering from ATTR. Delays or difficulties in patient enrollment or difficulties retaining trial participants, including as a result of the availability of existing treatments or the occurrence of adverse events, can result in increased costs, longer development times or termination of a clinical trial.

Clinical trials also require the review, oversight and approval of IRBs, which continually review clinical investigations and protect the rights and welfare of human subjects. Inability to obtain or delay in obtaining IRB approval can prevent or delay the initiation and completion of clinical trials, and the FDA or foreign regulatory authorities may decide not to consider any data or information derived from a clinical investigation not subject to initial and continuing IRB review and approval in support of a marketing application.

Our product candidates that we develop may encounter problems during clinical trials that will cause us, an IRB or regulatory authorities to delay, suspend or terminate these trials, or that will delay or confound the analysis of data from these trials. If we experience any such problems, we may not have the financial resources to continue development of the product candidate that is affected, or development of any of our other product candidates. We may also lose, or be unable to enter into, collaborative arrangements for the affected product candidate and for other product candidates we are developing.

A failure of one of more of our clinical trials can occur at any stage of testing. We may experience numerous unforeseen events during, or as a result of, pre-clinical testing and the clinical trial process that could delay or prevent regulatory approval or our ability to commercialize our product candidates, including:

- our pre-clinical tests or clinical trials may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional pre-clinical testing or clinical trials, or we may abandon projects that we expect to be promising;

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delays in filing INDs or comparable foreign applications or delays or failure in obtaining the necessary approvals from regulators or IRBs in order to commence a clinical trial at a prospective trial site, or their suspension or termination of a clinical trial once commenced;

conditions imposed on us by the FDA or comparable foreign authorities regarding the scope or design of our clinical trials;

problems in engaging IRBs to oversee clinical trials or problems in obtaining or maintaining IRB approval of trials;

delays in enrolling patients and volunteers into clinical trials, and variability in the number and types of patients and volunteers available for clinical trials;

high drop-out rates for patients and volunteers in clinical trials;

negative or inconclusive results from our clinical trials or the clinical trials of others for product candidates similar to ours;

inadequate supply or quality of product candidate materials or other materials necessary for the conduct of our clinical trials;

greater than anticipated clinical trial costs;

serious and unexpected drug-related side effects experienced by participants in our clinical trials or by individuals using drugs similar to our product candidates;

poor effectiveness of our product candidates during clinical trials;

unfavorable FDA or other regulatory agency inspection and review of a clinical trial site or records of any clinical or pre-clinical investigation;

failure of our third-party contractors or investigators to comply with regulatory requirements or otherwise meet their contractual obligations in a timely manner, or at all;

governmental or regulatory delays and changes in regulatory requirements, policy and guidelines, including the imposition of additional regulatory oversight around clinical testing generally or with respect to our technology in particular; or

varying interpretations of data by the FDA and similar foreign regulatory agencies.

Even if we successfully complete clinical trials of our product candidates, any given product candidate may not prove to be a safe and effective treatment for the diseases for which it was being tested.

The regulatory approval process may be delayed for any products we develop that require the use of specialized drug delivery devices, which may require us to incur additional costs and delay receipt of any potential product revenue.

Some product candidates that we develop may need to be administered using specialized drug delivery devices that deliver RNAi therapeutics directly to diseased parts of the body. While we expect to rely on drug delivery systems that have been approved by the FDA or other regulatory agencies to deliver drugs like ours to diseased parts of the body, we, or our collaborator, may need to modify the design or labeling of such delivery device for some products we may develop. In such an event, the FDA may regulate the product as a combination product or require additional approvals or clearances for the modified delivery device. Further, to the extent the specialized delivery device is owned by another company, we would need that company s cooperation to implement the necessary changes to the device, or its labeling, and to obtain any additional approvals or clearances. In cases where we do not have an ongoing collaboration with the company that makes the device, obtaining such additional approvals or clearances and the cooperation of such other company could significantly delay and increase the cost of obtaining marketing approval, which could reduce the commercial viability of our product candidate. In addition, the use of a specialized delivery system, even if previously approved, could

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complicate the design or analysis of clinical trials for our RNAi therapeutics. In summary, we may be unable to find, or experience delays in finding, suitable drug delivery systems to administer RNAi therapeutics directly to diseased parts of the body, which could negatively affect our ability to successfully commercialize these RNAi therapeutics.

We may be unable to obtain United States or foreign regulatory approval and, as a result, unable to commercialize our product candidates.

Our product candidates are subject to extensive governmental regulations relating to, among other things, research, testing, development, manufacturing, safety, efficacy, approval, recordkeeping, reporting, labeling, storage, marketing and distribution of drugs. Rigorous pre-clinical testing and clinical trials and an extensive regulatory approval process are required to be successfully completed in the United States and in many foreign jurisdictions before a new drug can be marketed. Satisfaction of these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. It is possible that none of the product candidates we may develop will obtain the regulatory approvals necessary for us or our collaborators to begin selling them.

We have very limited experience in conducting and managing the clinical trials necessary to obtain regulatory approvals, including approval by the FDA. The time required to obtain FDA and other approvals is unpredictable but typically takes many years following the commencement of clinical trials, depending upon the type, complexity and novelty of the product candidate. The standards that the FDA and its foreign counterparts use when regulating us are not always applied predictably or uniformly and can change. Any analysis we perform of data from pre-clinical and clinical activities is subject to confirmation and interpretation by regulatory authorities, which could delay, limit or prevent regulatory approval. We may also encounter unexpected delays or increased costs due to new government regulations, for example, from future legislation or administrative action, or from changes in FDA policy during the period of product development, clinical trials and FDA regulatory review. It is impossible to predict whether legislative changes will be enacted, or whether FDA or foreign regulations, guidance or interpretations will be changed, or what the impact of such changes, if any, may be.

Because the drugs we are developing may represent a new class of drug, the FDA and its foreign counterparts have not yet established any definitive policies, practices or guidelines in relation to these drugs. While we believe the product candidates that we are currently developing are regulated as new drugs under the Federal Food, Drug, and Cosmetic Act, the FDA could decide to regulate them or other products we may develop as biologics under the Public Health Service Act. The lack of policies, practices or guidelines may hinder or slow review by the FDA of any regulatory filings that we may submit. Moreover, the FDA may respond to these submissions by defining requirements we may not have anticipated. Such responses could lead to significant delays in the clinical development of our product candidates. In addition, because there may be approved treatments for some of the diseases for which we may seek approval, in order to receive regulatory approval, we may need to demonstrate through clinical trials that the product candidates we develop to treat these diseases, if any, are not only safe and effective, but safer or more effective than existing products. Furthermore, in recent years, there has been increased public and political pressure on the FDA with respect to the approval process for new drugs, and the FDA s standards, especially regarding drug safety, appear to have become more stringent.

Any delay or failure in obtaining required approvals could have a material adverse effect on our ability to generate revenues from the particular product candidate for which we are seeking approval. Furthermore, any regulatory approval to market a product may be subject to limitations on the approved uses for which we may market the product or the labeling or other restrictions. In addition, the FDA has the authority to require a Risk Evaluation and Mitigation Strategy, or REMS, plan as part of an NDA or biologics license application, or BLA, or after approval, which may impose further requirements or restrictions on the distribution or use of an approved drug or biologic, such as limiting prescribing to certain physicians or medical centers that have undergone specialized training, limiting treatment to patients who meet certain safe-use criteria and requiring treated patients to enroll in a registry. These limitations and restrictions may limit the size of the market for the product and affect reimbursement by third-party payors.

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We are also subject to numerous foreign regulatory requirements governing, among other things, the conduct of clinical trials, manufacturing and marketing authorization, pricing and third-party reimbursement. The foreign regulatory approval process varies among countries and includes all of the risks associated with FDA approval described above as well as risks attributable to the satisfaction of local regulations in foreign jurisdictions. Approval by the FDA does not ensure approval by regulatory authorities outside the United States and vice versa.

Even if we obtain regulatory approvals, our marketed drugs will be subject to ongoing regulatory review. If we fail to comply with continuing U.S. and foreign requirements, our approvals could be limited or withdrawn, we could be subject to other penalties, and our business would be seriously harmed.

Following any initial regulatory approval of any drugs we may develop, we will also be subject to continuing regulatory review, including the review of adverse drug experiences and clinical results that are reported after our drug products are made commercially available. This would include results from any postmarketing tests or surveillance to monitor the safety and efficacy of the drug product required as a condition of approval or agreed to by us. Any regulatory approvals that we receive for our product candidates may also be subject to limitations on the approved uses for which the product may be marketed. Other ongoing regulatory requirements include, among other things, submissions of safety and other post-marketing information and reports, registration and listing, as well as continued compliance with cGMP requirements and good clinical practices for any clinical trials that we conduct post-approval. In addition, we are conducting, and intend to continue to conduct, clinical trials for our product candidates, and we intend to seek approval to market our product candidates, in jurisdictions outside of the United States, and therefore will be subject to, and must comply with, regulatory requirements in those jurisdictions.

The FDA has significant post-market authority, including, for example, the authority to require labeling changes based on new safety information and to require post-market studies or clinical trials to evaluate serious safety risks related to the use of a drug and to require withdrawal of the product from the market. The FDA also has the authority to require a REMS plan after approval, which may impose further requirements or restrictions on the distribution or use of an approved drug.

The manufacturer and manufacturing facilities we use to make any of our product candidates will also be subject to periodic review and inspection by the FDA and other regulatory agencies. The discovery of any new or previously unknown problems with our third-party manufacturers, manufacturing processes or facilities, may result in restrictions on the drug or manufacturer or facility, including withdrawal of the drug from the market. We have recently developed cGMP capabilities and processes for the manufacture of ALN-TTR02 for Phase III clinical and early commercial use. We do not currently have the ability to manufacture material for a broader commercial scale. We may manufacture clinical trial materials or we may contract a third party to manufacture these materials for us. Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured products ourselves, including reliance on the third-party manufacturer for regulatory compliance. Our product promotion and advertising is also subject to regulatory requirements and continuing regulatory review.

If we or our collaborators, manufacturers or service providers fail to comply with applicable continuing regulatory requirements in the United States or foreign jurisdictions in which we may seek to market our products, we or they may be subject to, among other things, fines, warning letters, holds on clinical trials, refusal by the FDA to approve pending applications or supplements to approved applications, suspension or withdrawal of regulatory approval, product recalls and seizures, refusal to permit the import or export of products, operating restrictions, injunction, civil penalties and criminal prosecution.

Even if we receive regulatory approval to market our product candidates, the market may not be receptive to our product candidates upon their commercial introduction, which will prevent us from becoming profitable.

The product candidates that we are developing are based upon new technologies or therapeutic approaches. Key participants in pharmaceutical marketplaces, such as physicians, third-party payors and consumers, may not accept a product intended to improve therapeutic results based on RNAi technology. As a result, it may be more

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difficult for us to convince the medical community and third-party payors to accept and use our product, or to provide favorable reimbursement.

Other factors that we believe will materially affect market acceptance of our product candidates include:

- the timing of our receipt of any marketing approvals, the terms of any approvals and the countries in which approvals are obtained;
- the safety and efficacy of our product candidates, as demonstrated in clinical trials;
- relative convenience and ease of administration of our product candidates;
- the willingness of patients to accept potentially new routes of administration;
- the success of our physician education programs;
- the availability of adequate government and third-party payor reimbursement;
- the pricing of our products, particularly as compared to alternative treatments; and
- availability of alternative effective treatments for the diseases that product candidates we develop are intended to treat and the relative risks, benefits and costs of the treatments.

In addition, our estimates regarding the potential market size may be materially different from what we currently expect at the time we commence commercialization, which could result in significant changes in our business plan and may have a material adverse effect on our results of operations and financial condition.

If we or our collaborators, manufacturers or service providers fail to comply with healthcare laws and regulations, we or they could be subject to enforcement actions, which could affect our ability to develop, market and sell our products and may harm our reputation.

As a manufacturer of pharmaceuticals, we are subject to federal, state, and foreign healthcare laws and regulations pertaining to fraud and abuse and patients rights. These laws and regulations include:

- the U.S. federal healthcare program anti-kickback law, which prohibits, among other things, persons from soliciting, receiving or providing remuneration, directly or indirectly, to induce either the referral of an individual for a healthcare item or service, or the purchasing or ordering of an item or service, for which payment may be made under a federal healthcare program such as Medicare or Medicaid;
- the U.S. federal false claims law, which prohibits, among other things, individuals or entities from knowingly presenting or causing to be presented, claims for payment by government funded programs such as Medicare or Medicaid that are false or fraudulent, and which may apply to us by virtue of statements and representations made to customers or third parties;

the U.S. federal Health Insurance Portability and Accountability Act, or HIPAA, and Health Information Technology for Economic and Clinical Health, or HITECH, Act, which prohibit executing a scheme to defraud healthcare programs; impose requirements relating to the privacy, security, and transmission of individually identifiable health information; and require notification to affected individuals and regulatory authorities of certain breaches of security of individually identifiable health information;

the federal Open Payments regulations under the National Physician Payment Transparency Program have been issued under PPACA and will require that manufacturers of pharmaceutical and biological drugs covered by Medicare, Medicaid, and Children s Health Insurance Programs report all consulting fees, travel reimbursements, research grants, and other payments or gifts with values over $10 made to physicians and teaching hospitals; and

state laws comparable to each of the above federal laws, such as, for example, anti-kickback and false claims laws applicable to commercial insurers and other non-federal payors, requirements for mandatory corporate regulatory compliance programs, and laws relating to patient data privacy and security.

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If our operations are found to be in violation of any such requirements, we may be subject to penalties, including civil or criminal penalties, monetary damages, the curtailment or restructuring of our operations, loss of eligibility to obtain approvals from the FDA, or exclusion from participation in government contracting, healthcare reimbursement or other government programs, including Medicare and Medicaid, any of which could adversely our financial results. Although effective compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, these risks cannot be entirely eliminated. Any action against us for an alleged or suspected violation could cause us to incur significant legal expenses and could divert our management s attention from the operation of our business, even if our defense is successful. In addition, achieving and sustaining compliance with applicable laws and regulations may be costly to us in terms of money, time and resources.

If we or our collaborators, manufacturers or service providers fail to comply with applicable federal, state or foreign laws or regulations, we could be subject to enforcement actions, which could affect our ability to develop, market and sell our products successfully and could harm our reputation and lead to reduced acceptance of our products by the market. These enforcement actions include, among others:

- adverse regulatory inspection findings;
- warning letters;
- voluntary or mandatory product recalls or public notification or medical product safety alerts to healthcare professionals;
- restrictions on, or prohibitions against, marketing our products;
- restrictions on, or prohibitions against, importation or exportation of our products;
- suspension of review or refusal to approve pending applications or supplements to approved applications;
- exclusion from participation in government-funded healthcare programs;
- exclusion from eligibility for the award of government contracts for our products;
- suspension or withdrawal of product approvals;
- product seizures;
- injunctions; and
- civil and criminal penalties and fines.

Any drugs we develop may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, thereby harming our business.

The regulations that govern marketing approvals, pricing and reimbursement for new drugs vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. Although we intend to monitor these regulations, our programs are currently in the early stages of development and we will not be able to assess the impact of price regulations for a number of years. As a result, we might obtain regulatory approval for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product and negatively impact the revenues we are able to generate from the sale of the product in that country.

Our ability to commercialize any products successfully also will depend in part on the extent to which reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. Even if we succeed in bringing one or more products to the market, these products may not be considered cost-effective, and the amount reimbursed for any products

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may be insufficient to allow us to sell our products on a competitive basis. Because our programs are in the early stages of development, we are unable at this time to determine their cost effectiveness or the likely level or method of reimbursement. Increasingly, the third-party payors who reimburse patients or healthcare providers, such as government and private insurance plans, are requiring that drug companies provide them with predetermined discounts from list prices, and are seeking to reduce the prices charged or the amounts reimbursed for pharmaceutical products. If the price we are able to charge for any products we develop, or the reimbursement provided for such products, is inadequate in light of our development and other costs, our return on investment could be adversely affected.

We currently expect that any drugs we develop may need to be administered under the supervision of a physician on an outpatient basis. Under currently applicable U.S. law, certain drugs that are not usually self-administered (including injectable drugs) may be eligible for coverage under the Medicare Part B program if:

- they are incident to a physician s services;
- they are reasonable and necessary for the diagnosis or treatment of the illness or injury for which they are administered according to accepted standards of medical practice; and
- they have been approved by the FDA and meet other requirements of the statute.

There may be significant delays in obtaining coverage for newly-approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA. Moreover, eligibility for coverage does not imply that any drug will be reimbursed in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim payments for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement may be based on payments allowed for lower-cost drugs that are already reimbursed, may be incorporated into existing payments for other services and may reflect budgetary constraints or imperfections in Medicare data. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement rates. Our inability to promptly obtain coverage and adequate reimbursement rates from both government-funded and private payors for new drugs that we develop and for which we obtain regulatory approval could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products, and our overall financial condition.

We believe that the efforts of governments and third-party payors to contain or reduce the cost of healthcare and legislative and regulatory proposals to broaden the availability of healthcare will continue to affect the business and financial condition of pharmaceutical and biopharmaceutical companies. A number of legislative and regulatory changes in the healthcare system in the United States and other major healthcare markets have been proposed in recent years, and such efforts have expanded substantially in recent years. These developments have included prescription drug benefit legislation that was enacted and took effect in January 2006, healthcare reform legislation enacted by certain states, and major healthcare reform legislation that was passed by Congress and enacted into law in the United States in 2010. These developments could, directly or indirectly, affect our ability to sell our products, if approved, at a favorable price.

In particular, in March 2010, the Patient Protection and Affordable Care Act, or PPACA, and a related reconciliation bill were signed into law. This new legislation changes the current system of healthcare insurance and benefits intended to broaden coverage and control costs. The new law also contains provisions that will affect companies in the pharmaceutical industry and other healthcare related industries by imposing additional costs and changes to business practices. Provisions affecting pharmaceutical companies include the following:

- Mandatory rebates for drugs sold into the Medicaid program have been increased, and the rebate requirement has been extended to drugs used in risk-based Medicaid managed care plans.
- The 340B Drug Pricing Program under the Public Health Services Act has been extended to require mandatory discounts for drug products sold to certain critical access hospitals, cancer hospitals and other covered entities.

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Pharmaceutical companies are required to offer discounts on brand-name drugs to patients who fall within the Medicare Part D coverage gap, commonly referred to as the Donut Hole.

Pharmaceutical companies are required to pay an annual non-tax deductible fee to the federal government based on each company s market share of prior year total sales of branded products to certain federal healthcare programs, such as Medicare, Medicaid, Department of Veterans Affairs and Department of Defense. Since we expect our branded pharmaceutical sales to constitute a small portion of the total federal health program pharmaceutical market, we do not expect this annual assessment to have a material impact on our financial condition.

The new law provides that approval of an application for a follow-on biologic product may not become effective until 12 years after the date on which the reference innovator biologic product was first licensed by the FDA, with a possible six-month extension for pediatric products. After this exclusivity ends, it will be easier for generic manufacturers to enter the market, which is likely to reduce the pricing for such products and could affect our profitability.

The full effects of the U.S. healthcare reform legislation cannot be known until the new law is fully implemented through regulations or guidance issued by the Centers for Medicare & Medicaid Services and other federal and state healthcare agencies. The financial impact of the U.S. healthcare reform legislation over the next few years will depend on a number of factors, including but not limited, to the policies reflected in implementing regulations and guidance, and changes in sales volumes for products affected by the new system of rebates, discounts and fees. The new legislation may also have a positive impact on our future net sales, if any, by increasing the aggregate number of persons with healthcare coverage in the United States, but such increases are unlikely to be realized until approximately 2014 at the earliest.

Moreover, we cannot predict what healthcare reform initiatives may be adopted in the future. Further federal and state legislative and regulatory developments are likely, and we expect ongoing initiatives in the United States to increase pressure on drug pricing. Such reforms could have an adverse effect on anticipated revenues from product candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our overall financial condition and ability to develop drug candidates.

Our ability to obtain services, reimbursement or funding from the federal government may be impacted by possible reductions in federal spending.

U.S. federal government agencies currently face potentially significant spending reductions. Under the Budget Control Act of 2011, the failure of Congress to enact deficit reduction measures of at least $1.2 trillion for the years 2013 through 2021 triggered automatic cuts to most federal programs. These cuts would include aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, starting in 2013. Under the American Taxpayer Relief Act of 2012, which was enacted on January 1, 2013, the imposition of these automatic cuts was delayed until March 1, 2013. The full impact on our business of these automatic cuts, assuming they are implemented, is uncertain.

If federal spending is reduced, anticipated budgetary shortfalls may also impact the ability of relevant agencies, such as the FDA or NIH to continue to function at current levels. Amounts allocated to federal grants and contracts may be reduced or eliminated. These reductions may also impact the ability of relevant agencies to timely review and approve drug research and development, manufacturing, and marketing activities, which may delay our ability to develop, market and sell any products we may develop.

There is a substantial risk of product liability claims in our business. If we are unable to obtain sufficient insurance, a product liability claim against us could adversely affect our business.

Our business exposes us to significant potential product liability risks that are inherent in the development, testing, manufacturing and marketing of human therapeutic products. Product liability claims could delay or prevent completion of our clinical development programs. If we succeed in marketing products, such claims could result in an FDA investigation of the safety and effectiveness of our products, our manufacturing processes

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and facilities or our marketing programs, and potentially a recall of our products or more serious enforcement action, limitations on the approved indications for which they may be used, or suspension or withdrawal of approvals. Regardless of the merits or eventual outcome, liability claims may also result in injury to our reputation, costs to defend the related litigation, a diversion of management s time and our resources, and substantial monetary awards to trial participants or patients. We currently have product liability insurance that we believe is appropriate for our stage of development and may need to obtain higher levels prior to marketing any of our product candidates. Any insurance we have or may obtain may not provide sufficient coverage against potential liabilities. Furthermore, clinical trial and product liability insurance is becoming increasingly expensive. As a result, we may be unable to obtain sufficient insurance at a reasonable cost to protect us against losses caused by product liability claims that could have a material adverse effect on our business.

If we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected.

Our research and development involves the use of hazardous materials, chemicals and various radioactive compounds. We maintain quantities of various flammable and toxic chemicals in our facilities in Cambridge that are required for our research and development activities. We are subject to federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. We believe our procedures for storing, handling and disposing these materials in our Cambridge facilities comply with the relevant guidelines of the City of Cambridge, the Commonwealth of Massachusetts and the Occupational Safety and Health Administration of the U.S. Department of Labor. Although we believe that our safety procedures for handling and disposing of these materials comply with the standards mandated by applicable regulations, the risk of accidental contamination or injury from these materials cannot be eliminated. If an accident occurs, we could be held liable for resulting damages, which could be substantial. We are also subject to numerous environmental, health and workplace safety laws and regulations, including those governing laboratory procedures, exposure to blood-borne pathogens and the handling of biohazardous materials.

Although we maintain workers compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of these materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials. Additional federal, state and local laws and regulations affecting our operations may be adopted in the future. We may incur substantial costs to comply with, and substantial fines or penalties if we violate, any of these laws or regulations.

Risks Related to Patents, Licenses and Trade Secrets

If we are not able to obtain and enforce patent protection for our discoveries, our ability to develop and commercialize our product candidates will be harmed.

Our success depends, in part, on our ability to protect proprietary methods and technologies that we develop under the patent and other intellectual property laws of the United States and other countries, so that we can prevent others from unlawfully using our inventions and proprietary information. However, we may not hold proprietary rights to some patents required for us to commercialize our proposed products. Because certain U.S. patent applications are confidential until the patents issue, such as applications filed prior to November 29, 2000, or applications filed after such date which will not be filed in foreign countries, third parties may have filed patent applications for technology covered by our pending patent applications without our being aware of those applications, and our patent applications may not have priority over those applications. For this and other reasons, we may be unable to secure desired patent rights, thereby losing desired exclusivity. Further, we may be required to obtain licenses under third-party patents to market our proposed products or conduct our research and development or other activities. If licenses are not available to us on acceptable terms, we will not be able to market the affected products or conduct the desired activities.

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Our strategy depends on our ability to rapidly identify and seek patent protection for our discoveries. In addition, we may rely on third-party collaborators to file patent applications relating to proprietary technology that we develop jointly during certain collaborations. The process of obtaining patent protection is expensive and time-consuming. If our present or future collaborators fail to file and prosecute all necessary and desirable patent applications at a reasonable cost and in a timely manner, our business will be adversely affected. Despite our efforts and the efforts of our collaborators to protect our proprietary rights, unauthorized parties may be able to obtain and use information that we regard as proprietary. While issued patents are presumed valid, this does not guarantee that the patent will survive a validity challenge or be held enforceable. Any patents we have obtained, or obtain in the future, may be challenged, invalidated, adjudged unenforceable or circumvented by parties attempting to design around our intellectual property. Moreover, third parties or the United States Patent and Trademark Office, or USPTO, may commence interference proceedings involving our patents or patent applications. Any challenge to, finding of unenforceability or invalidation or circumvention of, our patents or patent applications, would be costly, would require significant time and attention of our management and could have a material adverse effect on our business.

Our pending patent applications may not result in issued patents. The patent position of pharmaceutical or biotechnology companies, including ours, is generally uncertain and involves complex legal and factual considerations. The standards that the USPTO and its foreign counterparts use to grant patents are not always applied predictably or uniformly and can change. Similarly, the ultimate degree of protection that will be afforded to biotechnology inventions, including ours, in the United States and foreign countries, remains uncertain and is dependent upon the scope of the protection decided upon by patent offices, courts and lawmakers. Moreover, there are periodic discussions in the Congress of the United States and in international jurisdictions about modifying various aspects of patent law. For example, the America Invents Act includes a number of changes to the patent laws of the United States. If any changes to the patent laws are enacted and do not provide adequate protection for discoveries, including our ability to pursue infringers of our patents for substantial damages, our business could be adversely affected. There is also no uniform, worldwide policy regarding the subject matter and scope of claims granted or allowable in pharmaceutical or biotechnology patents.

Accordingly, we do not know the degree of future protection for our proprietary rights or the breadth of claims that will be allowed in any patents issued to us or to others. We also rely to a certain extent on trade secrets, know-how and technology, which are not protected by patents, to maintain our competitive position. If any trade secret, know-how or other technology not protected by a patent were to be disclosed to or independently developed by a competitor, our business and financial condition could be materially adversely affected.

We license patent rights from third-party owners. If such owners do not properly or successfully obtain, maintain or enforce the patents underlying such licenses, our competitive position and business prospects will be harmed.

We are a party to a number of licenses that give us rights to third-party intellectual property that is necessary or useful for our business. In particular, we have obtained licenses from, among others, CRT, Isis, MIT, Whitehead, Max Planck Innovation, Tekmira, UTSW and Arrowhead. We also intend to enter into additional licenses to third-party intellectual property in the future.

Our success will depend in part on the ability of our licensors to obtain, maintain and enforce patent protection for our licensed intellectual property, in particular, those patents to which we have secured exclusive rights. Our licensors may not successfully prosecute the patent applications to which we are licensed. Even if patents issue in respect of these patent applications, our licensors may fail to maintain these patents, may determine not to pursue litigation against other companies that are infringing these patents, or may pursue such litigation less aggressively than we would. Without protection for the intellectual property we license, other companies might be able to offer substantially identical products for sale, which could adversely affect our competitive business position and harm our business prospects. In addition, we sublicense our rights under various third-party licenses to our collaborators. Any impairment of these sublicensed rights could result in

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reduced revenues under our collaboration agreements or result in termination of an agreement by one or more of our collaborators.

Other companies or organizations may challenge our patent rights or may assert patent rights that prevent us from developing and commercializing our products.

RNAi is a relatively new scientific field, the commercial exploitation of which has resulted in many different patents and patent applications from organizations and individuals seeking to obtain patent protection in the field. We have obtained grants and issuances of RNAi patents and have licensed many of these patents from third parties on an exclusive basis. The issued patents and pending patent applications in the United States and in key markets around the world that we own or license claim many different methods, compositions and processes relating to the discovery, development, manufacture and commercialization of RNAi therapeutics.

Specifically, we have a portfolio of patents, patent applications and other intellectual property covering: fundamental aspects of the structure and uses of siRNAs, including their manufacture and use as therapeutics, and RNAi-related mechanisms; chemical modifications to siRNAs that improve their suitability for therapeutic uses; siRNAs directed to specific targets as treatments for particular diseases; and delivery technologies, such as in the field of cationic liposomes.

As the field of RNAi therapeutics is maturing, patent applications are being fully processed by national patent offices around the world. There is uncertainty about which patents will issue, and, if they do, as to when, to whom, and with what claims. It is likely that there will be significant litigation and other proceedings, such as interference, reexamination and opposition proceedings, in various patent offices relating to patent rights in the RNAi field. For example, various third parties have initiated oppositions to patents in our Kreutzer-Limmer and Tuschl II series in the European Patent Office, or EPO, and in other jurisdictions. We expect that additional oppositions will be filed in the EPO and elsewhere, and other challenges will be raised relating to other patents and patent applications in our portfolio. In many cases, the possibility of appeal exists for either us or our opponents, and it may be years before final, unappealable rulings are made with respect to these patents in certain jurisdictions. The timing and outcome of these and other proceedings is uncertain and may adversely affect our business if we are not successful in defending the patentability and scope of our pending and issued patent claims. In addition, third parties may attempt to invalidate our intellectual property rights. Even if our rights are not directly challenged, disputes could lead to the weakening of our intellectual property rights. Our defense against any attempt by third parties to circumvent or invalidate our intellectual property rights could be costly to us, could require significant time and attention of our management and could have a material adverse effect on our business and our ability to successfully compete in the field of RNAi.

There are many issued and pending patents that claim aspects of oligonucleotide chemistry and modifications that we may need to apply to our siRNA therapeutic candidates. There are also many issued patents that claim targeting genes or portions of genes that may be relevant for siRNA drugs we wish to develop. Thus, it is possible that one or more organizations will hold patent rights to which we will need a license. If those organizations refuse to grant us a license to such patent rights on reasonable terms, we may not be able to market products or perform research and development or other activities covered by these patents.

If we become involved in patent litigation or other proceedings related to a determination of rights, we could incur substantial costs and expenses, substantial liability for damages or be required to stop our product development and commercialization efforts.

Third parties may sue us for infringing their patent rights. Likewise, we may need to resort to litigation to enforce a patent issued or licensed to us or to determine the scope and validity of proprietary rights of others. In addition, a third party may claim that we have improperly obtained or used its confidential or proprietary information. For example, in March 2011, Tekmira filed a civil complaint against us alleging, among other things, misappropriation of the plaintiffs confidential and proprietary information and trade secrets. In November 2012, we settled this litigation and restructured our contractual relationship with Tekmira. In connection with this restructuring, we incurred a $65.0 million charge to operating expenses during the quarter

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ended December 31, 2012. In addition, during the pendency of the litigation, we incurred significant costs, and the defense of this litigation diverted the attention of our management and other resources that would otherwise have been engaged in other activities.

Furthermore, third parties may challenge the inventorship of our patents or licensed patents. For example, in March 2011, the University of Utah, or Utah, filed a complaint in the United States District Court for the District of Massachusetts against us, Max Planck Gesellschaft Zur Foerderung Der Wissenschaften e.V. and Max Planck Innovation, together, Max Planck, Whitehead, MIT and UMass, claiming that a professor of Utah is the sole inventor, or in the alternative, a joint inventor of certain of our in-licensed patents. The original complaint was not served on any of the parties and, in July 2011, Utah filed an amended complaint containing substantially the same claims as the original complaint against us, Max Planck, Whitehead, MIT and UMass. The amended complaint alleges the defendants have incorrectly determined inventorship of some of our in-licensed patents and further claims unjust enrichment, unfair competition, false advertising and seeks correction of inventorship, injunctive relief and unspecified damages. In October 2011, we, Max Planck, Whitehead, MIT and UMass filed a motion to dismiss and UMass filed a motion to dismiss on separate grounds, which we, Max Planck, Whitehead and MIT have joined. In December 2011, Utah filed a second amended complaint dropping UMass as a defendant and adding as defendants several UMass officials. In June 2012, the Court denied both motions to dismiss. We, Max Planck, Whitehead, MIT and UMass have filed an appeal of the Court s ruling on the motion to dismiss for lack of jurisdiction and have filed a motion requesting that the Court stay the case pending the outcome of the appeal. In July 2012, the Court stayed discovery in the case pending the outcome of the defendants appeal. Oral arguments in the appeal are scheduled to be heard in early March 2013 in the United States Court of Appeals for the Federal Circuit. We intend to vigorously defend ourselves in this matter, however, litigation is subject to inherent uncertainty and a court could ultimately rule against us.

In addition, in connection with certain license and collaboration agreements, we have agreed to indemnify certain third parties for certain costs incurred in connection with litigation relating to intellectual property rights or the subject matter of the agreements. The cost to us of any litigation or other proceeding relating to intellectual property rights, even if resolved in our favor, could be substantial, and litigation would divert our management s efforts. Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. Uncertainties resulting from the initiation and continuation of any litigation could delay our research and development efforts and limit our ability to continue our operations.

If any parties successfully claim that our creation or use of proprietary technologies infringes upon or otherwise violates their intellectual property rights, we might be forced to pay damages, potentially including treble damages, if we are found to have willfully infringed on such parties patent rights. In addition to any damages we might have to pay, a court could require us to stop the infringing activity or obtain a license. Any license required under any patent may not be made available on commercially acceptable terms, if at all. In addition, such licenses are likely to be non-exclusive and, therefore, our competitors may have access to the same technology licensed to us. If we fail to obtain a required license and are unable to design around a patent, we may be unable to effectively market some of our technology and products, which could limit our ability to generate revenues or achieve profitability and possibly prevent us from generating revenue sufficient to sustain our operations. Moreover, we expect that a number of our collaborations will provide that royalties payable to us for licenses to our intellectual property may be offset by amounts paid by our collaborators to third parties who have competing or superior intellectual property positions in the relevant fields, which could result in significant reductions in our revenues from products developed through collaborations.

If we fail to comply with our obligations under any licenses or related agreements, we may be required to pay damages and could lose license or other rights that are necessary for developing and protecting our RNAi technology and any related product candidates that we develop, or we could lose certain exclusive rights to grant sublicenses.

Our current licenses impose, and any future licenses we enter into are likely to impose, various development, commercialization, funding, royalty, diligence, sublicensing, insurance, patent prosecution and enforcement, and other obligations on us. If we breach any of these obligations, or use the intellectual property

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licensed to us in an unauthorized manner, we may be required to pay damages and the licensor may have the right to terminate the license or render the license non-exclusive, which could result in us being unable to develop, manufacture and sell products that are covered by the licensed technology or enable a competitor to gain access to the licensed technology. Moreover, our licensors may own or control intellectual property that has not been licensed to us and, as a result, we may be subject to claims, regardless of their merit, that we are infringing or otherwise violating the licensor s rights. In addition, while we cannot currently determine the amount of the royalty obligations we will be required to pay on sales of future products, if any, the amounts may be significant. The amount of our future royalty obligations will depend on the technology and intellectual property we use in products that we successfully develop and commercialize, if any. Therefore, even if we successfully develop and commercialize products, we may be unable to achieve or maintain profitability.

Confidentiality agreements with employees and others may not adequately prevent disclosure of trade secrets and other proprietary information.

In order to protect our proprietary technology and processes, we rely in part on confidentiality agreements with our collaborators, employees, consultants, outside scientific collaborators and sponsored researchers, and other advisors. These agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. In addition, others may independently discover trade secrets and proprietary information, and in such cases we could not assert any trade secret rights against such party. Costly and time-consuming litigation could be necessary to enforce and determine the scope of our proprietary rights, and failure to obtain or maintain trade secret protection could adversely affect our competitive business position.

Risks Related to Competition

The pharmaceutical market is intensely competitive. If we are unable to compete effectively with existing drugs, new treatment methods and new technologies, we may be unable to commercialize successfully any drugs that we develop.

The pharmaceutical market is intensely competitive and rapidly changing. Many large pharmaceutical and biotechnology companies, academic institutions, governmental agencies and other public and private research organizations are pursuing the development of novel drugs for the same diseases that we are targeting or expect to target. Many of our competitors have:

- much greater financial, technical and human resources than we have at every stage of the discovery, development, manufacture and commercialization of products;
- more extensive experience in pre-clinical testing, conducting clinical trials, obtaining regulatory approvals, and in manufacturing, marketing and selling pharmaceutical products;
- product candidates that are based on previously tested or accepted technologies;
- products that have been approved or are in late stages of development; and
- collaborative arrangements in our target markets with leading companies and research institutions.

We will face intense competition from drugs that have already been approved and accepted by the medical community for the treatment of the conditions for which we may develop drugs. We also expect to face competition from new drugs that enter the market. We believe a significant number of drugs are currently under development, and may become commercially available in the future, for the treatment of conditions for which we may try to develop drugs. For instance, we are currently evaluating RNAi therapeutics for ATTR, hemophilia and RBD, AIP, severe hypercholesterolemia, hemoglobinopathies, including beta-thalassemia, RSV, liver cancers and HD, and have a number of additional discovery programs targeting other diseases. These drugs may be more effective, safer, less expensive, or marketed and sold more effectively, than any products we develop.

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If we successfully develop product candidates, and obtain approval for them, we will face competition based on many different factors, including:

- the safety and effectiveness of our products;
- the ease with which our products can be administered and the extent to which patients accept relatively new routes of administration;
- the timing and scope of regulatory approvals for these products;
- the availability and cost of manufacturing, marketing and sales capabilities;
- price;
- reimbursement coverage; and
- patent position.

Our competitors may develop or commercialize products with significant advantages over any products we develop based on any of the factors listed above or on other factors. Our competitors may therefore be more successful in commercializing their products than we are, which could adversely affect our competitive position and business. Competitive products may make any products we develop obsolete or noncompetitive before we can recover the expenses of developing and commercializing our product candidates. Such competitors could also recruit our employees, which could negatively impact our level of expertise and the ability to execute on our business plan. Furthermore, we also face competition from existing and new treatment methods that reduce or eliminate the need for drugs, such as the use of advanced medical devices. The development of new medical devices or other treatment methods for the diseases we are targeting could make our product candidates noncompetitive, obsolete or uneconomical.

We face competition from other companies that are working to develop novel drugs and technology platforms using technology similar to ours. If these companies develop drugs more rapidly than we do or their technologies, including delivery technologies, are more effective, our ability to successfully commercialize drugs may be adversely affected.

In addition to the competition we face from competing drugs in general, we also face competition from other companies working to develop novel drugs using technology that competes more directly with our own. We are aware of multiple companies that are working in the field of RNAi. In addition, we granted licenses or options for licenses to Isis, GeneCare Research Institute Co., Ltd., Benitec Ltd., Arrowhead and its subsidiary, Calando Pharmaceuticals, Inc., Tekmira, Quark Pharmaceuticals, Inc., Sylentis S.A.U. and others under which these companies may independently develop RNAi therapeutics against a limited number of targets. Any of these companies may develop its RNAi technology more rapidly and more effectively than us. Merck was one of our collaborators and a licensee under our intellectual property for specified disease targets until September 2007, at which time we and Merck agreed to terminate our collaboration. As a result of its acquisition of Sirna Therapeutics, Inc. in December 2006, and in light of the mutual termination of our collaboration, Merck, which has substantially more resources and experience in developing drugs than we do, may become a direct competitor.

In addition, as a result of agreements that we have entered into, Arrowhead, as the assignee of Roche, and Takeda have obtained non-exclusive licenses, and Novartis has obtained specific exclusive licenses for 31 gene targets, to certain aspects of our technology that give them the right to compete with us in certain circumstances We also compete with companies working to develop antisense-based drugs. Like RNAi therapeutics, antisense drugs target mRNAs, in order to suppress the activity of specific genes. Isis is currently marketing an antisense drug and has several antisense product candidates in clinical trials. The development of antisense drugs is more advanced than that of RNAi therapeutics, and antisense technology may become the preferred technology for drugs that target mRNAs to silence specific genes.

In addition to competition with respect to RNAi and with respect to specific products, we face substantial competition to discover and develop safe and effective means to deliver siRNAs to the relevant cell and tissue

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types. Safe and effective means to deliver siRNAs to the relevant cell and tissue types may be developed by our competitors, and our ability to successfully commercialize a competitive product would be adversely affected. In addition, substantial resources are being expended by third parties in the effort to discover and develop a safe and effective means of delivering siRNAs into the relevant cell and tissue types, both in academic laboratories and in the corporate sector. Some of our competitors have substantially greater resources than we do, and if our competitors are able to negotiate exclusive access to those delivery solutions developed by third parties, we may be unable to successfully commercialize our product candidates.

Risks Related to Our Common Stock

If our stock price fluctuates, purchasers of our common stock could incur substantial losses.

The market price of our common stock has fluctuated and may continue to fluctuate significantly in response to factors that are beyond our control. The stock market in general has recently experienced extreme price and volume fluctuations. The market prices of securities of pharmaceutical and biotechnology companies have been extremely volatile, and have experienced fluctuations that often have been unrelated or disproportionate to the operating performance of these companies. These broad market fluctuations could result in extreme fluctuations in the price of our common stock, which could cause purchasers of our common stock to incur substantial losses.

We may incur significant costs from class action litigation due to our expected stock volatility.

Our stock price may fluctuate for many reasons, including as a result of public announcements regarding the progress of our development efforts or the development efforts of our collaborators and/or competitors, the addition or departure of our key personnel, variations in our quarterly operating results and changes in market valuations of pharmaceutical and biotechnology companies. When the market price of a stock has been volatile as our stock price may be, holders of that stock have occasionally brought securities class action litigation against the company that issued the stock. If any of our stockholders were to bring a lawsuit of this type against us, even if the lawsuit is without merit, we could incur substantial costs defending the lawsuit. The lawsuit could also divert the time and attention of our management.

Sales of additional shares of our common stock, including by us or our directors and officers, could cause the price of our common stock to decline.

Sales of substantial amounts of our common stock in the public market, or the availability of such shares for sale, by us or our officers and directors, or others, including the issuance of common stock upon exercise of outstanding options, could adversely affect the price of our common stock.

Anti-takeover provisions in our charter documents and under Delaware law and our stockholder rights plan could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our certificate of incorporation and our bylaws may delay or prevent an acquisition of us or a change in our management. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Because our board of directors is responsible for appointing the members of our management team, these provisions could in turn affect any attempt by our stockholders to replace current members of our management team. These provisions include:

- a classified board of directors;
- a prohibition on actions by our stockholders by written consent;
- limitations on the removal of directors; and

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advance notice requirements for election to our board of directors and for proposing matters that can be acted upon at stockholder meetings.

In addition, our board of directors has adopted a stockholder rights plan, the provisions of which could make it difficult for a potential acquirer of Alnylam to consummate an acquisition transaction. Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. These provisions would apply even if the proposed merger or acquisition could be considered beneficial by some stockholders.

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ITEM 1B. UNRESOLVED STAFF COMMENTS

Not applicable.

ITEM 2. PROPERTIES

Our operations are based primarily in Cambridge, Massachusetts. As of January 31, 2013, we leased approximately 129,000 square feet of office and laboratory space in Cambridge, Massachusetts for our corporate headquarters and primary research facility, of which approximately 34,000 square feet is under sublease to a third party through September 2016, subject to an option to terminate in December 2013, with advance notice and payment of a termination fee. The lease for this property expires in September 2016, and we have the option to extend the lease for two successive five-year periods. In February 2012, we executed a lease for approximately 15,000 square feet of additional office and laboratory space in Cambridge, Massachusetts for our cGMP manufacturing facility. The lease for this property expires in August 2017, and we have the option to extend this lease for two successive five-year periods.

We believe that the total space available to us under our current leases will meet our needs for the foreseeable future and that additional space would be available to us on commercially reasonable terms if required.

ITEM 3. LEGAL PROCEEDINGS

University of Utah Litigation

On March 22, 2011, Utah filed a civil complaint in the United States District Court for the District of Massachusetts against us, Max Planck, Whitehead, MIT and UMass, claiming a professor at Utah is the sole inventor or, in the alternative, a joint inventor, of the Tuschl patents. Utah did not serve the original complaint on us or the other defendants. On July 6, 2011, Utah filed an amended complaint alleging substantially the same claims against us, Max Planck, Whitehead, MIT and UMass. The amended complaint was served on us on July 14, 2011. Utah is seeking changes to the inventorship of the Tuschl patents, unspecified damages and other relief. On October 31, 2011, we, Max Planck, Whitehead, MIT and UMass filed a motion to dismiss. Also on October 31, 2011, UMass filed a motion to dismiss on separate grounds, which we, Max Planck, Whitehead and MIT have joined. On December 31, 2011, the University filed a second amended complaint dropping UMass as a defendant and adding as defendants several UMass officials. In June 2012, the Court denied both motions to dismiss. We, Max Planck, Whitehead, MIT and UMass have filed an appeal of the Court s ruling on the motion to dismiss for lack of jurisdiction and have filed a motion requesting that the Court stay the case pending the outcome of the appeal. In July 2012, the Court stayed discovery in the case pending the outcome of the defendants appeal. Oral arguments in the appeal are scheduled to be heard in early March 2013 in the United States Court of Appeals for the Federal Circuit.

Although we believe we have meritorious defenses and intend to vigorously defend ourself in this matter, litigation is subject to inherent uncertainty and a court could ultimately rule against us. In addition, the defense of litigation and related matters are costly and may divert the attention of our management and other resources that would otherwise be engaged in other activities. We have not recorded an estimate of the possible loss associated with this legal proceeding due to the uncertainties related to both the likelihood and the amount of any possible loss or range of loss.

Tekmira Settlement Agreement

On November 12, 2012, we, TPC, Protiva and AlCana entered into a settlement agreement and general release resolving all ongoing litigation, as well as a patent interference proceeding between us and Protiva. The terms of the settlement agreement include mutual releases and dismissal with prejudice of all claims and counterclaims in the following litigation between the parties: (i) *Tekmira Pharmaceuticals Corp., et al. v. Alnylam Pharmaceuticals, Inc., et al.*, Civ. A. No. 11-1010-BLS2, pending in the Business Litigation Section of the Massachusetts Superior Court for Suffolk County; (ii) *Tekmira Pharmaceuticals Corp. v. Michael Hope, et*

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al., No. S117660, pending in the Supreme Court of British Columbia, Canada; (iii) *Alnylam Pharmaceuticals, Inc., et al. v. Tekmira Pharmaceuticals Corp.*, Civ. A. No. 1:12-CV-10087, pending in the United States District Court for the District of Massachusetts; and (iv) *Alnylam Pharmaceuticals, Inc., et al. v. Tekmira Pharmaceuticals Corp*., Court File No. T-1783-12, pending in the Federal Court of Canada. In addition, as part of the settlement agreement, the parties agreed to a covenant not to sue one another in the future on matters released under the settlement agreement, as well as substantial liquidated damages to be paid by any party that breaches such covenant. The parties have also agreed to resolve any future disputes that may arise over the next three years through binding arbitration.

Pursuant to the settlement agreement, we and Tekmira also agreed to resolve the interference proceeding declared by the United States Board of Patent Appeals and Interferences between the us and Protiva, captioned *Protiva Biotherapeutics, Inc. v. Alnylam Pharmaceuticals, Inc.*, Patent Interference No. 105792.

Contemporaneously with the execution of the settlement agreement, we and Tekmira restructured our contractual relationship and entered into a cross-license agreement that supersedes the prior license and manufacturing agreements among us, TPC and Protiva. In connection with this restructuring, we incurred a $65.0 million charge to operating expenses for the year ended December 31, 2012. A description of our 2012 cross-license agreement with Tekmira is set forth above under Strategic Alliances Delivery-Related Licenses and Collaborations Tekmira.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

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PART II

ITEM 5. MARKET FOR REGISTRANT S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Market Information

Our common stock began trading on The NASDAQ Global Select Market on May 28, 2004 under the symbol ALNY. Prior to that time, there was no established public trading market for our common stock. The following table sets forth the high and low sale prices per share for our common stock on The NASDAQ Global Select Market for the periods indicated:

Year Ended December 31, 2011:	High	Low
First Quarter	$ 12.34	$ 9.03
Second Quarter	$ 10.59	$ 8.80
Third Quarter	$ 10.37	$ 6.28
Fourth Quarter	$ 8.62	$ 5.88

Year Ended December 31, 2012:	High	Low
First Quarter	$ 13.75	$ 8.33
Second Quarter	$ 12.05	$ 9.51
Third Quarter	$ 21.38	$ 11.64
Fourth Quarter	$ 19.48	$ 14.88

Holders of record

At January 31, 2013, there were 41 holders of record of our common stock. Because many of our shares are held by brokers and other institutions on behalf of stockholders, we are unable to estimate the total number of beneficial holders represented by these record holders.

Dividends

We have never paid or declared any cash dividends on our common stock. We currently intend to retain any earnings for future growth and, therefore, do not expect to pay cash dividends in the foreseeable future.

Securities Authorized for Issuance Under Equity Compensation Plans

We intend to file with the SEC a definitive Proxy Statement, which we refer to herein as the Proxy Statement, not later than 120 days after the close of the fiscal year ended December 31, 2012. The information required by this item relating to our equity compensation plans is incorporated herein by reference to the information contained under the section captioned Equity Compensation Plan Information of the Proxy Statement.

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Stock Performance Graph

The following performance graph and related information shall not be deemed soliciting material or to be filed with the SEC, nor shall such information be incorporated by reference into any future filing under the Securities Act of 1933 or Securities Exchange Act of 1934, each as amended, except to the extent that we specifically incorporate it by reference into such filing.

The comparative stock performance graph below compares the five-year cumulative total stockholder return (assuming reinvestment of dividends, if any) from investing $100 on December 31, 2007, to the close of the last trading day of 2012, in each of (i) our common stock, (ii) the NASDAQ Stock Market (U.S.) Index and (iii) the NASDAQ Pharmaceutical Index. The stock price performance reflected in the graph below is not necessarily indicative of future price performance.

Comparison of Five-Year Cumulative Total Return

Among Alnylam Pharmaceuticals, Inc.,

NASDAQ Stock Market (U.S.) Index and NASDAQ Pharmaceutical Index

	12/31/2007	12/31/2008	12/31/2009	12/31/2010	12/30/2011	12/31/2012
Alnylam Pharmaceuticals, Inc.	$ 100.00	$ 85.04	$ 60.59	$ 33.91	$ 28.03	$ 62.76
NASDAQ Stock Market (U.S.) Index	$ 100.00	$ 48.19	$ 69.26	$ 82.22	$ 104.94	$ 123.87
NASDAQ Pharmaceutical Index	$ 100.00	$ 93.04	$ 104.55	$ 113.32	$ 121.44	$ 161.39

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ITEM 6. SELECTED CONSOLIDATED FINANCIAL DATA

The following selected consolidated financial data for each of the five years in the period ended December 31, 2012 are derived from our audited consolidated financial statements. The selected consolidated financial data set forth below should be read in conjunction with Management s Discussion and Analysis of Financial Condition and Results of Operations and the financial statements, and the related Notes, included elsewhere in this annual report on Form 10-K. Historical results are not necessarily indicative of future results.

Selected Consolidated Financial Data

(In thousands, except per share data)

	Year Ended December 31,				
	2012	2011	2010	2009	2008
Statements of Comprehensive Loss Data:					
Net revenues from research collaborators	$ 66,725	$ 82,757	$ 100,041	$ 100,533	$ 96,163
Operating expenses(1)	196,181	137,575	144,111	148,644	123,998
Loss from operations	(129,456)	(54,818)	(44,070)	(48,111)	(27,835)
Net loss	(106,014)	(57,649)	(43,515)	(47,590)	(26,249)
Net loss per common share basic and diluted	$ (2.11)	$ (1.36)	$ (1.04)	$ (1.14)	$ (0.64)
Weighted average common shares outstanding basic and diluted	50,286	42,410	42,040	41,633	41,077
(1) Non-cash stock-based compensation expenses included in operating expenses	$ 12,360	$ 16,676	$ 19,118	$ 19,727	$ 16,382

	December 31,				
	2012	2011	2010	2009	2008
Balance Sheet Data:					
Cash, cash equivalents and marketable securities	$ 226,228	$ 260,809	$ 349,904	$ 435,316	$ 512,709
Working capital	77,111	71,038	152,093	182,801	343,672
Total assets	287,520	281,917	393,265	481,385	554,676
Total stockholders equity	134,053	117,997	158,233	177,965	202,125

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ITEM 7. MANAGEMENT S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

Overview

We are a biopharmaceutical company developing novel therapeutics based on 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 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. 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 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 are also advancing other early stage programs, including ALN-AAT, an RNAi therapeutic targeting 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 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.

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.

In January 2012, we implemented a strategic corporate restructuring pursuant to which we reduced our overall workforce by approximately 33%, to approximately 115 employees. The goal of the strategic corporate restructuring was to align our resources to focus on what we believe to be our highest value opportunities, including a focus on our lead programs, while advancing other pipeline programs through existing alliances and new collaborations. The reduction in personnel costs, along with other external costs, resulted in significant savings in our 2012 operating expenses. The workforce reduction was substantially completed at the end of the first quarter of 2012. During the three months ended March 31, 2012, we substantially completed the implementation of the strategic corporate restructuring and recorded $3.9 million of restructuring-related costs in operating expenses, including employee severance, benefits and related costs. We paid substantially all of these restructuring costs during 2012. We do not expect to incur any additional significant costs associated with this restructuring.

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In November 2012, we, TPC, Protiva and AlCana entered into a settlement agreement and general release resolving all ongoing litigation, as well as a patent interference proceeding between us and Protiva. The terms of the settlement agreement include mutual releases and dismissal with prejudice of all claims and counterclaims in connection with all of the litigation pending between the parties. Contemporaneously with the execution of the settlement agreement, we and Tekmira restructured our contractual relationship and entered into a cross-license agreement that supersedes the prior license and manufacturing agreements among us, TPC and Protiva. In connection with this restructuring, we incurred a $65.0 million charge to operating expenses for the year ended December 31, 2012. A description of our 2012 cross-license agreement with Tekmira is set forth in Part I, Item 1, Strategic Alliances Delivery-Related Licenses and Collaborations Tekmira of this annual report on Form 10-K.

We have incurred significant losses since we commenced operations in 2002 and expect such losses to continue for the foreseeable future. At December 31, 2012, we had an accumulated deficit of $507.0 million. Historically, we have generated losses principally from costs associated with research and development activities, acquiring, filing and expanding intellectual property rights and general administrative costs. As a result of planned expenditures for research and development activities relating to our drug development programs, including the development of drug delivery technologies and clinical trial costs, extension of the capabilities of our technology platform, including through business initiatives, continued management and growth of our patent portfolio, collaborations and general corporate activities, we expect to incur additional operating losses for the foreseeable future. We anticipate that our operating results will fluctuate for the foreseeable future. Therefore, period-to-period comparisons should not be relied upon as predictive of the results in future periods.

Although we currently have programs focused on a number of therapeutic areas, we are unable to predict when, if ever, we will successfully develop or be able to commence sales of any product. To date, a substantial portion of our total net revenues has been derived from collaboration revenues from strategic alliances with Roche, Takeda, Cubist and Novartis, and from the United States government in connection with our development of treatments for hemorrhagic fever viruses, including Ebola. We expect our sources of potential funding for the next several years to be derived primarily from new and existing strategic alliances, which may include license and other fees, funded research and development and milestone payments, government and foundation funding, and proceeds from the sale of equity or debt.

In February 2012, we sold an aggregate of 8,625,000 shares of our common stock through an underwritten public offering at a price to the public of $10.75 per share. As a result of this offering, we received aggregate net proceeds of approximately $86.8 million, after deducting underwriting discounts and commissions and other estimated offering expenses of approximately $5.9 million. 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 this 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 the proceeds from these offerings 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.

Research and Development

Since our inception, we have focused on drug discovery and development programs. Research and development expenses represent a substantial percentage of our total operating expenses. Under our core product strategy, we expect to have five RNAi therapeutic programs in clinical development by the end of 2015, including programs in advanced stages, on our own or with one or more collaborators. While focusing our efforts on our core product strategy, we also intend to continue to advance additional partner-based development programs through existing or future alliances. In addition, we continue to work internally and with third-party collaborators to develop new technologies to deliver our RNAi therapeutics both directly to specific sites of disease, and systemically by intravenous or subcutaneous administration.

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There is a risk that any drug discovery or development program may not produce revenue for a variety of reasons, including the possibility that we will not be able to adequately demonstrate the safety and efficacy of the product candidate. Moreover, there are uncertainties specific to any new field of drug discovery, including RNAi. The successful development of any product candidate we develop is highly uncertain. Due to the numerous risks associated with developing drugs, we cannot reasonably estimate or know the nature, timing and estimated costs of the efforts necessary to complete the development of, or the period, if any, in which material net cash inflows will commence from, any potential product candidate. These risks include the uncertainty of:

our ability to discover new product candidates;

our ability to progress product candidates into pre-clinical and clinical trials;

the scope, rate of progress and cost of our pre-clinical trials and other research and development activities, including those related to developing safe and effective ways of delivering siRNAs into cells and tissues;

the scope, rate of progress and cost of any clinical trials we commence;

clinical trial results;

the cost of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights;

the terms, timing and success of any collaboration, licensing and other arrangements that we may establish;

the cost, timing and success of regulatory filings and approvals or potential changes in regulations that govern our industry or the way in which they are interpreted or enforced;

the cost and timing of establishing sufficient sales, marketing and distribution capabilities;

the cost and timing of establishing sufficient clinical and commercial supplies for any product candidates and products that we may develop;

limits on our ability to research, develop, or manufacture our product candidates as a result of contractual obligations to third parties or intellectual property held by third parties;

the costs associated with legal activities, including litigation, arising in the course of our business activities and our ability to prevail in any such legal disputes; and

the effect of competing technological and market developments.

Any failure to complete any stage of the development of any potential products in a timely manner could have a material adverse effect on our operations, financial position and liquidity. A discussion of some of the risks and uncertainties associated with completing our projects on schedule, or at all, and the potential consequences of failing to do so, are set forth in Part I, Item 1A of this annual report on Form 10-K under the heading Risk Factors.

Strategic Alliances

A significant component of our business plan is to enter into strategic alliances and collaborations with leading pharmaceutical and life sciences companies, academic institutions, research foundations and others, as appropriate, to gain access to funding, capabilities, technical resources and intellectual property to further our development efforts and to generate revenues. We also seek to form or advance new ventures and opportunities in areas outside our primary focus on RNAi therapeutics.

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

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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. At 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, MIT, UBC and AlCana, among others, to focus on various delivery strategies. We have also entered into license agreements with Isis, Max Planck Innovation, Tekmira, MIT, CRT, Whitehead and 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.

Critical Accounting Policies and Estimates

Our discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with GAAP. The preparation of our consolidated financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenues and expenses and disclosure of contingent liabilities in our consolidated financial statements. Actual results may differ from these estimates under different assumptions or conditions and could have a material impact on our reported results. While our significant accounting policies are more fully described in the Notes to our consolidated financial statements included elsewhere in this annual report on Form 10-K, we believe the following accounting policies to be the most critical in understanding the judgments and estimates we use in preparing our consolidated financial statements:

Revenue Recognition

Our business strategy includes entering into collaborative license and development agreements with with leading pharmaceutical and life sciences companies for the development and commercialization of our product candidates. We have entered into collaboration agreements with Novartis, Biogen Idec, Roche/Arrowhead, Takeda, Kyowa Hakko Kirin, Cubist, Ascletis, Monsanto, Genzyme and MedCo. The terms of the agreements typically include non-refundable license fees, funding of research and development, payments based upon achievement of clinical and pre-clinical development milestones, regulatory milestones, manufacturing services, sales milestones and royalties on product sales.

In January 2011, we adopted new authoritative guidance on revenue recognition for multiple element arrangements. The guidance, which applies to multiple element arrangements entered into or materially modified on or after January 1, 2011, amends the criteria for separating and allocating consideration in a multiple element arrangement by modifying the fair value requirements for revenue recognition and eliminating the use of the residual method. The fair value of deliverables under the arrangement may be derived using a best estimate of selling price if vendor specific objective evidence and third-party evidence is not available. Deliverables under the arrangement will be separate units of accounting provided that (i) a delivered item has value to the customer on a standalone basis and (ii) if the arrangement includes a general right of return relative to the delivered item, delivery or performance of the undelivered item is considered probable and substantially in the control of the vendor. The new guidance did not change the criteria for standalone value. As a biotechnology entity with unique and specialized delivered and undelivered performance obligations, we have been unable to demonstrate standalone value in our multiple element arrangements. For example, we applied the new rules to collaborations executed with Monsanto and Genzyme during 2012, but we were unable to demonstrate standalone value. In addition, we have not materially modified any of our multiple element arrangements. As such, we will continue to account for our other license and collaboration agreements under previously issued revenue recognition guidance for multiple element arrangements, as described below.

Non-refundable license fees are recognized as revenue upon delivery of the license only if we have a contractual right to receive such payment, the contract price is fixed or determinable, the collection of the

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resulting receivable is reasonably assured and we have no further performance obligations under the license agreement. Multiple element arrangements, such as license and development arrangements, are analyzed to determine whether the deliverables, which often include a license and performance obligations such as research and steering committee services, can be separated or whether they must be accounted for as a single unit of accounting. We recognize upfront license payments as revenue upon delivery of the license only if the license has standalone value and the fair value of the undelivered performance obligations, typically including research and/or steering committee services, can be determined. If the fair value of the undelivered performance obligations can be determined, such obligations would then be accounted for separately as performed. If the license is considered to either not have standalone value or have standalone value but the fair value of any of the undelivered performance obligations cannot be determined, the arrangement would then be accounted for as a single unit of accounting and the license payments and payments for performance obligations are recognized as revenue over the estimated period of when the performance obligations are performed.

Whenever we determine that an arrangement should be accounted for as a single unit of accounting, we must determine the period over which the performance obligations will be performed and revenue will be recognized. We recognize revenue using either a proportional performance or straight-line method. We recognize revenue using the proportional performance method when we can reasonably estimate the level of effort required to complete our performance obligations under an arrangement and such performance obligations are provided on a best-efforts basis. Direct labor hours or full-time equivalents are typically used as the measure of performance. The amount of revenue recognized under the proportional performance method is determined by multiplying the total payments under the contract, excluding royalties and payments contingent upon achievement of milestones, by the ratio of level of effort incurred to date to estimated total level of effort required to complete our performance obligations under the arrangement. Revenue is limited to the lesser of the cumulative amount of payments received or the cumulative amount of revenue earned, as determined using the proportional performance method, as of the period ending date.

If we cannot reasonably estimate the level of effort required to complete our performance obligations under an arrangement, we recognize revenue under the arrangement on a straight-line basis over the period we expect to complete our performance obligations. Revenue is limited to the lesser of the cumulative amount of payments received or the cumulative amount of revenue earned, as determined using the straight-line method, as of the period ending date.

Significant management judgment is required in determining the level of effort required under an arrangement and the period over which we are expected to complete our performance obligations under an arrangement. Steering committee services that are not inconsequential or perfunctory and that are determined to be performance obligations are combined with other research services or performance obligations required under an arrangement, if any, in determining the level of effort required in an arrangement and the period over which we expect to complete our aggregate performance obligations.

Many of our collaboration agreements entitle us to additional payments upon the achievement of performance-based milestones. These milestones are generally categorized into three types; development milestones which are generally based on the advancement of our pipeline and initiation of clinical trials, regulatory milestones which are generally based on the submission, filing or approval of regulatory applications such as an NDA in the United States, and commercialization milestones which are generally based on meeting specific thresholds of sales in certain geographic areas. If the achievement of a milestone is considered probable at the inception of the collaboration, the related milestone payment is included with other collaboration consideration, such as upfront fees and research funding, in our revenue model. Milestones that are tied to regulatory approval are not considered probable of being achieved until such approval is received. Milestones tied to counter-party performance are not included in our revenue model until the performance conditions are met.

We perform an assessment to determine whether a substantive milestone exists at the inception of our collaborative arrangements. In evaluating if a milestone is substantive, we consider whether uncertainty exists as to the achievement of the milestone event at the inception of the arrangement, the achievement of the milestone

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involves substantive effort and can only be achieved based in whole or part on the performance or the occurrence of a specific outcome resulting from our performance, the amount of the milestone payment appears reasonable either in relation to the effort expected to be expended or to the projected enhancement of the value of the delivered items, there is any future performance required to earn the milestone, and the consideration is reasonable relative to all deliverables and payment terms in the arrangement. When a substantive milestone is achieved, the accounting rules permit us to recognize revenue related to the milestone payment in its entirety.

To date, we have not recorded any substantive milestones under our collaborations because we have not identified any milestones that meet the required criteria listed above. We have deferred recognition of payments for achievement of non-substantive milestones and recognized revenue over the estimated period of performance applicable to each collaborative arrangement. As these milestones are achieved, we will recognize as revenue a portion of the milestone payment, which is equal to the percentage of the performance period completed, when the milestone is achieved, multiplied by the amount of the milestone payment, upon achievement of such milestone. We will recognize the remaining portion of the milestone payment over the remaining performance period under the proportional performance method or on a straight-line basis.

For revenue generating arrangements where we, as a vendor, provide consideration to a licensor or collaborator, as a customer, we apply the accounting standard that governs such transactions. This standard addresses the accounting for revenue arrangements where both the vendor and the customer make cash payments to each other for services and/or products. A payment to a customer is presumed to be a reduction of the selling price unless we receive an identifiable benefit for the payment and we can reasonably estimate the fair value of the benefit received. Payments to a customer that are deemed a reduction of selling price are recorded first as a reduction of revenue, to the extent of both cumulative revenue recorded to date and probable future revenues, which include any unamortized deferred revenue balances, under all arrangements with such customer, and then as an expense. Payments that are not deemed to be a reduction of selling price are recorded as an expense.

We evaluate our collaborative agreements for proper classification in our consolidated statements of comprehensive loss based on the nature of the underlying activity. Transactions between collaborators recorded in our consolidated statements of comprehensive loss are recorded on either a gross or net basis, depending on the characteristics of the collaborative relationship. We generally reflect amounts due under our collaborative agreements related to cost-sharing of development activities as a reduction of research and development expense.

Amounts received prior to satisfying the above revenue recognition criteria are recorded as deferred revenue in the accompanying consolidated balance sheets. Although we follow detailed guidelines in measuring revenue, certain judgments affect the application of our revenue policy. For example, in connection with our existing collaboration agreements, we have recorded on our balance sheet short-term and long-term deferred revenue based on our best estimate of when such revenue will be recognized. Short-term deferred revenue consists of amounts that are expected to be recognized as revenue in the next 12 months. Amounts that we expect will not be recognized prior to the next 12 months are classified as long-term deferred revenue. However, this estimate is based on our current operating plan and, if our operating plan should change in the future, we may recognize a different amount of deferred revenue over the next 12-month period.

The estimate of deferred revenue also reflects management s estimate of the periods of our involvement in certain of our collaborations. Our performance obligations under these collaborations consist of participation on steering committees and the performance of other research and development services. In certain instances, the timing of satisfying these obligations can be difficult to estimate. Accordingly, our estimates may change in the future. Such changes to estimates would result in a change in revenue recognition amounts. If these estimates and judgments change over the course of these agreements, it may affect the timing and amount of revenue that we recognize and record in future periods. At December 31, 2012, we had short-term and long-term deferred revenue of $31.4 million and $100.9 million, respectively, related to our collaborations.

We recognize revenue under government cost reimbursement contracts as we perform the underlying research and development activities.

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Roche/Arrowhead. We received aggregate proceeds from Roche of $331.0 million in August 2007, of which $278.2 million was recorded as deferred revenue in connection with this alliance. We and Roche established a discovery collaboration in October 2009, pursuant to the terms of the Roche license and collaboration agreement and 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 that 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 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. For purposes of potential future revenue recognition, we do not believe this milestone or any future milestones are substantive. 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.

We determined that the deliverables under these agreements included the license, the Alnylam Europe assets and employees, the steering committees (joint steering committee and future technology committee) and the services under the discovery collaboration. We also determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the license and assets of Alnylam Europe were not separable from the undelivered services (i.e., the steering committees and discovery collaboration) and, accordingly, the license and the services were treated as a single unit of accounting. When multiple deliverables are accounted for as a single unit of accounting, we base our revenue recognition pattern on the final deliverable. Under the Arrowhead alliance, the steering committee services and the discovery collaboration services were the final deliverables and all such services ended, contractually, in August 2012, five years from the effective date of the license and collaboration agreement.

We recognized revenue related to these agreements on a straight-line basis over five years because we could not reasonably estimate the total level of effort required to complete our service obligations under the license and collaboration agreement, and therefore, could not utilize a proportional performance model. At December 31, 2012, there was no remaining deferred revenue under the license and collaboration agreement as we recognized all remaining Roche/Arrowhead revenue during the quarter ended September 30, 2012. We will recognize future milestones under the license and collaboration agreement, if any, when such milestones are achieved.

Takeda. In consideration for the rights granted to Takeda under the Takeda agreement, Takeda paid us an upfront payment of $100.0 million in June 2008 and agreed to pay us an additional $50.0 million upon achievement of specified technology transfer milestones. Of this $50.0 million, $20.0 million was paid in October 2008, $20.0 million was paid in March 2010 and $10.0 million was paid in March 2011. 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 up to 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. For purposes of potential future revenue recognition, we do not believe this milestone or any

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future milestones are substantive. 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.

Pursuant to the Takeda agreement, we and Takeda have also agreed to collaborate on the research of RNAi therapeutics directed to one or two disease targets agreed to by the parties, subject to our existing contractual obligations with third parties. The collaboration is governed by a JTTC, a JRCC and a JDCC, each of which is comprised of an equal number of representatives from each party.

We have determined that the deliverables under the Takeda agreement include the license, the joint committees (the JTTC, JRCC and JDCC), the technology transfer activities and the services that we will be obligated to perform under the research collaboration with Takeda. We also have determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the license and undelivered services (i.e., the joint committees and the research collaboration) are not separable and, accordingly, the license and services are being treated as a single unit of accounting. Under the Takeda agreement, the last elements to be delivered are the JDCC and JTTC services, each of which has a life of no more than seven years. We are recognizing the upfront payment of $100.0 million and the technology transfer milestones of $50.0 million, the receipt of which we believed was probable at the commencement of the collaboration, on a straight-line basis over seven years because we are unable to reasonably estimate the level of effort to fulfill these obligations, primarily because the effort required under the research collaboration is largely unknown, and therefore, cannot utilize a proportional performance model. As future milestones are achieved, we will recognize as revenue a portion of the milestone payment equal to the percentage of the performance period completed when the milestone is achieved, multiplied by the amount of the milestone payment. At December 31, 2012, deferred revenue under the Takeda agreement was $52.8 million.

Kyowa Hakko Kirin. Under the terms of the Kyowa Hakko Kirin agreement, in June 2008, Kyowa Hakko Kirin paid us an upfront cash payment of $15.0 million. In addition, Kyowa Hakko Kirin is required to make payments to us upon achievement of specified development and sales milestones totaling up to $78.0 million, and double-digit royalty payments based on annual net sales, if any, of RNAi therapeutics for the treatment of RSV by Kyowa Hakko Kirin, its affiliates and sublicenses in the licensed territory. 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 Kyowa Hakko Kirin.

Our collaboration with Kyowa Hakko Kirin is governed by a joint steering committee that is comprised of an equal number of representatives from each party. We are responsible for supply of the product to Kyowa Hakko Kirin under a supply agreement unless Kyowa Hakko Kirin elects, prior to the first commercial sale of the product in the licensed territory, to manufacture the product itself or arrange for a third party to manufacture the product.

We have determined that the deliverables under the Kyowa Hakko Kirin agreement include the license, the joint steering committee, the manufacturing services and any additional RSV-specific RNAi therapeutic compounds that comprise the ALN-RSV program. We have determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the individual deliverables are not separable and, accordingly, must be accounted for as a single unit of accounting. We are currently unable to reasonably estimate our period of performance under the Kyowa Hakko Kirin agreement, as we are unable to estimate the timeline of our deliverables related to the fixed-price option granted to Kyowa Hakko Kirin for any additional compounds. We are deferring all revenue under the Kyowa Hakko Kirin agreement until we are able to reasonably estimate our period of performance. We will continue to reassess whether we can reasonably estimate the period of performance to fulfill our obligations under the Kyowa Hakko Kirin agreement. At December 31, 2012, deferred revenue under the Kyowa Hakko Kirin agreement was $15.5 million.

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Monsanto. 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. For purposes of potential future revenue recognition, we do not believe this milestone or any future milestones are substantive. 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.

Under the terms of the Monsanto agreement, in the event that during the exclusivity period Monsanto loses certain patent rights, and such loss 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.

We have determined that the significant deliverables under the Monsanto agreement include the license, the technology transfer activities and the services that we will be obligated to perform under the Monsanto discovery collaboration. We have also determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the license and undelivered technical transfer activities and Monsanto discovery collaboration services do not have standalone value due to the specialized nature of the services to be provided by us. In addition, while Monsanto has the ability to grant sublicenses, it cannot grant access to certain of our proprietary technology. The uniqueness of our services and the limited sublicense right are indicators that standalone value is not present in the arrangement. Therefore the deliverables are not separable and, accordingly, the license and undelivered technical transfer activities and Monsanto discovery collaboration services are being treated as a single unit of accounting. When multiple deliverables are accounted for as a single unit of accounting, we base our revenue recognition model on the final deliverable. Under the Monsanto agreement, the last deliverable to be completed is the Monsanto discovery collaboration, which must be completed within five years. We are recognizing revenue under the Monsanto agreement on a straight-line basis over five years. We are not utilizing a proportional performance model since we are unable to reasonably estimate the level of effort to fulfill these obligations, primarily because the effort required under the Monsanto discovery collaboration is largely unknown.

Genzyme. In consideration for the rights granted to Genzyme under the Genzyme agreement, Genzyme paid us an upfront cash payment of $22.5 million. Upon achievement of certain milestones, we will be entitled to receive milestone payments, up to an aggregate of $50.0 million, including up to $25.0 million in specified development milestones and $25.0 million in specified regulatory milestones. In addition, we will be entitled to tiered royalties expected to yield an effective royalty rate percentage ranging from the mid-teens to mid-twenties based on annual net sales, if any, of Licensed Products in the Genzyme territory by Genzyme, its affiliates and sublicensees. We could potentially earn the next development milestone payment of $7.0 million under the Genzyme agreement based upon the completion of a successful Phase II ALN-TTR clinical trial, as defined in the Genzyme agreement. For purposes of potential future revenue recognition, we do not believe this milestone or any future milestones are substantive**.** 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 Genzyme.

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Under the Genzyme agreement, the parties will collaborate in the development of licensed products, with Genzyme assuming primary responsibility for the development and commercialization of licensed products in the Genzyme territory and us retaining primary responsibility for the development and commercialization of licensed products in the rest of the world. The collaboration between Genzyme and us is governed by a joint steering committee that will be comprised of an equal number of representatives from each party. Genzyme is responsible, at its expense, for all development activities under the development plan that are reasonably necessary for the regulatory approval and commercialization of an RNAi therapeutic for the treatment of ATTR in the Genzyme territory.

The Genzyme agreement originally provided that if development of a Licensed Product was terminated by us or Genzyme under certain limited circumstances, Genzyme would have the right to terminate the Genzyme agreement and we would be required to refund amounts paid by Genzyme to us under the agreement prior to such termination. On February 19, 2013, we and Genzyme agreed to amend the Genzyme agreement to remove this provision.

We have determined that the deliverables under the Genzyme agreement include the license, the joint steering committee and any additional TTR-specific RNAi therapeutic compounds that comprise the ALN-TTR program. We also determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the license and undelivered joint steering committee and any additional TTR-specific RNAi therapeutic compounds do not have standalone value due to the specialized nature of the services to be provided by us. In addition, while Genzyme has the ability to grant sublicenses, it cannot sublicense all or substantially all of its rights under the Genzyme agreement. The uniqueness of our services and the limited sublicense right are indicators that standalone value is not present in the arrangement. Therefore the deliverables are not separable and, accordingly, the license and undelivered services are being treated as a single unit of accounting. We are currently unable to reasonably estimate our period of performance under the Genzyme agreement, as we are unable to estimate the timeline of our deliverables related to the option granted to Genzyme for any additional compounds. We are deferring all revenue under the Genzyme agreement until we are able to reasonably estimate our period of performance. We will continue to reassess whether we can reasonably estimate the period of performance to fulfill our obligations under the Genzyme agreement.

Cubist. In January 2009, we entered into a license and collaboration agreement with Cubist to develop and commercialize therapeutic products based on certain of our RNAi technology for the treatment of RSV. Licensed products initially included ALN-RSV01, as well as several other second-generation RNAi-based RSV inhibitors. In November 2009, we and Cubist entered into an amendment to our license and collaboration agreement, which provided that we and Cubist would focus our collaboration and joint development efforts on ALN-RSV02, a second-generation compound, intended for use in pediatric patients. In December 2010, we and Cubist jointly made a portfolio decision to put the development of ALN-RSV02 on hold. Pursuant to the terms of the amendment, we continued to develop ALN-RSV01 for adult transplant patients at our sole discretion and expense and Cubist had the right to opt into collaborating with us on ALN-RSV01, subject to specified 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 the license and collaboration agreement effective as of February 6, 2013. As of the effective date, the parties have no further rights and obligations under the license and collaboration agreement, notwithstanding anything to the contrary in the agreement.

Under the terms of the Cubist agreement, we and Cubist shared responsibility for developing licensed products in North America and each was responsible for one-half of the related development costs, subject to the terms of the November 2009 amendment. Our collaboration with Cubist for the development of licensed products in North America was governed by a joint steering committee comprised of an equal number of representatives from each party. Cubist had the sole right to commercialize licensed products in North America with costs associated with such activities and any resulting profits or losses to be split equally between us and Cubist. In consideration for the rights granted to Cubist under the agreement, in January 2009, Cubist paid us an upfront cash payment of $20.0 million.

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We determined that the deliverables under the Cubist agreement included the licenses, technology transfer related to the ALN-RSV program, the joint steering committee and the development and manufacturing services that we were obligated to perform during the development period. We also determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the licenses and undelivered services were not separable and, accordingly, the licenses and services were treated as a single unit of accounting. Under the Cubist agreement, the last element expected to be delivered was the development and manufacturing services, which had an expected life of approximately eight years. We were recognizing the upfront payment of $20.0 million on a straight-line basis over approximately eight years because we were unable to reasonably estimate the level of effort to fulfill our performance obligations, and therefore, could not utilize a proportional performance model. At December 31, 2012, deferred revenue under the Cubist agreement was $9.7 million. As a result of the termination of the Cubist agreement in February 2013 and the end of our performance obligations thereunder, we expect to recognize the remaining deferred revenue of $9.7 million during the first quarter of 2013.

Accounting for Income Taxes

We recognize the tax benefit from an uncertain tax position only if it is more likely than not that the tax position will be sustained upon examination by the taxing authorities, based on the technical merits of the tax position. The tax benefits recognized in our financial statements from such a position are measured based on the largest benefit that has a greater than 50% likelihood of being realized upon ultimate resolution. Our policy is to accrue interest and penalties related to unrecognized tax positions in income tax expense. As of December 31, 2012, we have not recorded significant interest and penalty expense related to uncertain tax positions.

We operate in the United States and Germany where our income tax returns are subject to audit and adjustment by local tax authorities. The nature of the uncertain tax positions is often very complex and subject to change, and the amounts at issue can be substantial. We develop our cumulative probability assessment of the measurement of uncertain tax positions using internal experience, judgment and assistance from professional advisors. We refine estimates as we become aware of additional information. Any outcome upon settlement that differs from our current estimate may result in additional tax expense in future periods. At December 31, 2012, we had no unrecognized tax benefits that, if recognized, would favorably impact our effective income tax rate in future periods.

We recognize income taxes when transactions are recorded in our consolidated statements of comprehensive loss, with deferred taxes provided for items that are recognized in different periods for financial statement and tax reporting purposes. We record a valuation allowance to reduce the deferred tax assets to the amount that is more likely than not to be realized. In addition, we estimate our exposures relating to uncertain tax positions and establish reserves for such exposures when they become probable and reasonably estimable.

For the year ended December 31, 2012, we recorded a benefit from income taxes of $10.6 million. For the years ended December 31, 2011 and 2010, we recorded a provision for income taxes of zero and $0.5 million, respectively. The benefit of $10.6 million for the year ended December 31, 2012 is due to the recognition of corresponding income tax expense, recorded in other comprehensive income, associated with the increase in the value of our investment in Regulus that we carried at fair market value during the same period. At December 31, 2012, we had a valuation allowance against our net deferred tax assets to the extent it is more likely than not that the assets will not be realized. At December 31, 2012, we had federal and state net operating loss carryforwards of $272.7 million and $337.8 million, respectively, to reduce future taxable income that will expire at various dates through 2032. At December 31, 2012, we had federal and state research and development credit carryforwards of $15.3 million and $5.6 million, respectively, available to reduce future tax liabilities that expire at various dates through 2032. At December 31, 2012, we had foreign tax credit carryforwards of $3.2 million available to reduce future tax liabilities that expire in 2017. At December 31, 2012, we had alternative minimum tax credits of $0.8 million available to reduce future regular tax liabilities to the extent such regular tax less other non-refundable credits exceeds the tentative minimum tax. We have a valuation allowance against the net operating loss and credit deferred tax assets as it is unlikely that we will realize these assets. Ownership changes, as defined in the Internal Revenue Code, including those resulting from the issuance of common stock in

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connection with our public offerings, may limit the amount of net operating loss and tax credit carryforwards that can be utilized to offset future taxable income or tax liability. The amount of the limitation is determined in accordance with Section 382 of the Internal Revenue Code. We have determined that based on our value, in the event there was an annual limitation under Section 382, all net operating loss and tax credit carryforwards would still be available to offset taxable income.

Accounting for Stock-Based Compensation

We have stock incentive plans and an employee stock purchase plan under which we grant equity instruments. We account for all stock-based awards granted to employees at their fair value and generally recognize compensation expense over the vesting period of the award. Determining the amount of stock-based compensation to be recorded requires us to develop estimates of fair values of stock options as of the grant date. We calculate the grant date fair values using the Black-Scholes valuation model. Our expected stock price volatility assumption is based on a combination of the historical and implied volatility of our publicly traded stock.

For stock option awards granted during the year ended December 31, 2012, we used a weighted-average expected stock-price volatility assumption of 57%. Our expected life assumption is based on our historical data. Our weighted average expected term was 5.7 years for the year ended December 31, 2012. We utilize a dividend yield of zero based on the fact that we have never paid cash dividends and currently have no intention to pay cash dividends. The risk-free interest rate used for each grant is based on the U.S. Treasury yield curve in effect at the time of grant for instruments with a similar expected life.

For stock-based awards granted to non-employees, we generally recognize compensation expense over the vesting period of the award, which is generally the period during which services are rendered by such non-employees. At the end of each financial reporting period prior to vesting, we re-measure the value of these stock-based awards (as calculated using the Black-Scholes option-pricing model) using the then current fair value of our common stock. Stock options granted to non-employees, other than members of our board of directors and scientific advisory board members, generally vest over the service period.

The fair value of restricted stock awards granted to employees is based upon the quoted closing market price per share on the date of grant, adjusted for assumed forfeitures. For performance-based restricted stock awards, the value of the awards is measured when we determine the achievement of such performance conditions is deemed probable. This determination requires significant judgment by management. Expense is recognized over the vesting period, commencing when we determine that it is probable that the awards will vest.

At December 31, 2012, the estimated fair value of unvested employee awards was $17.5 million, net of estimated forfeitures. We will recognize this amount over the weighted average remaining vesting period of approximately 2.3 years for these awards. Stock-based employee compensation expense was $11.4 million for the year ended December 31, 2012. However, we cannot currently predict the total amount of stock-based compensation expense to be recognized in any future period because such amounts will depend on levels of stock-based payments granted in the future as well as the portion of the awards that actually vest. The stock compensation accounting standard requires forfeitures to be estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates. The term forfeitures is distinct from cancellations or expirations and represents only the unvested portion of the surrendered stock option. We currently expect, based on an analysis of our historical forfeitures, excluding the impact of our corporate restructurings, that approximately 67% of our stock options will actually vest, and therefore have applied an annual forfeiture rate of 9.5% to all unvested employee stock options at December 31, 2012. Ultimately, the actual expense recognized over the vesting period will only be for those shares that vest.

Accounting for Joint Venture

From the formation of Regulus in September 2007 to October 2012, we accounted for our interest in Regulus using the equity method of accounting. We reviewed the consolidation guidance that defines a variable interest entity, or VIE, and concluded that Regulus qualified as a VIE during such time period. We recorded any

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gains or losses recognized from the issuance of stock by its equity method investee as other income (expense) in our consolidated statements of comprehensive loss. We did not consolidate Regulus financial results as we lacked the power to direct the activities that could significantly impact the economic success of Regulus. Under equity method accounting, because we had guaranteed the debt of Regulus, we were required to continue to recognize our share of any future losses which resulted in the carrying amount of our investment in Regulus to be reduced below zero. In October 2012, Regulus completed an initial public offering, resulting in our ownership percentage decreasing from approximately 44% to 17% of Regulus outstanding common stock. Based upon our new ownership percentage of 17%, as well as qualitative factors, we do not believe that we have the ability to exercise significant influence over the operating decisions and financial policies of Regulus and have therefore discontinued the equity method of accounting for Regulus. Accordingly, beginning in October 2012, we accounted for our investment in Regulus as an available-for-sale marketable security. For additional details on the accounting for our investment in Regulus, see Note 10 to our consolidated financial statements included in this annual report on Form 10-K.

Estimated Liability for Development Costs

We record accrued liabilities related to expenses for which service providers have not yet billed us with respect to products or services that we have received, specifically related to ongoing pre-clinical studies and clinical trials. These costs primarily relate to third-party clinical management costs, laboratory and analysis costs, toxicology studies and investigator fees. We have multiple product candidates in concurrent pre-clinical studies and clinical trials at multiple clinical sites throughout the world. In order to ensure that we have adequately provided for ongoing pre-clinical and clinical development costs during the period in which we incur such costs, we maintain an accrual to cover these expenses. We update our estimate for this accrual on at least a quarterly basis. The assessment of these costs is a subjective process that requires judgment. Upon settlement, these costs may differ materially from the amounts accrued in our consolidated financial statements. Our historical accrual estimates have not been materially different from our actual costs.

Results of Operations

The following data summarizes the results of our operations for the periods indicated, in thousands:

	Year Ended December 31,		
	2012	2011	2010
Net revenues from research collaborators	$ 66,725	$ 82,757	$ 100,041
Operating expenses	196,181	137,575	144,111
Loss from operations	(129,456)	(54,818)	(44,070)
Net loss	$ (106,014)	$ (57,649)	$ (43,515)

The increase in operating expenses for the year ended December 31, 2012 resulted from a $65.0 million charge to operating expenses in connection with the restructuring of our license agreement with Tekmira in November 2012, which is described below under the heading Restructuring of Tekmira licensing agreement.

Discussion of Results of Operations for 2012 and 2011

Net Revenues from Research Collaborators

We generate revenues through research collaborations. The following table summarizes our total consolidated net revenues from research collaborators, for the periods indicated, in thousands:

	Year Ended December 31,	
	2012	2011
Roche/Arrowhead	$ 37,318	$ 55,978
Takeda	21,973	22,248
Monsanto	1,954	
Other	5,480	4,531
Total net revenues from research collaborators	$ 66,725	$ 82,757

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Net revenues from research collaborators declined for the year ended December 31, 2012 as compared to the year ended December 31, 2011 due primarily to the completion of our remaining performance obligations under the Roche/Arrowhead alliance in August 2012. As a result of the termination of the Cubist agreement in February 2013 and the end of our performance obligations thereunder, we expect to recognize the remaining deferred revenue under the Cubist agreement of $9.7 million during the first quarter of 2013. We expect net revenues from research collaborators to decrease significantly during 2013 on a comparative basis due to the completion of our remaining performance obligations under the Roche/Arrowhead alliance in the third quarter of 2012.

We also had $132.3 million of deferred revenue at December 31, 2012, which consists of payments we have received from collaborators, primarily Takeda, Kyowa Hakko Kirin, Cubist, Monsanto and Genzyme, but have not yet recognized pursuant to our revenue recognition policies.

For the foreseeable future, we expect our revenues to continue to be derived primarily from our alliances with Takeda and Monsanto, and other strategic alliances, as well as new collaborations, foundation funding, government contracts and licensing activities.

Operating Expenses

The following table summarizes our operating expenses for the periods indicated, in thousands and as a percentage of total operating expenses, together with the changes, in thousands and percentages:

	2012	% of Total Operating Expenses	2011	% of Total Operating Expenses	Increase (Decrease) $	Increase (Decrease) %
Research and development	$ 86,569	44%	$ 99,295	72%	$ (12,726)	(13)%
General and administrative	44,612	23%	38,280	28%	6,332	17%
Restructuring of Tekmira license agreement	65,000	33%			65,000	100%
Total operating expenses	$ 196,181	100%	$ 137,575	100%	$ 58,606	43%

Research and development. The following table summarizes the components of our research and development expenses for the periods indicated, in thousands and as a percentage of total research and development expenses, together with the changes, in thousands and percentages:

	2012	% of Expense Category	2011	% of Expense Category	Increase (Decrease) $	Increase (Decrease) %
Research and development						
Compensation and related	$ 20,438	24%	$ 23,743	24%	$ (3,305)	(14)%
Clinical trial and manufacturing	15,930	18%	25,258	26%	(9,328)	(37)%
External services	13,743	16%	15,653	16%	(1,910)	(12)%
Facilities-related	12,647	15%	12,751	13%	(104)	(1)%
Non-cash stock-based compensation	8,041	9%	10,921	11%	(2,880)	(26)%
License fees	5,693	7%	1,381	1%	4,312	312%
Lab supplies and materials	4,422	5%	6,283	6%	(1,861)	(30)%
Restructuring	2,817	3%			2,817	100%
Other	2,838	3%	3,305	3%	(467)	(14)%
Total research and development expenses	$ 86,569	100%	$ 99,295	100%	$ (12,726)	(13)%

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Research and development expenses decreased during the year ended December 31, 2012 as compared to the year ended December 31, 2011 due primarily to lower clinical trial and manufacturing expenses related to our ALN-RSV, ALN-PCS and ALN-VSP programs and decreases in compensation-related expenses. Partially offsetting these decreases were additional expenses related to the advancement of our ALN-TTR program, as well as license fees due to certain entities, primarily fees due to Isis as a result of the Monsanto and Genzyme alliances. Also included in the year ended December 31, 2012 is a one-time charge related to our January 2012 strategic corporate restructuring, including employee severance, benefits and other related costs.

We expect to continue to devote a substantial portion of our resources to research and development expenses as we continue development of our and our collaborators product candidates and focus on continuing to develop drug delivery-related technologies. We expect that research and development expenses will remain consistent in 2013.

A significant portion of our research and development costs are not tracked by project as they benefit multiple projects or our technology platform and because our most-advanced programs are not yet in late-stage clinical development. However, our collaboration agreements contain cost-sharing arrangements pursuant to which certain costs incurred under the project are reimbursed. Costs reimbursed under the agreements typically include certain direct external costs and a negotiated full-time equivalent labor rate for the actual time worked on the project. In addition, we have been reimbursed under government contracts for certain allowable costs including direct internal and external costs. As a result, although a significant portion of our research and development expenses are not tracked on a project-by-project basis, we do track direct external costs attributable to, and the actual time our employees worked on, our collaborations and government contracts.

General and administrative. The following table summarizes the components of our general and administrative expenses for the periods indicated, in thousands and as a percentage of total general and administrative expenses, together with the changes, in thousands and percentages:

	2012	% of Expense Category	2011	% of Expense Category	Increase (Decrease) $	Increase (Decrease) %
General and administrative						
Consulting and professional services	$ 28,949	65%	$ 21,032	55%	$ 7,917	38%
Compensation and related	6,384	14%	7,074	18%	(690)	(10)%
Non-cash stock-based compensation	4,319	10%	5,755	15%	(1,436)	(25)%
Facilities-related	1,648	4%	2,254	6%	(606)	(27)%
Restructuring	890	2%			890	100%
Other	2,422	5%	2,165	6%	257	12%
Total general and administrative expenses	$ 44,612	100%	$ 38,280	100%	$ 6,332	17%

The increase in general and administrative expenses during the year ended December 31, 2012 as compared to the year ended December 31, 2011 was due primarily to higher consulting and professional services expenses related to business activities, primarily legal activities, a description of which is set forth in Part I, Item 3, Legal Proceedings, of this annual report on Form 10-K. Also included in the year ended December 31, 2012 is a one-time charge related to our January 2012 strategic corporate restructuring, including employee severance, benefits and other related costs. These increases were partially offset by a decrease in all compensation expenses and facilities-related expenses due primarily to the reduction in workforce in connection with the January 2012 strategic corporate restructuring. We expect that general and administrative expenses will decrease significantly in 2013, due primarily to lower consulting and professional services related to legal activities.

Restructuring of Tekmira license agreement. For the year ended December 31, 2012, we incurred a $65.0 million charge to operating expenses in connection with the restructuring of our license agreement with

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Tekmira in November 2012. Specifically, we made a one-time payment of $30.0 million to Tekmira for the termination of, and our release from, all of our obligations under the manufacturing agreement with TPC, including without limitation the obligations to obtain materials and/or services from TPC. Further, we elected to buy-down certain future potential milestone and royalty payments due to Tekmira for certain of our RNAi therapeutics, formulated using LNP technology. Specifically, pursuant to the cross-license agreement, we made a one-time payment of $35.0 million to Tekmira, which amount constituted payment for the termination of the 2008 license agreements with TPC and Protiva and the parties rights and obligations thereunder, as well as the buy-down of certain milestone payments and the significant reduction of royalty rates for ALN-VSP, ALN-PCS and ALN-TTR. In addition, under the 2012 cross-license agreement, we will be obligated to pay TPC an aggregate of $10.0 million in contingent milestone payments related to advancement of ALN-VSP and ALN-TTR, which now represent the only potential milestones due to Tekmira for ALN-VSP, ALN-PCS and ALN-TTR LNP-based RNAi therapeutics. Specifically, we will be obligated to pay TPC a $5.0 million milestone payment upon each of (i) the initiation of a Phase III clinical trial of an LNP-based ALN-TTR therapeutic, and (ii) the manufacture of ALN-VSP clinical trial material for use in China. A description of our 2012 cross-license agreement with Tekmira is set forth in Part I, Item 1, Strategic Alliances Delivery-Related Licenses and Collaborations Tekmira of this annual report on Form 10-K.

Other income (expense)

We incurred $4.5 million equity in loss of joint venture (Regulus Therapeutics Inc.) for the year ended December 31, 2012 as compared to $3.5 million for the year ended December 31, 2011 related to our share of the net losses incurred by Regulus.

Interest income was $1.0 million in 2012 as compared to $1.2 million in 2011. The decrease in 2012 was due primarily to lower average interest rates as well as lower average cash, cash equivalent and fixed income marketable securities balances.

Other income was $16.4 million in 2012 due primarily to a gain recorded in connection with the issuance of common stock by Regulus. In October 2012, Regulus completed an initial public offering, resulting in the Company s ownership percentage decreasing from approximately 44% to 17% of Regulus outstanding common stock. As a result of this issuance of stock by Regulus, we recognized a gain of $16.1 million. Other expense in 2011 was $0.5 million and was due primarily to an impairment charge related to our former investment in Tekmira equity securities, as the decrease in the fair value of this investment was deemed to be other than temporary.

Our benefit in income taxes was $10.6 million in 2012 as compared to zero for 2011. The increase in 2012 was due to our recognition of corresponding income tax benefit associated with the increase in the value of our investment in Regulus that we carried at fair market value during the same respective period.

Discussion of Results of Operations for 2011 and 2010

Net Revenues from Research Collaborators

We generate revenues through research collaborations. The following table summarizes our total consolidated net revenues from research collaborators, for the periods indicated, in thousands:

	Year Ended December 31,	
	2011	**2010**
Roche/Arrowhead	$ 55,978	$ 55,978
Takeda	22,248	22,250
Novartis	149	9,313
Government contract	152	4,335
Other research collaborator	3,158	5,159
InterfeRx program, research reagent license and other	1,072	3,006
Total net revenues from research collaborators	$ 82,757	$ 100,041

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The decrease in Novartis revenues for the year ended December 31, 2011 as compared to the year ended December 31, 2010 was due primarily to the planned completion of the fifth and final year of the research program under the Novartis collaboration and license agreement in October 2010. The decrease in government contract revenues for the year ended December 31, 2011 as compared to the year ended December 31, 2010 was primarily the result of the completion of our contract with the National Institute of Allergy and Infectious Diseases in December 2010. The decrease in other research collaborator revenues for the year ended December 31, 2011 as compared to the year ended December 31, 2010 was primarily the result of the $1.9 million sublicense fee recognized in 2010 in connection with Regulus 2010 alliance with Sanofi, representing 7.5% of the $25.0 million upfront payment from Sanofi to Regulus. The decrease in InterfeRx program, research reagent license and other revenues for the year ended December 31, 2011 as compared to the year ended December 31, 2010 was due primarily to the substantial completion of our Alnylam Biotherapeutics collaborations in 2010.

We had $140.9 million of deferred revenue at December 31, 2011, which consisted of payments we had received from collaborators, primarily Roche/Arrowhead, Takeda, Kyowa Hakko Kirin and Cubist, that we had yet to recognize pursuant to our revenue recognition policies.

Operating Expenses

The following table summarizes our operating expenses for the periods indicated, in thousands and as a percentage of total operating expenses, together with the changes, in thousands and percentages:

	2011	% of Total Operating Expenses	2010	% of Total Operating Expenses	Increase (Decrease) $	Increase (Decrease) %
Research and development	$ 99,295	72%	$ 106,384	74%	$ (7,089)	(7)%
General and administrative	38,280	28%	37,727	26%	553	1%
Total operating expenses	$ 137,575	100%	$ 144,111	100%	$ (6,536)	(5)%

Research and development. The following table summarizes the components of our research and development expenses for the periods indicated, in thousands and as a percentage of total research and development expenses, together with the changes, in thousands and percentages:

	2011	% of Expense Category	2010	% of Expense Category	Increase (Decrease) $	Increase (Decrease) %
Research and development						
Clinical trial and manufacturing	$ 25,258	26%	$ 20,607	20%	$ 4,651	23%
Compensation and related	23,743	24%	24,053	23%	(310)	(1)%
External services	15,653	16%	22,471	21%	(6,818)	(30)%
Facilities-related	12,751	13%	12,051	11%	700	6%
Non-cash stock-based compensation	10,921	11%	11,689	11%	(768)	(7)%
Lab supplies and materials	6,283	6%	7,775	7%	(1,492)	(19)%
License fees	1,381	1%	2,407	2%	(1,026)	(43)%
Restructuring			1,863	2%	(1,863)	(100)%
Other	3,305	3%	3,468	3%	(163)	(5)%
Total research and development expenses	$ 99,295	100%	$ 106,384	100%	$ (7,089)	(7)%

Research and development expenses decreased during the year ended December 31, 2011 as compared to year ended December 31, 2010 due primarily to lower external services expenses related to pre-clinical expenses

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in connection with our ALN-PCS program as we advanced this program to a Phase I clinical trial. In addition, external services expenses decreased due to research funding paid to Isis in 2010 in connection with our ssRNAi collaborative effort with Isis, which we terminated in November 2010. Also contributing to the decrease were restructuring expenses related to employee severance, benefits and related costs incurred in connection with our September 2010 corporate restructuring. Lab supplies and materials expenses decreased during the year ended December 31, 2011 as compared to the year ended December 31, 2010 due primarily to the reduction in workforce in connection with our September 2010 corporate restructuring. Partially offsetting these decreases was an increase in clinical trial and manufacturing expenses due primarily to increased clinical trial expenses for our ALN-PCS program.

General and administrative. The following table summarizes the components of our general and administrative expenses for the periods indicated, in thousands and as a percentage of total general and administrative expenses, together with the changes, in thousands and percentages:

	2011	% of Expense Category	2010	% of Expense Category	Increase (Decrease) $	Increase (Decrease) %
General and administrative						
Consulting and professional services	$ 21,032	55%	$ 18,753	50%	$ 2,279	12%
Compensation and related	7,074	18%	6,202	16%	872	14%
Non-cash stock-based compensation	5,755	15%	7,429	20%	(1,674)	(23)%
Facilities-related	2,254	6%	2,379	6%	(125)	(5)%
Insurance	717	2%	759	2%	(42)	(6)%
Restructuring			330	1%	(330)	(100)%
Other	1,448	4%	1,875	5%	(427)	(23)%
Total general and administrative expenses	$ 38,280	100%	$ 37,727	100%	$ 553	1%

The slight increase in general and administrative expenses during the year ended December 31, 2011 as compared to the year ended December 31, 2010 was due primarily to higher consulting and professional services expenses related to business activities, primarily legal activities, a description of which is set forth in Part I, Item 3, Legal Proceedings, of this annual report on Form 10-K.

Other income (expense)

We incurred $3.5 million equity in loss of joint venture (Regulus Therapeutics Inc.) for the year ended December 31, 2011 as compared to $7.6 million for the year ended December 31, 2010 related to our share of the net losses incurred by Regulus. The decrease in equity in loss of joint venture (Regulus Therapeutics Inc.) for the year ended December 31, 2011 was due primarily to sublicense fees paid in connection with the strategic alliance formed by Regulus with Sanofi in June 2010.

Interest income was $1.2 million in 2011 as compared to $2.3 million in 2010. The decrease in 2011 was due primarily to lower average interest rates as well as lower average cash, cash equivalent and fixed income marketable securities balances.

Other expense was $0.5 million in 2011 and was due primarily to an impairment charge related to our former investment in Tekmira equity securities, as the decrease in the fair value of this investment was deemed to be other than temporary. Other income in 2010 was $6.4 million and was due primarily to a $4.4 million gain on the issuance of stock of Regulus, an equity-method investee, due to the increase in valuation of Regulus as a result of the $10.0 million equity investment Sanofi made in Regulus. In addition, in 2010, we received $2.0 million in connection with awards under the federal government s Qualifying Therapeutic Discovery Project Program.

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Liquidity and Capital Resources

The following table summarizes our cash flow activities for the periods indicated, in thousands:

	Year Ended December 31,		
	2012	2011	2010
Net loss	$ (106,014)	$ (57,649)	$ (43,515)
Adjustments to reconcile net loss to net cash (used in) provided by operating activities	(630)	26,509	38,734
Changes in operating assets and liabilities	(8,965)	(55,928)	(79,560)
Net cash used in operating activities	(115,609)	(87,068)	(84,341)
Net cash provided by investing activities	3,374	81,959	17,838
Net cash provided by financing activities	93,412	738	3,663
Effect of exchange rate on cash			(29)
Net decrease in cash and cash equivalents	(18,823)	(4,371)	(62,869)
Cash and cash equivalents, beginning of period	70,228	74,599	137,468
Cash and cash equivalents, end of period	$ 51,405	$ 70,228	$ 74,599

Since we commenced operations in 2002, we have generated significant losses. At December 31, 2012, we had an accumulated deficit of $507.0 million. At December 31, 2012, we had cash, cash equivalents and fixed income marketable securities of $226.2 million, excluding our investment in equity securities of Regulus, compared to cash, cash equivalents and fixed income marketable securities of $260.8 million at December 31, 2011. Included in our December 31, 2012 cash, cash equivalents and fixed income marketable securities are the proceeds from our sale, in February 2012, of an aggregate of 8,625,000 shares of our common stock through an underwritten public offering at a price to the public of $10.75 per share. As a result of this offering, we received aggregate net proceeds of approximately $86.8 million, after deducting underwriting discounts and commissions and other estimated offering expenses of approximately $5.9 million. 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 this 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 the proceeds from these offerings 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.

We invest primarily in cash equivalents, U.S. government obligations, high-grade corporate notes and commercial paper. Our investment objectives are, primarily, to assure liquidity and preservation of capital and, secondarily, to obtain investment income. All of our investments in debt securities are recorded at fair value and are available-for-sale. Fair value is determined based on quoted market prices and models using observable data inputs. We have not recorded any impairment charges to our fixed income marketable securities at December 31, 2012.

Operating activities

We have required significant amounts of cash to fund our operating activities as a result of net losses since our inception. The increase in net cash used in operating activities for the year ended December 31, 2012 compared to the year ended December 31, 2011 was due primarily to our net loss and other changes in our working capital, adjustments for noncash gains and benefits of $26.9 million and a decrease in deferred revenue of $8.6 million. The increase in net cash used in operating activities for the year ended December 31, 2011 compared to the year ended December 31, 2010 was due primarily to our net loss and other changes in our working capital, as well as a decrease in deferred revenue of $70.3 million. The increase in net cash used in

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operating activities for the year ended December 31, 2010 compared to the year ended December 31, 2009 was due primarily to our net loss and other changes in our working capital, as well as a decrease in deferred revenue of $60.7 million. Cash used in operating activities is adjusted for non-cash items to reconcile net loss to net cash provided by or used in operating activities. These non-cash adjustments consist primarily of stock-based compensation, equity in loss of joint venture (Regulus Therapeutics Inc.) and depreciation and amortization.

We expect that we will require significant amounts of cash to fund our operating activities for the foreseeable future as we continue to develop and advance our research and development initiatives. The actual amount of overall expenditures will depend on numerous factors, including the timing of expenses, the timing and terms of collaboration agreements or other strategic transactions, if any, and the timing and progress of our research and development efforts.

Investing activities

For the year ended December 31, 2012, net cash provided by investing activities of $3.4 million resulted primarily from sales and maturities of fixed income marketable securities of $11.9 million offset by purchases of property and equipment of $8.3 million primarily in connection with the build-out of our cGMP manufacturing facility. For the year ended December 31, 2011, net cash provided by investing activities of $82.0 million resulted primarily from net sales and maturities of fixed income marketable securities of $83.3 million, offset by purchases of property and equipment of $1.3 million. For the year ended December 31, 2010, net cash provided by investing activities of $17.8 million resulted primarily from net sales and maturities of fixed income marketable securities of $22.5 million, offset by purchases of property and equipment of $4.7 million.

Financing activities

For the year ended December 31, 2012, net cash of $93.4 million provided by financing activities was due primarily to proceeds of $86.8 million received from our February 2012 underwritten public offering, as well proceeds of $7.0 million from the issuance of common stock in connection with stock option exercises and other types of equity. For the year ended December 31, 2011, net cash provided by financing activities of $0.7 million was due to proceeds from the issuance of common stock in connection with stock option exercises and other types of equity. For the year ended December 31, 2010, net cash provided by financing activities of $3.7 million was due to proceeds of $1.0 million from our issuance of common stock to Novartis in April 2010, as well as proceeds of $2.7 million from the issuance of common stock in connection with stock option exercises and other types of equity.

Operating Capital Requirements

We do not know when, if ever, we will successfully develop or be able to commence sales of any product. Therefore, we anticipate that we will continue to generate significant losses for the foreseeable future as a result of planned expenditures for research and development activities relating to our drug development programs, including the development of drug delivery technologies and clinical trial costs, extension of the capabilities of our technology platform, including through business initiatives, continued management and growth of our patent portfolio, collaborations and general corporate activities. In February 2012, we sold an aggregate of 8,625,000 shares of our common stock through an underwritten public offering at a price to the public of $10.75 per share. As a result of the offering, we received aggregate net proceeds of approximately $86.8 million, after deducting underwriting discounts and commissions and other estimated offering expenses of approximately $5.9 million. 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 this 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 the proceeds from these offerings 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. Based on our current operating plan, we believe that our existing cash, cash equivalents and fixed

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income marketable securities, together with the cash we expect to generate under our current alliances, will be sufficient to fund our planned operations through at least the end of 2016. For reasons discussed below, we may require significant additional funds earlier than we currently expect in order to develop, conduct clinical trials for and commercialize any product candidates.

In the future, we may seek additional funding through additional collaborative arrangements and public or private financings. In December 2012, we filed an automatically effective shelf registration statement with the SEC for an indeterminate number of shares. During the recent downturn in global financial markets, some companies have experienced difficulties raising capital, which has had a material adverse impact on their liquidity. The recent economic downturn has diminished the availability of capital and may limit our ability to access these markets to obtain financing in the future. As a result of these and other factors, additional funding may not be available to us on acceptable terms or at all. In addition, the terms of any additional financing may further adversely affect the holdings or the rights of our stockholders. For example, if we raise additional funds by issuing equity securities, further dilution to our existing stockholders may result. In addition, as a condition to providing additional funds to us, future investors may demand, and may be granted, rights superior to those of existing stockholders. If we are unable to obtain funding on a timely basis, we may be required to significantly delay or curtail one or more of our research or development programs. We also could be required to seek funds through arrangements with collaborators or others that may require us to relinquish rights to some of our technologies or product candidates that we would otherwise pursue.

Even if we are able to raise additional funds in a timely manner, our future capital requirements may vary from what we expect and will depend on many factors, including:

- our progress in demonstrating that siRNAs can be active as drugs;
- our ability to develop relatively standard procedures for selecting and modifying siRNA product candidates;
- progress in our research and development programs, as well as the magnitude of these programs;
- the timing, receipt and amount of milestone and other payments, if any, from present and future collaborators, if any;
- the timing, receipt and amount of funding under future government or foundation contracts, if any;
- our ability to maintain and establish additional collaborative arrangements and/or new business initiatives;
- the resources, time and costs required to successfully initiate and complete our pre-clinical and clinical trials, obtain regulatory approvals, and obtain and maintain licenses to third-party intellectual property;
- our ability to manufacture, or contract with third-parties for the manufacture of, our product candidates for clinical testing and commercial sale;
- the resources, time and cost required for the preparation, filing, prosecution, maintenance and enforcement of patent claims;
- our ability to achieve anticipated cost reductions as a result of, and to successfully manage the potential impact of, our January 2012 strategic corporate restructuring and workforce reduction on our culture, collaborative relationships and business operations;

the costs associated with legal activities, including litigation, arising in the course of our business activities and our ability to prevail in any such legal disputes;

progress in the research and development programs of Regulus; and

the timing, receipt and amount of sales and royalties, if any, from our potential products.

Off-Balance Sheet Arrangements

In connection with our license agreements with Max Planck relating to the Tuschl I and II patent applications, we are required to indemnify Max Planck for certain damages arising in connection with the

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intellectual property rights licensed under the agreements. Under this indemnification agreement with Max Planck, we are responsible for paying the costs of any litigation relating to the license agreements or the underlying intellectual property rights. In connection with our research agreement with AlCana, we have agreed to indemnify AlCana for certain legal costs, subject to certain exceptions and limitations. Amounts paid under the AlCana indemnification agreement in connection with the legal proceedings described in Part I, Item 3, Legal Proceedings, of this annual report on Form 10-K were charged, or are being charged, to general and administrative expense. We have also agreed to indemnify Genzyme for legal costs and other losses or amounts required to be paid by Genzyme, if any, in connection with or related to certain of our ongoing litigation matters. In addition, we are a party to a number of agreements entered into in the ordinary course of business, which contain typical provisions that obligate us to indemnify the other parties to such agreements upon the occurrence of certain events. These indemnification obligations are considered off-balance sheet arrangements in accordance with GAAP. To date, other than certain costs associated with the certain previously settled litigation related to the Tuschl patents, and the Tekmira litigation described in Part I, Item 3, Legal Proceedings, of this annual report on Form 10-K, we have not encountered material costs as a result of such obligations and have not accrued any liabilities related to such obligations in our consolidated financial statements.

See Note 6 to our consolidated financial statements included in this annual report on Form 10-K for further discussion of these indemnification agreements and guarantee obligations.

Contractual Obligations

In the table below, we set forth our enforceable and legally binding obligations and future commitments at December 31, 2012, as well as obligations related to contracts that we are likely to continue, regardless of the fact that they were cancelable at December 31, 2012. Some of the figures that we include in this table are based on management s estimates and assumptions about these obligations, including their duration, the possibility of renewal, anticipated actions by third parties and other factors. Because these estimates and assumptions are necessarily subjective, the obligations we will actually pay in future periods may vary from those reflected in the table.

	Payments Due by Period				
Contractual Obligations	**2013**	**2014 and 2015**	**2016 and 2017**	**After 2017**	**Total**
Operating lease obligations(1)	$ 6,065	$ 12,853	$ 5,556	$	$ 24,474
Purchase commitments(2)	$ 10,343	$ 725	$	$	$ 11,068
Technology license commitments(3)	$ 14,463	$ 2,381	$ 1,566	$ 9,159	$ 27,569
Total contractual cash obligations	$ 30,871	$ 15,959	$ 7,122	$ 9,159	$ 63,111

(1) Relates to our Cambridge, Massachusetts non-cancelable operating lease agreements.

(2) Includes commitments related to purchase orders, clinical and pre-clinical agreements, and other purchase commitments for goods or services.

(3) Relates to our fixed payment obligations under license agreements, as well as other payments related to technology research and development.

We in-license technology from a number of sources. Pursuant to these in-license agreements, we will be required to make additional payments if and when we achieve specified development, regulatory and commercialization milestones. To the extent we are unable to reasonably predict the likelihood, timing or amount of such payments, we have excluded them from the table above.

Recent Accounting Pronouncements

In May 2011, the Financial Accounting Standards Board, or FASB, issued a new accounting standard that clarifies the application of certain existing fair value measurement guidance and expands the disclosures for fair value measurements that are estimated using significant unobservable (Level 3) inputs. This standard is effective

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on a prospective basis for annual and interim reporting periods beginning on or after December 15, 2011. We adopted this amendment on January 1, 2012. The adoption of this new standard did not have a material impact on our consolidated financial statements.

In June 2011, the FASB issued an amendment to the accounting guidance for presentation of comprehensive income. Under the amended guidance, a company may present the total of comprehensive income, the components of net income and the components of other comprehensive income either in a single continuous statement of comprehensive income or in two separate but consecutive statements. In either case, a company is required to present each component of net income along with total net income, each component of other comprehensive income along with a total for other comprehensive income and a total amount for comprehensive income. For public companies, the amendment is effective for fiscal years, and interim periods within those years, beginning after December 15, 2011, and shall be applied retrospectively. We adopted this amendment on January 1, 2012. Other than a change in presentation, the adoption of this guidance did not have a material impact on our consolidated financial statement.

In February 2013, the FASB issued amendments to the accounting guidance for presentation of comprehensive income to improve the reporting of reclassifications out of accumulated other comprehensive income. The amendments do not change the current requirements for reporting net income or other comprehensive income, but do require an entity to provide information about the amounts reclassified out of accumulated other comprehensive income by component. In addition, an entity is required to present, either on the face of the statement where the net income is presented or in the notes, significant amounts reclassified out of accumulated other comprehensive income by the respective line items of net income but only if the amount reclassified is required under GAAP to be reclassified to net income in its entirety in the same reporting period. For other amounts that are not required under GAAP to be reclassified in their entirety to net income, an entity is required to cross-reference to other disclosures required under GAAP that provide additional detail about these amounts. For public companies, these amendments are effective prospectively for reporting periods beginning after December 15, 2012. Other than a change in presentation, we do not believe the adoption of this guidance will have a material impact on our consolidated financial statements.

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ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

As part of our investment portfolio, we own financial instruments that are sensitive to market risks. The investment portfolio is used to preserve our capital until it is required to fund operations, including our research and development activities. Our fixed income marketable securities consist of U.S. government obligations, high-grade corporate notes and commercial paper. All of our investments in debt securities are classified as available-for-sale and are recorded at fair value. Our available-for-sale investments in debt securities are sensitive to changes in interest rates and changes in the credit ratings of the issuers. Interest rate changes would result in a change in the net fair value of these financial instruments due to the difference between the market interest rate and the market interest rate at the date of purchase of the financial instrument. If market interest rates were to increase immediately and uniformly by 50 basis points, or one-half of a percentage point, from levels at December 31, 2012, the net fair value of our interest-sensitive financial instruments would have resulted in a hypothetical decline of $0.9 million. A downgrade in the credit rating of an issuer of a debt security or further deterioration of the credit markets could result in a decline in the fair value of the debt instruments. Our investment guidelines prohibit investment in auction rate securities and we do not believe we have any direct exposure to losses relating from mortgage-based securities or derivatives related thereto such as credit-default swaps. We did not record any impairment charges to our fixed income marketable securities during the year ended December 31, 2012.

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ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

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Management s Annual Report on Internal Control Over Financial Reporting

The management of the Company is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rule 13a-15(f) or 15d-15(f) promulgated under the Securities Exchange Act of 1934 as a process designed by, or under the supervision of, the company s principal executive and principal financial officers and effected by the company s board of directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles and includes those policies and procedures that:

- Pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of the assets of the Company;

- Provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the Company are being made only in accordance with authorizations of management and directors of the Company; and

- Provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of the Company s assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

The Company s management assessed the effectiveness of the Company s internal control over financial reporting as of December 31, 2012. In making this assessment, the Company s management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in Internal Control-Integrated Framework.

Based on its assessment, management concluded that, as of December 31, 2012, the Company s internal control over financial reporting is effective based on those criteria.

The effectiveness of the Company s internal control over financial reporting as of December 31, 2012 has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in their report. This report appears on page 105.

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Report of Independent Registered Public Accounting Firm

To the Board of Directors and Stockholders of Alnylam Pharmaceuticals, Inc.

In our opinion, based on our audits and the report of other auditors with respect to the consolidated financial statement as of and for the years ended December 31, 2011 and 2010, the accompanying consolidated balance sheets and the related consolidated statements of operations and comprehensive loss, stockholders equity and cash flows present fairly, in all material respects, the financial position of Alnylam Pharmaceuticals, Inc. and its subsidiaries at December 31, 2012 and 2011, and the results of their operations and their cash flows for each of the three years in the period ended December 31, 2012 in conformity with accounting principles generally accepted in the United States of America. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2012, based on criteria established in *Internal Control - Integrated Framework* issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). The Company s management is responsible for these financial statements, for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Management s Annual Report on Internal Control over Financial Reporting. Our responsibility is to express opinions on these financial statements and on the Company s internal control over financial reporting based on our integrated audits. We did not audit the 2011 or 2010 financial statements of Regulus Therapeutics Inc., an approximate 45 percent-owned equity investment, insofar as it relates to the Company s net investment in (approximately $0.6 million at December 31, 2011) and equity in the net loss (approximately $3.5 million and $7.6 million for the years ended December 31, 2011 and 2010, respectively) of Regulus Therapeutics, Inc.. The financial statements of Regulus Therapeutics, Inc. were audited by other auditors whose report thereon has been furnished to us, and our opinion on the financial statements expressed herein, insofar as it relates to the amounts included for Regulus Therapeutics, Inc., is based solely on the report of the other auditors. We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the financial statements are free of material misstatement and whether effective internal control over financial reporting was maintained in all material respects. Our audits of the financial statements included examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits and the report of other auditors provide a reasonable basis for our opinions.

A company s internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company s internal control over financial reporting includes those policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company s assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ PricewaterhouseCoopers LLP

Boston, Massachusetts

February 19, 2013

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ALNYLAM PHARMACEUTICALS, INC.

CONSOLIDATED BALANCE SHEETS

(In thousands, except share and per share amounts)

	December 31, 2012	December 31, 2011
ASSETS		
Current assets:		
Cash and cash equivalents	$ 51,405	$ 70,228
Marketable securities	71,407	76,174
Billed and unbilled collaboration receivables	104	1,468
Prepaid expenses and other current assets	2,540	4,158
Total current assets	125,456	152,028
Marketable securities	103,416	114,407
Investment in equity securities of Regulus Therapeutics Inc	38,748	
Property and equipment, net	19,799	14,643
Other assets	101	839
Total assets	$ 287,520	$ 281,917
LIABILITIES AND STOCKHOLDERS EQUITY		
Current liabilities:		
Accounts payable	$ 4,420	$ 5,800
Accrued expenses	11,558	12,340
Deferred rent	950	484
Deferred revenue	31,417	62,366
Total current liabilities	48,345	80,990
Deferred rent, net of current portion	4,248	3,727
Deferred revenue, net of current portion	100,874	78,487
Other long-term liabilities		716
Total liabilities	153,467	163,920
Commitments and contingencies (Note 6)		
Stockholders equity:		
Preferred stock, $0.01 par value per share, 5,000,000 shares authorized and no shares issued and outstanding at December 31, 2012 and 2011		
Common stock, $0.01 par value per share, 125,000,000 shares authorized; 52,489,936 shares issued and outstanding at December 31, 2012; 42,721,942 shares issued and outstanding at December 31, 2011	525	427
Additional paid-in capital	624,876	518,731
Accumulated other comprehensive income (loss)	15,662	(165)
Accumulated deficit	(507,010)	(400,996)
Total stockholders equity	134,053	117,997
Total liabilities and stockholders equity	$ 287,520	$ 281,917

The accompanying notes are an integral part of these consolidated financial statements.

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ALNYLAM PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS

(In thousands, except per share amounts)

	Year Ended December 31,		
	2012	2011	2010
Net revenues from research collaborators	$ 66,725	$ 82,757	$ 100,041
Operating expenses:			
Research and development(1)	86,569	99,295	106,384
General and administrative(1)	44,612	38,280	37,727
Restructuring of Tekmira license agreement	65,000		
Total operating expenses	196,181	137,575	144,111
Loss from operations	(129,456)	(54,818)	(44,070)
Other income (expense):			
Equity in loss of joint venture (Regulus Therapeutics Inc.)	(4,522)	(3,505)	(7,639)
Gain on issuance of stock by Regulus Therapeutics Inc.	16,084		4,421
Interest income	977	1,205	2,305
Other income (expense)	331	(531)	1,982
Total other income (expense)	12,870	(2,831)	1,069
Loss before income taxes	(116,586)	(57,649)	(43,001)
Benefit from (provision for) income taxes	10,572		(514)
Net loss	$ (106,014)	$ (57,649)	$ (43,515)
Net loss per common share basic and diluted	$ (2.11)	$ (1.36)	$ (1.04)
Weighted average common shares used to compute basic and diluted net loss per common share	50,286	42,410	42,040
Comprehensive loss:			
Net loss	$ (106,014)	$ (57,649)	$ (43,515)
Foreign currency translation			(29)
Unrealized gain (loss) on marketable securities, net of tax	15,827	(879)	27
Comprehensive loss	$ (90,187)	$ (58,528)	$ (43,517)

(1) Non-cash stock-based compensation expenses included in operating expenses are as follows:

Research and development	$ 8,041	$ 10,921	$ 11,689
General and administrative	4,319	5,755	7,429

The accompanying notes are an integral part of these consolidated financial statements.

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ALNYLAM PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF STOCKHOLDERS EQUITY

(In thousands, except share amounts)

	Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Stockholders Equity
	Shares	Amount				
Balance at December 31, 2009	41,837,427	$ 418	$ 476,663	$ 716	$ (299,832)	$ 177,965
Exercise of common stock options	227,970	2	1,731			1,733
Issuance of common stock under other types of equity plans	164,656	2	2,423			2,425
Issuance of restricted stock	113,370	1	(1)			
Stock-based compensation expense			19,118			19,118
Foreign currency translation				(29)		(29)
Joint venture stock-based compensation (Regulus Therapeutics Inc.)			289			289
Tax benefit from stock-based compensation			220			220
Other comprehensive income				27		27
Net loss					(43,515)	(43,515)
Balance at December 31, 2010	42,343,423	423	500,443	714	(343,347)	158,233
Exercise of common stock options	16,800		103			103
Issuance of common stock under other types of equity plans	124,815	2	1,021			1,023
Issuance of restricted stock	236,904	2	(2)			
Stock-based compensation expense			16,676			16,676
Joint venture stock-based compensation (Regulus Therapeutics Inc.)			370			370
Tax benefit from stock-based compensation			120			120
Other comprehensive loss				(879)		(879)
Net loss					(57,649)	(57,649)
Balance at December 31, 2011	42,721,942	427	518,731	(165)	(400,996)	117,997
Exercise of common stock options	661,909	7	6,395			6,402
Issuance of common stock under other types of equity plans	97,459	1	878			879
Issuance of restricted stock, net of cancellations and tax withholdings	383,626	4	(523)			(519)
Issuance of common stock, net of offering costs	8,625,000	86	86,714			86,800
Stock-based compensation expense			12,360			12,360
Joint venture stock-based compensation (Regulus Therapeutics Inc.)			321			321
Other comprehensive income				15,827		15,827
Net loss					(106,014)	(106,014)
Balance at December 31, 2012	52,489,936	$ 525	$ 624,876	$ 15,662	$ (507,010)	$ 134,053

The accompanying notes are an integral part of these consolidated financial statements.

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ALNYLAM PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

(In thousands)

	Year Ended December 31,		
	2012	**2011**	**2010**
Cash flows from operating activities:			
Net loss	$ (106,014)	$ (57,649)	$ (43,515)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	9,035	5,125	4,941
Deferred income taxes			10,742
Non-cash stock-based compensation	12,360	16,676	19,118
Charge for 401(k) company stock match	364	488	495
Equity in loss of joint venture (Regulus Therapeutics Inc.)	4,522	3,505	7,639
Tax benefit from stock-based compensation		120	220
Other than temporary impairment on equity securities		595	
Realized gain on sale of marketable securities	(255)		
Gain on issuance of stock by joint venture	(16,084)		(4,421)
Benefit from intraperiod tax allocation on marketable securities	(10,572)		
Changes in operating assets and liabilities:			
Proceeds from landlord tenant improvements	1,780		
Billed and unbilled collaboration receivables	1,364	1,982	2,594
Income taxes receivable		10,669	(10,669)
Prepaid expenses and other assets	1,780	2,731	(2,738)
Accounts payable	(1,736)	(3,512)	(3,177)
Income taxes payable			(5,516)
Accrued expenses and other	(3,591)	2,457	651
Deferred revenue	(8,562)	(70,255)	(60,705)
Net cash used in operating activities	(115,609)	(87,068)	(84,341)
Cash flows from investing activities:			
Purchases of property and equipment	(8,348)	(1,291)	(4,732)
Increase in restricted cash	(162)		
Purchases of marketable securities	(277,129)	(293,115)	(390,473)
Sales and maturities of marketable securities	289,013	376,365	413,043
Net cash provided by investing activities	3,374	81,959	17,838
Cash flows from financing activities:			
Proceeds from exercise of stock options and other types of equity	6,971	738	2,670
Proceeds from issuance of common stock, net of offering costs	86,800		
Payments for repurchase of common stock for employee tax withholding	(359)		
Proceeds from issuance of shares to Novartis			993
Net cash provided by financing activities	93,412	738	3,663
Effect of exchange rate on cash			(29)
Net decrease in cash and cash equivalents	(18,823)	(4,371)	(62,869)
Cash and cash equivalents, beginning of period	70,228	74,599	137,468
Cash and cash equivalents, end of period	$ 51,405	$ 70,228	$ 74,599
Supplemental disclosure of cash flows:			
(Cash paid for income taxes) proceeds from income tax refunds	$ (17)	$ 10,657	$ (5,767)

Supplemental disclosure of noncash investing activities:			
Fixed asset expenditures included in accounts payable and accrued expenses	$ 1,441	$	$

The accompanying notes are an integral part of these consolidated financial statements.

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ALNYLAM PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. NATURE OF BUSINESS

Alnylam Pharmaceuticals, Inc. (the Company or Alnylam) commenced operations on June 14, 2002 as a biopharmaceutical company seeking to develop and commercialize novel therapeutics based on RNA interference (RNAi). Alnylam is focused on discovering, developing and commercializing RNAi therapeutics by establishing strategic alliances with leading pharmaceutical and life sciences companies, establishing and maintaining a strong intellectual property position in the RNAi field, generating revenues through licensing agreements, and ultimately developing and commercializing RNAi therapeutics for its own account. The Company has devoted substantially all of its efforts to business planning, research and development, acquiring, filing and expanding intellectual property rights, recruiting management and technical staff, and raising capital.

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Basis of Presentation and Principles of Consolidation

The Company comprises four entities, Alnylam Pharmaceuticals, Inc. (the parent company) and three wholly-owned subsidiaries (Alnylam U.S., Inc., Alnylam Europe AG (Alnylam Europe) and Alnylam Securities Corporation). Alnylam Pharmaceuticals, Inc. is a Delaware corporation that was formed on May 8, 2003. Alnylam U.S., Inc. is also a Delaware corporation that was formed on June 14, 2002. Alnylam Securities Corporation is a Massachusetts corporation that was formed on December 19, 2006. Alnylam Europe was incorporated in Germany in June 2000 under the name Ribopharma AG. The Company acquired Alnylam Europe in July 2003.

The accompanying consolidated financial statements reflect the operations of the Company and its wholly-owned subsidiaries. All intercompany accounts and transactions have been eliminated.

Reclassifications

Certain reclassifications have been made to prior years consolidated financial statements to conform to the 2012 presentation.

Use of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the United States of America (GAAP) requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates.

Concentrations of Credit Risk and Significant Customers

Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash, cash equivalents and fixed income marketable securities. At December 31, 2012 and 2011, substantially all of the Company s cash, cash equivalents and fixed income marketable securities were invested in money market mutual funds, commercial paper, corporate notes and U.S. government securities through highly rated financial institutions. Investments are restricted, in accordance with the Company s investment policy, to a concentration limit per issuer.

To date, the Company s revenues from collaborations have been generated from primarily F. Hoffmann-La Roche Ltd and certain of its affiliates (collectively, Roche) (which assigned its rights and obligations to Arrowhead Research Corporation (Arrowhead) in 2011), Takeda Pharmaceutical Company Limited (Takeda), and Novartis Pharma AG and one of its affiliates (collectively, Novartis). In addition, the

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ALNYLAM PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

Company and Medtronic, Inc. (Medtronic) formed a collaboration with CHDI Foundation, Inc. (CHDI) to advance ALN-HTT, a novel drug-device combination for the treatment of Huntington s disease. Under this collaboration, CHDI agreed to initially fund approximately 50% of the costs of this program up to the point at which an investigational new drug application could be filed. In April 2012, the Company exercised its option under the Medtronic agreement to opt-out of the 50-50 expense/profit share arrangement of the ALN-HTT program and move to a royalty and milestone licensing structure. In connection with the Company s opt-out, in May 2012, CHDI notified the Company and Medtronic that it would cease further funding of the ALN-HTT program pursuant to the terms of the CHDI agreement. The Company recorded the funding received from CHDI as a reduction to research and development expense. For the year ended December 31, 2012, the composition of the Company s billed and unbilled collaboration receivables was entirely composed of amounts due from the U.S. Government for the wind-down of completed government contracts.

The following table summarizes customers that represent greater than 10% of the Company s net revenues from research collaborators, for the periods indicated:

	Year Ended December 31,		
	2012	2011	2010
Roche/Arrowhead	56%	68%	56%
Takeda	33%	27%	22%

The following table summarizes customers with amounts due that represent greater than 10% of the Company s billed and unbilled collaboration receivables balance, at the periods indicated:

	At December 31,	
	2012	2011
U.S. Government	100%	*%
CHDI		51%
GSK		20%
Medtronic		13%

* Represents 10% or less

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ALNYLAM PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

Fair Value Measurements

The fair value is the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. The following tables present information about the Company s assets that are measured at fair value on a recurring basis at December 31, 2012 and 2011, and indicate the fair value hierarchy of the valuation techniques the Company utilized to determine such fair value. In general, fair values determined by Level 1 inputs utilize quoted prices (unadjusted) in active markets for identical assets or liabilities. Fair values determined by Level 2 inputs utilize data points that are observable, such as quoted prices (adjusted), interest rates and yield curves. Fair values determined by Level 3 inputs utilize unobservable data points for the asset or liability, and include situations where there is little, if any, market activity for the asset or liability. The fair value hierarchy level is determined by the lowest level of significant input. Financial assets and liabilities measured at fair value on a recurring basis are summarized as follows, in thousands:

Description	At December 31, 2012	Quoted Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents	$ 50,213	$ 50,213	$	$
Marketable securities (fixed income):				
Corporate notes	91,523		91,523	
U.S. Government obligations	60,661		60,661	
Commercial paper	22,639		22,639	
Marketable securities (Regulus equity holdings)	38,748		38,748	
Total	$ 263,784	$ 50,213	$ 213,571	$

Description	At December 31, 2011	Quoted Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents	$ 67,024	$ 67,024	$	$
Marketable securities (fixed income):				
Corporate notes	104,839		104,839	
U.S. Government obligations	73,722		73,722	
Commercial paper	11,395		11,395	
Marketable securities (equity holdings)	625		625	
Total	$ 257,605	$ 67,024	$ 190,581	$

For the years ended December 31, 2012 and 2011, there were no transfers between Level 1 and Level 2 financial assets. The carrying amounts reflected in the Company s consolidated balance sheets for cash, billed and unbilled collaboration receivables, other current assets, accounts payable and accrued expenses approximate fair value due to their short-term maturities.

Investments in Marketable Securities

The Company invests its excess cash balances in short-term and long-term marketable debt and equity securities. The Company classifies its investments in marketable debt securities as either held-to-maturity or

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ALNYLAM PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

available-for-sale based on facts and circumstances present at the time it purchased the securities. At each balance sheet date presented, the Company classified all of its investments in debt and equity securities as available-for-sale. The Company reports available-for-sale investments at fair value at each balance sheet date and includes any unrealized holding gains and losses (the adjustment to fair value) in accumulated other comprehensive income (loss), a component of stockholders equity. Realized gains and losses are determined using the specific identification method and are included in other income. If any adjustment to fair value reflects a decline in the value of the investment, the Company considers all available evidence to evaluate the extent to which the decline is other than temporary and, if so, marks the investment to market through a charge to its consolidated statements of comprehensive loss. The Company did not record any impairment charges related to its fixed income marketable securities during the years ended December 31, 2012, 2011 or 2010. During 2011, the Company recorded an impairment charge of $0.6 million related to its former investment in equity securities of Tekmira Pharmaceuticals Corporation (TPC), as the decrease in the fair value of this investment was deemed to be other than temporary. The Company s marketable securities are classified as cash equivalents if the original maturity, from the date of purchase, is 90 days or less, and as marketable securities if the original maturity, from the date of purchase, is in excess of 90 days. The Company s cash equivalents are composed of money market funds, U.S. government obligations and commercial paper. At December 31, 2012, the Company accounts for its investment in Regulus as an available-for-sale marketable security. At December 31, 2012, the fair value of these equity securities was $38.7 million. As a result of the Regulus initial public offering, the Company s carrying amount in these equity securities was $12.4 million, with a gross unrealized gain of $26.3 million recorded in other comprehensive income.

The Company obtains fair value measurement data for its marketable securities from independent pricing services. The Company performs validation procedures to ensure the reasonableness of this data. This includes meeting with the independent pricing services to understand the methods and data sources used. Additionally, the Company performs its own review of prices received from the independent pricing services by comparing these prices to other sources and confirming those securities are trading in active markets.

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ALNYLAM PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

The following tables summarize the Company s marketable securities at December 31, 2012 and 2011, in thousands:

	December 31, 2012			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Commercial paper (Due within 1 year)	$ 22,650	$ 1	$ (12)	$ 22,639
Corporate notes (Due within 1 year)	41,249	23	(4)	41,268
Corporate notes (Due after 1 year through 2 years)	50,322	5	(72)	50,255
U.S. Government obligations (Due within 1 year)	7,500			7,500
U.S. Government obligations (Due after 1 year through 2 years)	53,168	2	(9)	53,161
Total	$ 174,889	$ 31	$ (97)	$ 174,823

	December 31, 2011			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Commercial paper (Due within 1 year)	$ 11,397	$	$ (2)	$ 11,395
Corporate notes (Due within 1 year)	51,273	19	(47)	51,245
Corporate notes (Due after 1 year through 2 years)	53,592	50	(48)	53,594
U.S. Government obligations (Due within 1 year)	13,532	2		13,534
U.S. Government obligations (Due after 1 year through 2 years)	60,202	7	(21)	60,188
Equity securities	750		(125)	625
Total	$ 190,746	$ 78	$ (243)	$ 190,581

Estimated Liability for Development Costs

The Company records accrued liabilities related to expenses for which service providers have not yet billed the Company with respect to products or services that the Company has received, specifically related to ongoing pre-clinical studies and clinical trials. These costs primarily relate to third-party clinical management costs, laboratory and analysis costs, toxicology studies and investigator fees. The Company has multiple product candidates in concurrent pre-clinical studies and clinical trials at multiple clinical sites throughout the world. In order to ensure that the Company has adequately provided for ongoing pre-clinical and clinical development costs during the period in which the Company incurs such costs, the Company maintains an accrual to cover these expenses. The Company updates the estimate for this accrual on at least a quarterly basis. The assessment of these costs is a subjective process that requires judgment. Upon settlement, these costs may differ materially from the amounts accrued in the Company s consolidated financial statements. The Company s historical accrual estimates have not been materially different from the Company s actual costs.

Revenue Recognition

The Company has entered into collaboration agreements with leading pharmaceutical and life sciences companies, including Novartis, Biogen Idec Inc. (Biogen Idec), Roche, Takeda, Kyowa Hakko Kirin Co., Ltd. (Kyowa Hakko Kirin), Cubist Pharmaceuticals, Inc. (Cubist), Monsanto Company (Monsanto) Genzyme

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ALNYLAM PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

Corporation (Genzyme) and The Medicines Company (MedCo). The terms of the Company s collaboration agreements typically include non-refundable license fees, funding of research and development, payments based upon achievement of clinical and pre-clinical development milestones, regulatory milestones, manufacturing services, sales milestones and royalties on product sales.

In January 2011, the Company adopted new authoritative guidance on revenue recognition for multiple element arrangements. The guidance, which applied to multiple element arrangements entered into or materially modified on or after January 1, 2011, amended the criteria for separating and allocating consideration in a multiple element arrangement by modifying the fair value requirements for revenue recognition and eliminating the use of the residual method. The fair value of deliverables under the arrangement may be derived using a best estimate of selling price if vendor specific objective evidence and third-party evidence is not available. Deliverables under the arrangement could be considered separate units of accounting provided that (i) a delivered item has value to the customer on a standalone basis and (ii) if the arrangement includes a general right of return relative to the delivered item, delivery or performance of the undelivered item is considered probable and substantially in the control of the vendor. The new guidance did not change the criteria for standalone value. As a biotechnology entity with unique and specialized delivered and undelivered performance obligations, the Company has been unable to demonstrate standalone value in its multiple element arrangements. For example, the Company applied the new rules to collaborations executed with Monsanto and Genzyme during 2012, but it was unable to demonstrate standalone value. In addition, the Company has not materially modified any of its multiple element arrangements. As such, the Company will continue to account for other license and collaboration agreements under previously issued revenue recognition guidance for multiple element arrangements, as described below.

Non-refundable license fees are recognized as revenue upon delivery of the license only if the Company has a contractual right to receive such payment, the contract price is fixed or determinable, the collection of the resulting receivable is reasonably assured and the Company has no further performance obligations under the license agreement. Multiple element arrangements, such as license and development arrangements, are analyzed to determine whether the deliverables, which often include a license and performance obligations such as research and steering committee services, can be separated or whether they must be accounted for as a single unit of accounting. The Company recognizes upfront license payments as revenue upon delivery of the license only if the license has standalone value and the fair value of the undelivered performance obligations, typically including research and/or steering committee services, can be determined. If the fair value of the undelivered performance obligations can be determined, such obligations are accounted for separately as such obligations are fulfilled. If the license is considered to either not have standalone value or have standalone value but the fair value of any of the undelivered performance obligations cannot be determined, the arrangement would then be accounted for as a single unit of accounting and the license payments and payments for performance obligations are recognized as revenue over the estimated period of when the performance obligations are performed.

Whenever the Company determines that an arrangement should be accounted for as a single unit of accounting, the Company determines the period over which the performance obligations will be performed and revenue will be recognized. Revenue is recognized using either a proportional performance or straight-line method. The Company recognizes revenue using the proportional performance method when the level of effort required to complete its performance obligations under an arrangement can be reasonably estimated and such performance obligations are provided on a best-efforts basis. Direct labor hours or full-time equivalents are typically used as the measure of performance. The amount of revenue recognized under the proportional performance method is determined by multiplying the total payments under the contract, excluding royalties and payments contingent upon achievement of milestones, by the ratio of level of effort incurred to date to estimated total level of effort required to complete the Company s performance obligations under the arrangement. Revenue is limited to the lesser of the cumulative amount of payments received or the cumulative amount of revenue earned, as determined using the proportional performance method, as of the period ending date.

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ALNYLAM PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

If the Company cannot reasonably estimate the level of effort to complete its performance obligations under an arrangement, the Company recognizes revenue under the arrangement on a straight-line basis over the period the Company is expected to complete its performance obligations. Revenue is limited to the lesser of the cumulative amount of payments received or the cumulative amount of revenue earned, as determined using the straight-line method, as of the period ending date.

Significant management judgment is required in determining the level of effort required under an arrangement and the period over which the Company is expected to complete its performance obligations under an arrangement. Steering committee services that are not inconsequential or perfunctory and that are determined to be performance obligations are combined with other research services or performance obligations required under an arrangement, if any, in determining the level of effort required in an arrangement and the period over which the Company expects to complete its aggregate performance obligations.

Many of the Company s collaboration agreements entitle it to additional payments upon the achievement of performance-based milestones. These milestones are generally categorized into three types; development milestones which are generally based on the advancement of the Company s pipeline and initiation of clinical trials, regulatory milestones which are generally based on the submission, filing or approval of regulatory applications such as a new drug application in the United States, and commercialization milestones which are generally based on meeting specific thresholds of sales in certain geographic areas. If the achievement of a milestone is considered probable at the inception of the collaboration, the related milestone payment is included with other collaboration consideration, such as upfront fees and research funding, in the Company s revenue model. Milestones that are tied to regulatory approval are not considered probable of being achieved until such approval is received. Milestones tied to counter-party performance are not included in the Company s revenue model until the performance conditions are met.

The Company performs an assessment to determine whether a substantive milestone exists at the inception of its collaborative arrangements. In evaluating if a milestone is substantive, the Company considers whether uncertainty exists as to the achievement of the milestone event at the inception of the arrangement, the achievement of the milestone involves substantive effort and can only be achieved based in whole or part on the performance or the occurrence of a specific outcome resulting from the Company s performance, the amount of the milestone payment appears reasonable either in relation to the effort expected to be expended or to the projected enhancement of the value of the delivered items, there is any future performance required to earn the milestone, and the consideration is reasonable relative to all deliverables and payment terms in the arrangement. When a substantive milestone is achieved, the accounting rules permit the Company to recognize revenue related to the milestone payment in its entirety.

To date, the Company has not recorded any substantive milestones under its collaborations because the Company has not identified any milestones that meet the required criteria listed above. The Company has deferred recognition of payments for achievement of non-substantive milestones and recognized revenue over the estimated period of performance applicable to each collaborative arrangement. As these milestones are achieved, the Company will recognize as revenue a portion of the milestone payment, which is equal to the percentage of the performance period completed when the milestone is achieved, multiplied by the amount of the milestone payment, upon achievement of such milestone. The Company will recognize the remaining portion of the milestone payment over the remaining performance period under the proportional performance method or on a straight-line basis.

For revenue generating arrangements where the Company, as a vendor, provides consideration to a licensor or collaborator, as a customer, the Company applies the accounting standard that governs such transactions. This standard addresses the accounting for revenue arrangements where both the vendor and the customer make cash payments to each other for services and/or products. A payment to a customer is presumed to be a reduction of the selling price unless the Company receives an identifiable benefit for the payment and it can reasonably estimate the fair value of the benefit received. Payments to a customer that are deemed a reduction of selling

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

price are recorded first as a reduction of revenue, to the extent of both cumulative revenue recorded to date and probable future revenues, which include any unamortized deferred revenue balances, under all arrangements with such customer, and then as an expense. Payments that are not deemed to be a reduction of selling price are recorded as an expense.

The Company evaluates its collaborative agreements for proper classification in its consolidated statements of comprehensive loss based on the nature of the underlying activity. Transactions between collaborators recorded in the Company s consolidated statements of comprehensive loss are recorded on either a gross or net basis, depending on the characteristics of the collaborative relationship. The Company generally reflects amounts due under its collaborative agreements related to cost-sharing of development activities as a reduction of research and development expense.

Amounts received prior to satisfying the above revenue recognition criteria are recorded as deferred revenue in the accompanying consolidated balance sheets. Although the Company follows detailed guidelines in measuring revenue, certain judgments affect the application of its revenue policy. For example, in connection with the Company s existing collaboration agreements, the Company has recorded on its balance sheet short-term and long-term deferred revenue based on its best estimate of when such revenue will be recognized. Short-term deferred revenue consists of amounts that are expected to be recognized as revenue in the next 12 months. Amounts that the Company expects will not be recognized within the next 12 months are classified as long-term deferred revenue. However, this estimate is based on the Company s current operating plan and, if its operating plan should change in the future, the Company may recognize a different amount of deferred revenue over the next 12-month period.

The estimate of deferred revenue also reflects management s estimate of the periods of the Company s involvement in certain of its collaborations. The Company s performance obligations under these collaborations consist of participation on steering committees and the performance of other research and development services. In certain instances, the timing of satisfying these obligations can be difficult to estimate. Accordingly, the Company s estimates may change in the future. Such changes to estimates would result in a change in revenue recognition amounts. If these estimates and judgments change over the course of these agreements, it may affect the timing and amount of revenue that the Company recognizes and records in future periods. At December 31, 2012, the Company had short-term and long-term deferred revenue of $31.4 million and $100.9 million, respectively, related to its collaborations.

The Company recognizes revenue under government cost reimbursement contracts as the Company performs the underlying research and development activities.

Income Taxes

The Company uses the asset and liability method of accounting for income taxes. Under the asset and liability method, deferred tax assets and liabilities reflect the impact of temporary differences between amounts of assets and liabilities for financial reporting purposes and such amounts as measured under enacted tax laws. A valuation allowance is required to offset any net deferred tax assets if, based upon the available evidence, it is more likely than not that some or all of the deferred tax asset will not be realized.

The Company accounts for uncertain tax positions using a more-likely-than-not threshold for recognizing and resolving uncertain tax positions. The evaluation of uncertain tax positions is based on factors that include, but are not limited to, changes in tax law, the measurement of tax positions taken or expected to be taken in tax returns, the effective settlement of matters subject to audit, new audit activity and changes in facts or circumstances related to a tax position. The Company s policy is to accrue interest and penalties related to unrecognized tax positions in income tax expense. As of December 31, 2012, the Company has not recorded significant interest and penalty expense related to uncertain tax positions.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

Research and Development Costs

The Company expenses research and development costs as incurred. Included in research and development costs are wages, benefits and other operating costs, facilities, supplies, external services, clinical trial and manufacturing costs, and overhead directly related to the Company s research and development operations, as well as costs to acquire technology licenses.

The Company has entered into several license agreements for rights to utilize certain technologies. The terms of the licenses may provide for upfront payments, annual maintenance payments, milestone payments based upon certain specified events being achieved and royalties on product sales. The Company charges costs to acquire and maintain licensed technology that has not reached technological feasibility and does not have alternative future use to research and development expense as incurred. During the years ended December 31, 2012, 2011 and 2010, the Company charged to research and development expense costs associated with license fees of $5.7 million, $1.4 million and $2.4 million, respectively.

Accounting for Stock-Based Compensation

The Company has stock incentive plans and an employee stock purchase plan under which it grants equity instruments. The Company accounts for all stock-based awards granted to employees at their fair value and generally recognizes compensation expense over the vesting period of the award. Determining the amount of stock-based compensation to be recorded requires the Company to develop estimates of fair values of stock options as of the grant date. The Company calculates the grant date fair values using the Black-Scholes valuation model. The Company s expected stock price volatility assumption is based on a combination of the historical and implied volatility of the Company s publicly traded stock.

For stock-based awards granted to non-employees, the Company generally recognizes compensation expense over the vesting period of the award, which is generally the period during which services are rendered by such non-employees. At the end of each financial reporting period prior to vesting, the Company re-measures the value of these stock-based awards (as calculated using the Black-Scholes option-pricing model) using the then-current fair value of the Company s common stock. Stock options granted by the Company to non-employees, other than members of the Company s Board of Directors and Scientific Advisory Board members, generally vest over the service period.

The fair value of restricted stock awards granted to employees is based upon the quoted closing market price per share on the date of grant, adjusted for assumed forfeitures. For performance-based restricted stock awards, the value of the awards is measured when the Company determines that the achievement of such performance conditions is deemed probable. This determination requires significant judgment by management. Expense is recognized over the vesting period, commencing when the Company determines that it is probable that the awards will vest.

Accounting for Joint Venture

From the formation of Regulus in September 2007 to October 2012, the Company accounted for its interest in Regulus using the equity method of accounting. The Company reviewed the consolidation guidance that defines a variable interest entity (VIE) and concluded that Regulus qualified as a VIE during such time period. The Company recorded any gains or losses recognized from the issuance of stock by its equity method investee as other income (expense) in its consolidated statements of comprehensive loss. The Company did not consolidate Regulus financial results as the Company lacked the power to direct the activities that could significantly impact the economic success of Regulus. In October 2012, Regulus completed an initial public offering, resulting in the Company s ownership percentage decreasing from approximately 44% to 17% of Regulus outstanding common stock. Based upon the Company s new ownership percentage of 17%, as well as

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

qualitative factors, the Company does not believe that it has the ability to exercise significant influence over the operating decisions and financial policies of Regulus and has therefore discontinued the equity method of accounting for Regulus. Accordingly, beginning in October 2012, the Company has accounted for its investment in Regulus as an available-for-sale marketable security. For additional details on the accounting for the Company s investment in Regulus, see Note 10.

Comprehensive Loss

Comprehensive loss is comprised of net loss and certain changes in stockholders equity that are excluded from net loss. The Company includes foreign currency translation adjustments in other comprehensive loss for Alnylam Europe as the functional currency is not the United States dollar. The Company also includes unrealized gains and losses on certain marketable securities in other comprehensive loss.

Net Loss Per Common Share

The Company computes basic net loss per common share by dividing net loss by the weighted average number of common shares outstanding. The Company computes diluted net loss per common share by dividing net loss by the weighted average number of common shares and dilutive potential common share equivalents then outstanding. Potential common shares consist of shares issuable upon the exercise of stock options (using the treasury stock method), and unvested restricted stock awards. Because the inclusion of potential common shares would be anti-dilutive for all periods presented, diluted net loss per common share is the same as basic net loss per common share.

The following table sets forth for the periods presented the potential common shares (prior to consideration of the treasury stock method) excluded from the calculation of net loss per common share because their inclusion would be anti-dilutive, in thousands:

	December 31,		
	2012	2011	2010
Options to purchase common stock	8,932	9,779	8,975
Unvested restricted common stock	604	312	113
	9,536	10,091	9,088

Segment Information

The Company operates in a single reporting segment, the discovery, development and commercialization of RNAi therapeutics.

Subsequent Events

The Company evaluated all events or transactions that occurred after December 31, 2012 up through the date these consolidated financial statements were issued. During this period, the Company did not have any material recognized subsequent events. However, the Company did have the following nonrecognized subsequent events, which are more fully described in Notes 3, 7 and 12:

In January 2013, the Company sold an aggregate of 9,200,000 shares of its common stock through an underwritten public offering at a price to the public of $20.13 per share. See Note 7.

In January 2013, the Company and MedCo entered into a license and collaboration agreement (the MedCo Agreement), pursuant to which the Company granted to MedCo an exclusive license to develop and commercialize specified RNAi therapeutics targeting proprotein convertase subtilisin/kexin type 9 (PCSK9). See Note 12.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

In February 2013, Cubist notified the Company that it would not exercise its opt-in right for the Company s ALN-RSV01 program for the treatment of respiratory syncytial virus infection in lung transplant patients. In light of this determination, the parties mutually agreed to terminate their license and collaboration agreement entered into in January 2009 (the Cubist Agreement). See Note 3.

On February 19, 2013, the Company and Genzyme entered into an amendment to their license and collaboration agreement (the Genzyme Agreement). See Note 3.

Recent Accounting Pronouncements

In May 2011, the Financial Accounting Standards Board (FASB) issued a new accounting standard that clarifies the application of certain existing fair value measurement guidance and expands the disclosures for fair value measurements that are estimated using significant unobservable (Level 3) inputs. This standard is effective on a prospective basis for annual and interim reporting periods beginning on or after December 15, 2011. The Company adopted this amendment on January 1, 2012. The adoption of this new standard did not have a material impact on the Company s consolidated financial statements.

In June 2011, the FASB issued an amendment to the accounting guidance for presentation of comprehensive income. Under the amended guidance, a company may present the total of comprehensive income, the components of net income and the components of other comprehensive income either in a single continuous statement of comprehensive income or in two separate but consecutive statements. In either case, a company is required to present each component of net income along with total net income, each component of other comprehensive income along with a total for other comprehensive income and a total amount for comprehensive income. For public companies, the amendment is effective for fiscal years, and interim periods within those years, beginning after December 15, 2011, and shall be applied retrospectively. The Company adopted this amendment on January 1, 2012. Other than a change in presentation, the adoption of this guidance did not have a material impact on the Company s consolidated financial statements.

In February 2013, the FASB issued amendments to the accounting guidance for presentation of comprehensive income to improve the reporting of reclassifications out of accumulated other comprehensive income. The amendments do not change the current requirements for reporting net income or other comprehensive income, but do require an entity to provide information about the amounts reclassified out of accumulated other comprehensive income by component. In addition, an entity is required to present, either on the face of the statement where the net income is presented or in the notes, significant amounts reclassified out of accumulated other comprehensive income by the respective line items of net income but only if the amount reclassified is required under GAAP to be reclassified to net income in its entirety in the same reporting period. For other amounts that are not required under GAAP to be reclassified in their entirety to net income, an entity is required to cross-reference to other disclosures required under GAAP that provide additional detail about these amounts. For public companies, these amendments are effective prospectively for reporting periods beginning after December 15, 2012. Other than a change in presentation, the Company does not believe the adoption of this guidance will have a material impact on the Company s consolidated financial statements.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

3. SIGNIFICANT AGREEMENTS

The following table summarizes the Company s total consolidated net revenues from research collaborators, for the periods indicated, in thousands:

	Year Ended December 31,		
	2012	**2011**	**2010**
Roche/Arrowhead	$ 37,318	$ 55,978	$ 55,978
Takeda	21,973	22,248	22,250
Cubist	2,777	2,467	2,363
Monsanto	1,954		
Novartis	60	149	9,313
Government contract		152	4,335
Other	2,643	1,763	5,802
Total net revenues from research collaborators	$ 66,725	$ 82,757	$ 100,041

Platform Alliances

Roche/Arrowhead Alliance

In July 2007, the Company and, for limited purposes, Alnylam Europe, entered into a license and collaboration agreement (the LCA) with Roche. Under the LCA, which became effective in August 2007, the Company granted Roche a non-exclusive license to the Company s intellectual property, including delivery-related intellectual property existing as of the date of the LCA, to develop and commercialize therapeutic products that function through RNAi, subject to the Company s 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 LCA. As a result of the assignment, Arrowhead owns all of the rights and obligations of Roche under the LCA. The license is initially limited to four therapeutic areas, and may be expanded to include additional therapeutic areas upon payment to the Company by Arrowhead of an additional $50.0 million for each additional therapeutic area, if any.

In consideration for the rights the Company granted under the LCA, Roche paid the Company $273.5 million in upfront cash payments. In addition, in exchange for the Company s contributions under the LCA, for each RNAi therapeutic product developed by Arrowhead, its affiliates or sublicensees under the LCA, the Company is 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. The Company could potentially earn the next development milestone payment of $1.0 million under the LCA based upon the initiation of the first Phase I clinical trial by Arrowhead for an RNAi therapeutic product. For purposes of potential future revenue recognition, the Company does not believe this milestone or any future milestones are substantive. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, the Company may not receive any milestone or royalty payments from Arrowhead. Under the LCA, the Company and Roche also established a discovery collaboration in October 2009 (Discovery Collaboration), subject to the Company s existing contractual obligations to third parties.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

The term of the LCA 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. Arrowhead may terminate the LCA, on a licensed product-by-licensed product, licensed patent-by-licensed patent, and country-by-country basis, upon 180-days prior written notice, but is required to continue to make milestone and royalty payments to the Company if any royalties were payable on net sales of a terminated licensed product during the previous 12 months. The LCA may also be terminated by either party in the event the other party fails to cure a material breach under the LCA.

In July 2007, the Company executed a common stock purchase agreement (the Common Stock Purchase Agreement) with Roche Finance Ltd, an affiliate of Roche. In connection with the execution of the LCA and the Common Stock Purchase Agreement, the Company also executed a share purchase agreement (the Alnylam Europe Purchase Agreement) with Alnylam Europe and Roche Beteiligungs GmbH, an affiliate of Roche (Roche Germany). Under the terms of the Alnylam Europe Purchase Agreement, the Company sold substantially all of the non-intellectual property assets of Alnylam Europe to Roche Germany for an aggregate purchase price of $15.0 million.

In summary, the Company received upfront payments totaling $331.0 million under the Roche alliance, which included an upfront payment under the LCA of $273.5 million, $42.5 million under the Common Stock Purchase Agreement and $15.0 million under the Alnylam Europe Purchase Agreement. The Company initially recorded $278.2 million of these proceeds as deferred revenue in connection with this alliance.

The Company determined that the deliverables under these agreements included the license, the Alnylam Europe assets and employees, the steering committees (joint steering committee and future technology committee) and the services under the Discovery Collaboration. The Company also determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the license and assets of Alnylam Europe are not separable from the undelivered services (i.e., the steering committees and Discovery Collaboration) and, accordingly the license and the services were treated as a single unit of accounting. When multiple deliverables are accounted for as a single unit of accounting, the Company bases its revenue recognition pattern on the final deliverable. Under the Arrowhead alliance, the steering committee services and the Discovery Collaboration services are the final deliverables and all such services ended, contractually, in August 2012, five years from the effective date of the LCA.

The Company recognized the revenue related to these agreements on a straight-line basis over five years because the Company could not reasonably estimate the total level of effort required to complete its service obligations under the LCA, and therefore, could not utilize a proportional performance model. At December 31, 2012, there was no remaining deferred revenue under the LCA as the Company recognized all remaining Roche/Arrowhead revenue during the quarter ended September 30, 2012. The Company will recognize future milestones under the LCA, if any, when such milestones are achieved.

Takeda Alliance

In May 2008, the Company entered into a license and collaboration agreement (the Takeda Agreement) with Takeda to pursue the development and commercialization of RNAi therapeutics. Under the Takeda Agreement, the Company granted to Takeda a non-exclusive, worldwide, royalty-bearing license to the Company s intellectual property, including delivery-related intellectual property, controlled by the Company as of the date of the agreement or during the five years thereafter, to develop, manufacture, use and commercialize RNAi therapeutics, subject to the Company s 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 is the Company s exclusive platform partner in the Asian territory, as defined in the Takeda Agreement, through May 2013.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

In consideration for the rights granted to Takeda under the Takeda Agreement, Takeda agreed to pay the Company $150.0 million in upfront and near-term technology transfer payments. In addition, the Company has 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 Collaboration Agreement. In June 2008, Takeda paid the Company an upfront payment of $100.0 million and agreed to pay to the Company an additional $50.0 million upon achievement of specified technology transfer milestones. Of this $50.0 million, $20.0 million was paid to the Company in October 2008, $20.0 million was paid to the Company in March 2010, and $10.0 million was paid to the Company in March 2011 (collectively, the Technology Transfer Milestones). If Takeda elects to expand its license to additional therapeutic areas, Takeda will be required to pay the Company $50.0 million for each additional field selected, if any. In addition, for each RNAi therapeutic product developed by Takeda, its affiliates and sublicensees, the Company is entitled to receive specified development, regulatory and commercialization milestone payments, totaling up to $171.0 million per product, together with up to 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. The Company 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. For purposes of potential future revenue recognition, the Company does not believe this milestone or any future milestones are substantive. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, the Company may not receive any additional milestone payments or any royalty payments from Takeda.

Pursuant to the Takeda Agreement, the Company and Takeda are also collaborating on the research of RNAi therapeutics directed to one or two disease targets agreed to by the parties (the Research Collaboration), subject to the Company s existing contractual obligations with third parties. Takeda also has the option, subject to certain conditions, to collaborate with the Company 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 the Company s RNAi therapeutic products in the Asian territory, excluding the Company s ALN-RSV, ALN-TTR and ALN-PCS programs. In addition to the 50-50 profit sharing option, the Company has 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 (the JTTC), a joint research collaboration committee (the JRCC) and a joint delivery collaboration committee (the JDCC), 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 (1) the expiration of the Company s last-to-expire patent covering a licensed product and (2) the last-to-expire term of a profit sharing agreement in the event the Company elects to enter into such an agreement. 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 the Company, provided, however, that Takeda is required to continue to make royalty payments to the Company for the duration of the royalty term with respect to a licensed product.

The Company has determined that the deliverables under the Takeda Agreement include the license, the joint committees (the JTTC, JRCC and JDCC), the technology transfer activities and the services that the Company will be obligated to perform under the Research Collaboration. The Company also determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

license and undelivered services (i.e., the joint committees and the Research Collaboration) are not separable and, accordingly, the license and services are being treated as a single unit of accounting. When multiple deliverables are accounted for as a single unit of accounting, the Company bases its revenue recognition pattern on the final deliverable. Under the Takeda Agreement, the last elements to be delivered are the JDCC and JTTC services, each of which has a life of no more than seven years.

The Company is recognizing the upfront payment of $100.0 million and the Technology Transfer Milestones of $50.0 million, the receipt of which the Company believed was probable at the commencement of the collaboration, on a straight-line basis over seven years because the Company is unable to reasonably estimate the level of effort to fulfill these obligations, primarily because the effort required under the Research Collaboration is largely unknown, and therefore, cannot utilize a proportional performance model. As future milestones are achieved, if any, the Company will recognize as revenue a portion of the milestone payment equal to the percentage of the performance period completed when the milestone is achieved, multiplied by the amount of the milestone payment. At December 31, 2012, deferred revenue under the Takeda Agreement was $52.8 million.

Monsanto Alliance

In August 2012, the Company and Monsanto Company (Monsanto) entered into a license and collaboration agreement (the Monsanto Agreement), pursuant to which the Company granted to Monsanto a worldwide, exclusive, royalty bearing right and license, including the right to grant sublicenses, to the Company s RNAi platform technology and intellectual property controlled by the Company as of the date of the Monsanto Agreement or during the 30 months thereafter, in the field of agriculture. The Monsanto Agreement also includes the transfer of technology from the Company to Monsanto and a collaborative research project (the Monsanto Discovery Collaboration). Under the Monsanto Agreement, Monsanto will be the Company s exclusive collaborator in the agriculture field for a ten-year period (the Exclusivity Period).

In consideration for the rights granted to Monsanto under the Monsanto Agreement, Monsanto paid the Company $29.2 million in upfront cash payments. Monsanto is also required to make near-term milestone payments to the Company upon the achievement of specified technology transfer and patent-related milestones. The Company is also entitled to receive additional funding for collaborative research efforts. In the aggregate, the Company can earn up to $5.0 million in potential future milestone payments and research funding under the Monsanto Agreement. In addition, Monsanto is required to pay to the Company a percentage of specified fees from certain sublicense agreements Monsanto may enter into that include access to the Company s 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. In December 2012, the Company received a milestone payment of $1.5 million of the $5.0 million in potential milestone payments under the Monsanto Agreement based upon the achievement of a specified patent-related event. The Company could potentially earn the next milestone payment of $2.5 million under the Monsanto Agreement based upon the completion of technology transfer activities. For purposes of potential future revenue recognition, the Company does not believe this milestone or any future milestones are substantive. Due to the uncertainty of the application of RNAi technology in the field of agriculture, the Company 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. The Company estimates that its 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 the Company, provided,

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however, that Monsanto is required to continue to make royalty payments to the Company 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 agreement.

The Company determined that the significant deliverables under the Monsanto Agreement include the license, the technology transfer activities and the services that the Company will be obligated to perform under the Monsanto Discovery Collaboration. The Company also determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the license and undelivered technical transfer activities and Monsanto Discovery Collaboration services do not have standalone value due to the specialized nature of the services to be provided by the Company. In addition, while Monsanto has the ability to grant sublicenses, it cannot grant access to certain of the Company s proprietary technology. The uniqueness of the Company s services and the limited sublicense right are indicators that standalone value is not present in the arrangement. Therefore the deliverables are not separable and, accordingly, the license and undelivered technical transfer activities and Monsanto Discovery Collaboration services are being treated as a single unit of accounting. When multiple deliverables are accounted for as a single unit of accounting, the Company bases its revenue recognition model on the final deliverable. Under the Monsanto Agreement, the last deliverable to be completed is the Monsanto Discovery Collaboration, which must be completed within five years. The Company is recognizing revenue under the Monsanto Agreement on a straight-line basis over five years. The Company is not utilizing a proportional performance model since it is unable to reasonably estimate the level of effort to fulfill these obligations, primarily because the effort required under the Monsanto Discovery Collaboration is largely unknown.

The Company received a payment of $29.2 million from Monsanto in August 2012, which was initially recorded as deferred revenue. Under the terms of the Monsanto Agreement, in the event that during the Exclusivity Period Monsanto loses certain patent rights, and such loss has a material adverse effect on the Licensed Products, then the Company would be required to pay Monsanto up to $5.0 million as liquidated damages, and Monsanto s royalty obligations to the Company under the Monsanto Agreement would be reduced or, under certain circumstances, terminated. The Company has the right to cure any such loss of patent rights under the Monsanto Agreement. The Company has determined that this amount is not fixed and determinable and therefore, the Company has excluded this amount from its revenue model and is deferring the recognition of $5.0 million of revenue. The Company will continue to reassess when this amount can be considered fixed and determinable. If the achievement of a milestone is considered probable at the inception of the collaboration, the Company s policy is to include the related payment in its revenue model. The Company has concluded that the receipt of the technology transfer payment of $2.5 million is probable, and has therefore included this amount in the Company s revenue model. As future milestones are achieved, if any, the Company will recognize as revenue a portion of the milestone payment equal to the percentage of the performance period completed when the milestone is achieved, multiplied by the amount of the milestone payment. At December 31, 2012, deferred revenue under the Monsanto Agreement was $28.7 million.

Discovery and Development Alliances

Isis Collaboration and License Agreement

In April 2009, the Company and Isis amended and restated their existing strategic collaboration and license agreement (as amended and restated, the Amended and Restated Isis 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 the Company licenses to its current and future patents and patent applications relating to chemistry and to RNA-targeting mechanisms for the research, development and commercialization of double-stranded RNA (dsRNA) products. The Company has the right to use Isis technologies in its development programs or in collaborations and Isis agreed not to grant licenses under these patents to any other organization for the discovery, development and commercialization of dsRNA products

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designed to work through an RNAi mechanism, except in the context of a collaboration in which Isis plays an active role. The Company granted Isis non-exclusive licenses to its current and future patents and patent applications relating to RNA-targeting mechanisms and to chemistry for research use. The Company also granted Isis the non-exclusive right to develop and commercialize dsRNA products developed using RNAi technology against a limited number of targets. In addition, the Company granted Isis non-exclusive rights to research, develop and commercialize single-stranded RNA products. In August 2012, the Company and Isis amended the Amended and Restated Isis Agreement to provide for the discovery, development and commercialization of dsRNA products by the Company or its sublicensees in the field of agriculture.

In 2004, under the terms of the original Isis agreement, the Company paid Isis an upfront license fee of $5.0 million. The Company also agreed to pay Isis milestone payments, totaling up to approximately $3.4 million, upon the occurrence of specified development and regulatory events, and royalties on sales, if any, for each product that the Company or a collaborator develops using Isis intellectual property. In addition, the Company agreed to pay to Isis a percentage of specified fees from strategic collaborations the Company may enter into that include access to Isis intellectual property.

Isis agreed to pay the Company, per therapeutic target, a license fee of $0.5 million, and milestone payments totaling approximately $3.4 million, payable upon the occurrence of specified development and regulatory events, and royalties on sales, if any, for each product developed by Isis or a collaborator that utilizes the Company s intellectual property. Isis has the right to elect up to ten non-exclusive target licenses under the agreement and has the right to purchase one additional non-exclusive target per year during the term of the collaboration.

As part of the Amended and Restated Isis Agreement, the Company and Isis established a collaborative effort focused on single-stranded RNAi (ssRNAi) technology and the Company obtained from Isis a co-exclusive, worldwide license to research, develop and commercialize ssRNAi products. The Company paid Isis $11.0 million in license fees upon signing the agreement in connection with the ssRNAi research program. In November 2010, the Company exercised its right to terminate the ssRNAi collaborative effort, and all licenses to ssRNAi products granted by Isis to the Company, and any obligation thereunder requiring the Company to provide further research funding or pay additional license fees, milestone payments, royalties or sublicense payments to Isis for such ssRNAi products, also terminated. The termination of this collaborative effort did not affect the remainder of the Amended and Restated Isis Agreement, including the Company s licenses to Isis current and future patents and patent applications relating to dsRNAs, which remains in effect.

The term of the Amended and Restated Isis Agreement generally ends upon the expiration of the last-to-expire patent licensed thereunder, whether such patent is a patent licensed by the Company to Isis, or vice versa. As the license will include additional patents, if any, filed to cover future inventions, if any, the date of expiration cannot be determined at this time.

During 2012, as a result of certain payments received by the Company in connection with the Monsanto and Genzyme alliances, the Company paid $2.5 million to Isis. These license fees were charged to research and development expense.

Novartis Alliance

In the second half of 2005, the Company entered into a series of transactions with Novartis, which included a stock purchase agreement, an investor rights agreement (the Investor Rights Agreement) and a research collaboration and license agreement (the Collaboration and License Agreement) (collectively the Novartis Agreements). The Collaboration and License Agreement had a five-year research term. In October 2010, the research program under the Collaboration and License Agreement was substantially completed in accordance with the terms of the Collaboration and License Agreement, subject to certain surviving rights and obligations of the parties.

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In September 2010, Novartis exercised its right under the Collaboration and License Agreement to select 31 designated gene targets, for which Novartis has exclusive rights to discover, develop and commercialize RNAi therapeutic products using the Company s intellectual property and technology, including delivery-related intellectual property and related technology. Under the terms of the Collaboration and License Agreement, for any RNAi therapeutic products Novartis develops against these targets, the Company is entitled to receive milestone payments upon achievement of certain specified development and annual net sales events, up to an aggregate of $75.0 million per therapeutic product, as well as royalties on annual net sales of any such product. For purposes of potential future revenue recognition, the Company does not believe these milestones are substantive. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, the Company may not receive any milestone or royalty payments from Novartis.

Novartis may terminate the Collaboration and License Agreement in the event that the Company materially breaches its obligations. The Company may terminate the Collaboration and License Agreement with respect to particular programs, products and/or countries in the event of specified material breaches by Novartis of its obligations, or in its entirety under specified circumstances for multiple such breaches.

The Company initially deferred the non-refundable $10.0 million upfront payment and the $6.4 million premium paid on the common stock of the Company purchased by Novartis. These payments, in addition to research funding and certain milestone payments, together totaled approximately $64.0 million, and are being amortized into revenue using the proportional performance method over the estimated duration of the Collaboration and License Agreement. Under this method, the Company estimates the level of effort to be expended over the term of the agreement and recognizes revenue based on the lesser of the amount calculated based on proportional performance of total expected revenue or the amount of non-refundable payments earned.

The Company believes the estimated period of performance under the Collaboration and License Agreement is ten years, which includes the five-year term of the agreement and limited support as part of a technology transfer until 2015, the fifth anniversary of the completion of the research term under the Collaboration and License Agreement. The Company continues to use an expected term of ten years in its proportional performance model. The Company reevaluates the expected term when new information is known that could affect the Company s estimate. In the event the Company s period of performance is different than estimated, the Company will adjust the amount of revenue recognized on a prospective basis. At December 31, 2012, deferred revenue under the Novartis Collaboration and License Agreement was $0.2 million.

At December 31, 2012, Novartis owned approximately 7.7% of the Company s outstanding common stock.

Product Alliances

Kyowa Hakko Kirin Alliance

In June 2008, the Company entered into a license and collaboration agreement (the KHK Agreement) with Kyowa Hakko Kirin. Under the KHK Agreement, the Company granted Kyowa Hakko Kirin an exclusive license to its intellectual property in Japan and other markets in Asia (the Licensed Territory) for the development and commercialization of an RNAi therapeutic for the treatment of respiratory syncytial virus (RSV) infection. The KHK Agreement covers ALN-RSV01, as well as additional RSV-specific RNAi therapeutic compounds that comprise the ALN-RSV program (Additional Compounds). The Company retains all development and commercialization rights worldwide outside of the Licensed Territory.

Under the terms of the KHK Agreement, in June 2008, Kyowa Hakko Kirin paid the Company an upfront cash payment of $15.0 million. In addition, Kyowa Hakko Kirin is required to make payments to the Company upon achievement of specified development and sales milestones totaling up to $78.0 million, and royalty payments based on annual net sales, if any, of RNAi therapeutics for the treatment of RSV by Kyowa Hakko

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Kirin, its affiliates and sublicensees in the Licensed Territory. For purposes of potential future revenue recognition, the Company does not believe these milestones are substantive. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, the Company may not receive any milestone or royalty payments from Kyowa Hakko Kirin.

The collaboration between Kyowa Hakko Kirin and the Company is governed by a joint steering committee that is comprised of an equal number of representatives from each party. Under the agreement, Kyowa Hakko Kirin is establishing a development plan for the ALN-RSV program relating to the development activities to be undertaken in the Licensed Territory, with the initial focus on Japan. Kyowa Hakko Kirin is responsible, at its expense, for all development activities under the development plan that are reasonably necessary for the regulatory approval and commercialization of an RNAi therapeutic for the treatment of RSV in Japan and the rest of the Licensed Territory. The Company is responsible for supply of the product to Kyowa Hakko Kirin under a supply agreement unless Kyowa Hakko Kirin elects, prior to the first commercial sale of the product in the Licensed Territory, to manufacture the product itself or arrange for a third party to manufacture the product.

The term of the KHK Agreement generally ends on a country-by-country basis upon the later of (1) the expiration of the Company s last-to-expire patent covering a licensed product and (2) the tenth anniversary of the first commercial sale in the country of sale. Additional patent filings relating to the collaboration may be made in the future. The KHK Agreement may be terminated by either party in the event the other party fails to cure a material breach under the agreement. In addition, Kyowa Hakko Kirin may terminate the agreement without cause upon 180-days prior written notice to the Company, subject to certain conditions.

The Company has determined that the deliverables under the KHK Agreement include the license, the joint steering committee, the manufacturing services and any Additional Compounds. The Company has determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the individual deliverables are not separable and, accordingly, must be accounted for as a single unit of accounting. When multiple deliverables are accounted for as a single unit of accounting, the Company bases its revenue recognition pattern on the final deliverable.

The Company is currently unable to reasonably estimate its period of performance under the KHK Agreement, as it is unable to estimate the timeline of its deliverables related to the fixed-price option granted to Kyowa Hakko Kirin for any Additional Compounds. The Company is deferring all revenue under the KHK Agreement until it is able to reasonably estimate its period of performance. The Company will continue to reassess whether it can reasonably estimate the period of performance to fulfill its obligations under the KHK Agreement. At December 31, 2012, deferred revenue under the KHK Agreement was $15.5 million.

Genzyme Alliance

In October 2012, the Company and Genzyme entered into the Genzyme Agreement pursuant to which the Company granted to Genzyme an exclusive license in Japan and the Asia-Pacific region (the Genzyme Territory) to develop and commercialize RNAi therapeutics targeting transthyretin (TTR) for the treatment of transthyretin-mediated amyloidosis (ATTR) and other human diseases. The Genzyme Agreement covers ALN-TTR02 and ALN-TTRsc, and may in the future cover additional TTR-specific RNAi therapeutic compounds that comprise the Company s TTR program (together, Licensed Products), subject, in the case of Improvement Products (as defined in the Genzyme Agreement), to specified additional terms and conditions. The Company retains all development and commercialization rights worldwide outside of the Genzyme Territory.

In consideration for the rights granted to Genzyme under the Genzyme Agreement, Genzyme paid the Company an upfront cash payment of $22.5 million. Upon achievement of certain milestones, the Company will be entitled to receive milestone payments, up to an aggregate of $50.0 million, including up to $25.0 million in specified development milestones and $25.0 million in specified regulatory milestones. In addition, the Company

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will be entitled to tiered royalties expected to yield an effective royalty rate percentage ranging from the mid-teens to mid-twenties based on annual net sales, if any, of Licensed Products in the Genzyme Territory by Genzyme, its affiliates and sublicensees. The Company could potentially earn the next development milestone payment of $7.0 million under the Genzyme Agreement based upon the completion of a successful Phase II ALN-TTR clinical trial, as defined in the Genzyme Agreement. For purposes of potential future revenue recognition, the Company does not believe this milestone or any future milestones are substantive. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, the Company may not receive any milestone or royalty payments from Genzyme.

Under the Genzyme Agreement, the parties will collaborate in the development of Licensed Products, with Genzyme assuming primary responsibility for the development and commercialization of Licensed Products in the Genzyme Territory and the Company retaining primary responsibility for the development and commercialization of Licensed Products in the rest of the world. The collaboration between Genzyme and the Company is governed by a joint steering committee that will be comprised of an equal number of representatives from each party. Under the agreement, Genzyme is establishing a development plan for the ALN-TTR program relating to the development activities to be undertaken in the Genzyme Territory. Genzyme is responsible, at its expense, for all development activities under the development plan that are reasonably necessary for the regulatory approval and commercialization of an RNAi therapeutic for the treatment of ATTR in the Genzyme Territory. The Company and Genzyme intend to enter into a supply agreement to provide for supply of Licensed Products to Genzyme for clinical trials, and, at Genzyme s request, commercial sales. Genzyme may elect, at any time during the term of the Genzyme Agreement, to manufacture Licensed Products itself or arrange for a third party to manufacture the product.

Genzyme also has a right of first negotiation in the event that the Company desires to grant any third party rights to develop and/or commercialize a Licensed Product for the treatment of ATTR or other human diseases outside of the Genzyme Territory.

The Company has agreed to indemnify Genzyme for legal costs and other losses or amounts required to be paid by Genzyme, if any, in connection with or related to certain of the Company s ongoing litigation matters. Unless terminated earlier in accordance with the terms of the agreement, the Genzyme Agreement expires on a Licensed Product-by-Licensed Product and country-by-country basis upon the latest to occur of (1) the expiration of the last valid claim of the Company patents or joint patents covering a Licensed Product, (2) the expiration of the Regulatory Exclusivity (as defined in the Genzyme Agreement), and (3) twenty-five years from first commercial sale of such Licensed Product in such country. The Company estimates that its fundamental RNAi patents covering ALN-TTR compounds under the Genzyme Agreement will expire both in and outside of the United States generally between 2016 and 2021. The Company also estimates that its patents covering ALN-TTR compounds under the Genzyme Agreement in the United States and elsewhere will expire in 2032. These patent rights are subject to potential patent term extensions and/or supplemental protection certificates extending such terms in countries where such extensions may become available. In addition, more patent filings relating to the collaboration may be made in the future. Either party may terminate the Genzyme Agreement in the event the other party fails to cure a material breach or in the event that development ends after a specified time period without regulatory approval of a Licensed Product. The Company may terminate the agreement upon patent-related challenges by Genzyme. Genzyme has the right to terminate the agreement without cause at any time upon six months prior written notice. Genzyme may also terminate the agreement upon forty-five days prior written notice if Genzyme determines that specified success criteria have not been met following the completion of a Phase II clinical trial.

During the period from the effective date of the Genzyme Agreement until the first commercial sale of a Licensed Product in a country in the Genzyme Territory, and thereafter during any period during which Genzyme is paying the Company any royalties on net sales of any Licensed Product in such country, neither party will,

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alone or with an affiliate or agreed upon third party, develop or commercialize in such country, any product for the treatment of ATTR, other than a Licensed Product or an agreed complementary product, without the prior written agreement of the other party.

The Genzyme Agreement originally provided that if development of a Licensed Product was terminated by the Company or Genzyme under certain limited circumstances, Genzyme would have the right to terminate the Genzyme Agreement and the Company would be required to refund amounts paid by Genzyme to the Company under the agreement prior to such termination. On February 19, 2013, the Company and Genzyme agreed to amend the Genzyme Agreement to remove this provision.

The Company has determined that the significant deliverables under the Genzyme Agreement include the license, the joint steering committee and any additional TTR-specific RNAi therapeutic compounds that comprise the ALN-TTR program. The Company also determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the license and undelivered joint steering committee and any additional TTR-specific RNAi therapeutic compounds do not have standalone value due to the specialized nature of the services to be provided by the Company. In addition, while Genzyme has the ability to grant sublicenses, it cannot sublicense all or substantially all of its rights under the Genzyme Agreement. The uniqueness of the Company s services and the limited sublicense right are indicators that standalone value is not present in the arrangement. Therefore the deliverables are not separable and, accordingly, the license and undelivered services are being treated as a single unit of accounting. When multiple deliverables are accounted for as a single unit of accounting, the Company bases its revenue recognition pattern on the final deliverable.

The Company is currently unable to reasonably estimate its period of performance under the Genzyme Agreement, as it is unable to estimate the timeline of its deliverables related to the deliverable for any additional TTR-specific RNAi therapeutic compounds. The Company is deferring all revenue under the Genzyme Agreement until it is able to reasonably estimate its period of performance. The Company will continue to reassess whether it can reasonably estimate the period of performance to fulfill its obligations under the Genzyme Agreement. At December 31, 2012, deferred revenue under the Genzyme Agreement was $22.5 million.

Cubist Alliance

In January 2009, the Company entered into the Cubist Agreement to develop and commercialize therapeutic products based on certain of the Company s RNAi technology for the treatment of RSV infection. Licensed products initially included ALN-RSV01, as well as several other second-generation RNAi-based RSV inhibitors. In November 2009, the Company and Cubist entered into an amendment to the Cubist Agreement (the Amendment), which provided that the Company and Cubist would focus their collaboration and joint development efforts on ALN-RSV02, a second-generation compound, intended for use in pediatric patients. In December 2010, the Company and Cubist jointly made a portfolio decision to put the development of ALN-RSV02 on hold. Pursuant to the terms of the Amendment, the Company continued to develop ALN-RSV01 for adult transplant patients at its sole discretion and expense and Cubist had the right to opt into collaborating with the Company on ALN-RSV01, subject to specified conditions.

In February 2013, Cubist notified the Company that it would not exercise its opt-in right for ALN-RSV01. In light of this determination, the Company and Cubist mutually agreed to terminate the license and collaboration agreement effective as of February 6, 2013 (the Effective Date). As of the Effective Date, the parties have no further rights and obligations under the Cubist Agreement, notwithstanding anything to the contrary in the Cubist Agreement.

In consideration for the rights granted to Cubist under the Cubist Agreement, in January 2009, Cubist paid the Company an upfront cash payment of $20.0 million. Under the terms of the Cubist Agreement, the Company and Cubist shared responsibility for developing licensed products in North America and each was responsible for one-half of the related development costs, subject to the terms of the Amendment. The Company s collaboration

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with Cubist for the development of licensed products in North America was governed by a joint steering committee comprised of an equal number of representatives from each party. Cubist had the sole right to commercialize licensed products in North America with costs associated with such activities and any resulting profits or losses to be split equally between the Company and Cubist.

The Company determined that the deliverables under the Cubist Agreement included the licenses, technology transfer related to the ALN-RSV program, the joint steering committee and the development and manufacturing services that the Company was obligated to perform during the development period. The Company also determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the licenses and undelivered services were not separable and, accordingly, the licenses and services were treated as a single unit of accounting. When multiple deliverables are accounted for as a single unit of accounting, the Company bases its revenue recognition pattern on the final deliverable. Under the Cubist Agreement, the last element to be delivered was the development and manufacturing services, which had an expected life of approximately eight years.

The Company was recognizing the upfront payment of $20.0 million on a straight-line basis over approximately eight years because the Company was unable to reasonably estimate the level of effort to fulfill its performance obligations, and therefore, could not utilize a proportional performance model. At December 31, 2012, deferred revenue under the Cubist Agreement was $9.7 million. As a result of the termination of the Cubist Agreement in February 2013 and the end of the Company s performance obligations thereunder, the Company expects to recognize the remaining deferred revenue of $9.7 million during the first quarter of 2013.

4. PROPERTY AND EQUIPMENT, NET

Property and equipment consist of the following at December 31, 2012 and 2011, in thousands:

		December 31,	
	Useful Life	2012	2011
Laboratory equipment	5 years	$ 21,201	$ 19,994
Computer equipment and software	3 years	4,203	4,112
Furniture and fixtures	5 years	1,793	1,784
Leasehold improvements	*	19,862	19,676
Construction in progress		8,209	
		55,268	45,566
Less: accumulated depreciation		(35,469)	(30,923)
		$ 19,799	$ 14,643

* Shorter of asset life or lease term

The Company s construction in progress balance is due to the construction of the Company s manufacturing facility.

During the years ended December 31, 2012, 2011 and 2010, the Company recorded $4.6 million, $5.0 million and $4.8 million, respectively, of depreciation expense related to its property and equipment.

5. 2012 RESTRUCTURING

In January 2012, the Company s Board of Directors approved, and the Company implemented, a strategic corporate restructuring pursuant to which the Company reduced its overall workforce by approximately 33%, to approximately 115 employees.

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During the three months ended March 31, 2012, the Company substantially completed the implementation of the strategic corporate restructuring and recorded $3.9 million of restructuring-related costs in operating expenses, including employee severance, benefits and related costs. The Company paid substantially all of these restructuring costs during 2012. The Company did not incur any additional significant costs associated with this restructuring and does not expect to incur any additional significant costs in the future.

The following table summarizes the components of the Company s restructuring expenses recorded in operating expenses and in current liabilities, in thousands:

	Original Charges and Amounts Accrued	(Reversals) or Adjustments to Charges	Amounts Paid Through December 31, 2012	Amounts Accrued at December 31, 2012
Employee severance, benefits and related costs	$ 3,909	$ (202)	$ 3,666	$ 41

6. COMMITMENTS AND CONTINGENCIES

Purchase Commitments

The Company has future purchase commitments totaling $11.1 million at December 31, 2012, of which $10.3 million is expected to be incurred in 2013 and $0.8 million is expected to be incurred past 2013. These commitments are related to purchase orders, clinical and pre-clinical agreements, and other purchase commitments for goods or services.

Technology License Commitments

The Company has licensed from third parties the rights to use certain technologies in its research processes as well as in any products the Company may develop including these licensed technologies. In accordance with the related license agreements, the Company is required to make certain fixed payments to the licensor or a designee of the licensor over various agreement terms. Many of these agreement terms are consistent with the remaining lives of the underlying intellectual property that the Company has licensed. At December 31, 2012, the Company was committed to make the following fixed, estimated and cancelable payments under existing license agreements, in thousands:

Year Ending December 31,	
2013	$ 14,463
2014	1,563
2015	818
2016	773
2017	793
Thereafter	9,159
Total	$ 27,569

Operating Leases

The Company leases office and laboratory space located at 300 Third Street, Cambridge, Massachusetts (the Premises) for its corporate headquarters and primary research facility under a non-cancelable operating lease agreement (the Third Street Lease) with ARE-MA Region No. 28 LLC (the Landlord). Under the Third Street Lease, the Company leases a total of approximately 129,000 square feet of office and laboratory space at the Premises. The term of the Third Street Lease expires in September 2016. The Company has the option to extend the Third Street Lease for two successive five-year extensions.

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The Company separately agreed, with the Landlord s consent, to sublease a portion of the Premises consisting of 34,014 square feet (the Subleased Premises) beginning on September 1, 2010 pursuant to a sublease agreement between the Company and sanofi-aventis U.S. Inc. (Sanofi) dated August 3, 2010 (the Sublease). In November 2011, the Company and Sanofi entered into a first amendment to the Sublease, pursuant to which the Company agreed, with the Landlord s consent, to extend the Sublease of the Subleased Premises through September 30, 2016 (the Sublease, as so amended by the first amendment, the Amended Sublease). Pursuant to the terms of the Amended Sublease, Sanofi has an option to terminate the Amended Sublease on December 31, 2013, with advance notice and payment of a termination fee to the Company. A one-time upfront payment from Sanofi, together with the future rental payments by Sanofi under the Amended Sublease will partially offset the Company s obligations under the Third Street Lease through 2016 by approximately $10.0 million. In connection with the execution of the Amended Sublease, the Company and the Landlord entered into an amendment to the Third Street Lease (the Third Street Lease, as so amended, the Amended Third Street Lease) to, among other things, change the allocation as between the Company and the Landlord of Excess Income (as defined in the Amended Third Street Lease) received by the Company in connection with any assignment or subletting of any or all of the Premises (including the Subleased Premises).

On February 10, 2012, the Company entered into a non-cancelable real property lease agreement (the BMR Lease) with BMR-Fresh Pond Research Park LLC (BMR) for the Company s manufacturing facility. Under the BMR Lease, the Company leases approximately 15,000 square feet of office and laboratory space located at 665 Concord Avenue, Cambridge, Massachusetts. The term of the BMR Lease expires August 31, 2017. The Company has the option to extend the BMR Lease for two successive five-year extensions.

From 2004 through 2008, the Company received $7.3 million in leasehold improvement incentives from the Landlord in connection with the Third Street Lease. In addition, the Company received $1.8 million in leasehold improvement incentives from BMR during the year ended December 31, 2012. These leasehold improvement incentives are being accounted for as a reduction in rent expense ratably over the Amended Third Street and BMR Lease terms. The balance from these leasehold improvement incentives is included in current portion of deferred rent and deferred rent, net of current portion in the consolidated balance sheets at December 31, 2012 and 2011.

Total rent expense, including operating expenses, under the Company s real property leases was $6.4 million, $6.5 million and $6.4 million for the years ended December 31, 2012, 2011 and 2010, respectively.

Future minimum payments under the Company s non-cancelable leases are approximately as follows, in thousands:

Year Ending December 31,	
2013	6,065
2014	6,303
2015	6,550
2016	5,192
2017	364
Total	$ 24,474

Litigation

University of Utah Litigation

On March 22, 2011, The University of Utah (Utah) filed a civil complaint in the United States District Court for the District of Massachusetts against the Company, Max Planck Gesellschaft Zur Foerderung Der Wissenschaften e.V. and Max Planck Innovation GmbH (together, Max Planck), the Whitehead Institute for

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Biomedical Research (Whitehead), the Massachusetts Institute of Technology (MIT) and the University of Massachusetts (UMass), claiming a professor at Utah is the sole inventor or, in the alternative, a joint inventor, of the Tuschl patents. Utah did not serve the original complaint on the Company or the other defendants. On July 6, 2011, Utah filed an amended complaint alleging substantially the same claims against the Company, Max Planck, Whitehead, MIT and UMass. The amended complaint was served on the Company on July 14, 2011. Utah is seeking changes to the inventorship of the Tuschl patents, unspecified damages and other relief. On October 31, 2011, the Company, Max Planck, Whitehead, MIT and UMass filed a motion to dismiss. Also on October 31, 2011, UMass filed a motion to dismiss on separate grounds, which the Company, Max Planck, Whitehead and MIT have joined. On December 31, 2011, the University filed a second amended complaint dropping UMass as a defendant and adding as defendants several UMass officials. In June 2012, the Court denied both motions to dismiss. The Company, Max Planck, Whitehead, MIT and UMass have filed an appeal of the Court s ruling on the motion to dismiss for lack of jurisdiction and have filed a motion requesting that the Court stay the case pending the outcome of the appeal. In July 2012, the Court stayed discovery in the case pending the outcome of the defendants appeal. Oral arguments in the appeal are scheduled to be heard in early March 2013 in the United States Court of Appeals for the Federal Circuit.

Although the Company believes it has meritorious defenses and intends to vigorously defend itself in this matter, litigation is subject to inherent uncertainty and a court could ultimately rule against the Company. In addition, the defense of litigation and related matters are costly and may divert the attention of the Company s management and other resources that would otherwise be engaged in other activities. The Company has not recorded an estimate of the possible loss associated with this legal proceeding due to the uncertainties related to both the likelihood and the amount of any possible loss or range of loss.

The Company s accounting policy for accrual of legal costs is to recognize such expenses as incurred.

Tekmira Settlement Agreement

On November 12, 2012, the Company, TPC, Protiva Biotherapeutics, Inc., a wholly owned subsidiary of TPC (Protiva, and together with TPC, Tekmira) and AlCana Technologies, Inc. (AlCana) entered into a settlement agreement and general release resolving all ongoing litigation, as well as a patent interference proceeding between the Company and Protiva. The terms of the settlement agreement include mutual releases and dismissal with prejudice of all claims and counterclaims in the following litigation between the parties: (i) *Tekmira Pharmaceuticals Corp., et al. v. Alnylam Pharmaceuticals, Inc., et al.*, Civ. A. No. 11-1010-BLS2, pending in the Business Litigation Section of the Massachusetts Superior Court for Suffolk County; (ii) *Tekmira Pharmaceuticals Corp. v. Michael Hope, et al*., No. S117660, pending in the Supreme Court of British Columbia, Canada; (iii) *Alnylam Pharmaceuticals, Inc., et al. v. Tekmira Pharmaceuticals Corp.*, Civ. A. No. 1:12-CV-10087, pending in the United States District Court for the District of Massachusetts; and (iv) *Alnylam Pharmaceuticals, Inc., et al. v. Tekmira Pharmaceuticals Corp*., Court File No. T-1783-12, pending in the Federal Court of Canada. In addition, as part of the settlement agreement, the parties agreed to a covenant not to sue one another in the future on matters released under the settlement agreement, as well as substantial liquidated damages to be paid by any party that breaches such covenant. The parties have also agreed to resolve any future disputes that may arise over the next three years through binding arbitration.

Pursuant to the settlement agreement, the Company and Tekmira also agreed to resolve the interference proceeding declared by the United States Board of Patent Appeals and Interferences between the Company and Protiva, captioned *Protiva Biotherapeutics, Inc. v. Alnylam Pharmaceuticals, Inc.*, Patent Interference No. 105792.

Contemporaneously with the execution of the settlement agreement, the Company and Tekmira restructured their contractual relationship and entered into a cross-license agreement that supersedes the prior license and manufacturing agreements among the Company, TPC and Protiva. In connection with this restructuring, the Company incurred a $65.0 million charge to operating expenses for the year ended December 31, 2012. Specifically, the Company made a one-time payment of $30.0 million to Tekmira for the termination of, and its release from, all of its obligations under

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the manufacturing agreement with TPC, including without limitation the obligations to obtain materials and/or services from TPC. Further, the Company elected to buy-down certain future potential milestone and royalty payments due to Tekmira for certain of the Company s RNAi therapeutics, formulated using LNP technology. Specifically, pursuant to the cross-license agreement, the Company made a one-time payment of $35.0 million to Tekmira, which amount constituted payment for the termination of the 2008 license agreements with TPC and Protiva and the parties rights and obligations thereunder, as well as the buy-down of certain milestone payments and the significant reduction of royalty rates for ALN-VSP, ALN-PCS and ALN-TTR. In addition, under the 2012 cross-license agreement, the Company will be obligated to pay TPC an aggregate of $10.0 million in contingent milestone payments related to advancement of ALN-VSP and ALN-TTR, which now represent the only potential milestones due to Tekmira for ALN-VSP, ALN-PCS and ALN-TTR lipid nanoparticle (LNP)-based RNAi therapeutics. Specifically, the Company will be obligated to pay TPC a $5.0 million milestone payment upon each of (i) the initiation of a Phase III clinical trial of an LNP-based ALN-TTR therapeutic, and (ii) the manufacture of ALN-VSP clinical trial material for use in China. The Company will expense these potential milestones when incurred and record them as research and development expense. A description of the Company s cross-license agreement with Tekmira is included in Part I, Item 1, Delivery-Related Licenses and Collaborations Tekmira, of this annual report on Form 10-K.

Indemnifications

Licensor indemnification In connection with the Company s license agreements with Max Planck relating to the Tuschl I and Tuschl II patent applications, the Company is required to indemnify Max Planck for certain damages arising in connection with the intellectual property rights licensed under the agreements. Under the Max Planck indemnification agreement, the Company is responsible for paying the costs of any litigation relating to the license agreements or the underlying intellectual property rights, including the costs associated with certain litigation regarding the Tuschl patents, which was settled during 2011. In connection with the Company s research agreement with AlCana, the Company agreed to indemnify AlCana for certain legal costs, subject to certain exceptions and limitations, associated with the Tekmira litigation described above. These indemnification costs were charged to general and administrative expense. The Company has also agreed to indemnify Genzyme for legal costs and other losses or amounts required to be paid by Genzyme, if any, in connection with or related to certain of the Company s ongoing litigation matters.

The Company is also a party to a number of agreements entered into in the ordinary course of business, which contain typical provisions that obligate the Company to indemnify the other parties to such agreements upon the occurrence of certain events. Such indemnification obligations are usually in effect from the date of execution of the applicable agreement for a period equal to the applicable statute of limitations.

The maximum potential future liability of the Company under any such indemnification provisions is uncertain. However, to date, other than certain costs associated with the certain previously settled litigation related to the Tuschl patents, and the Tekmira litigation described in Part I, Item 3, Legal Proceedings, of this annual report on Form 10-K, the Company has not incurred material costs to defend lawsuits or settle claims related to these indemnification provisions. The Company has determined that the estimated aggregate fair value of its potential liabilities under all such indemnification provisions is minimal and has not recorded any liability related to such indemnification provisions at December 31, 2012 or 2011.

7. STOCKHOLDERS EQUITY

Preferred Stock

The Company has authorized up to 5,000,000 shares of preferred stock, $0.01 par value per share, for issuance. The preferred stock will have such rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, as shall be determined by the Company s Board of Directors upon its issuance. At December 31, 2012 and 2011, there were no shares of preferred stock outstanding.

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ALNYLAM PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

Stockholder Rights Agreement

On July 13, 2005, the Board of Directors of the Company declared a dividend of one right (collectively, the Rights) to buy one one-thousandth of a share of newly designated Series A Junior Participating Preferred Stock (Series A Junior Preferred Stock) for each outstanding share of the Company s common stock to stockholders of record at the close of business on July 26, 2005. Initially, the Rights are not exercisable and will be attached to all certificates representing outstanding shares of common stock. The Rights will expire at the close of business on July 13, 2015 unless earlier redeemed or exchanged. Until a Right is exercised, the holder thereof will have no rights as a stockholder of the Company, including the right to vote or to receive dividends. Subject to the terms and conditions of the rights agreement (the Rights Agreement), the Rights will become exercisable upon the earlier of (1) ten business days following the later of (a) the first date of a public announcement that a person or group (an Acquiring Person) acquires, or obtained the right to acquire, beneficial ownership of 20% or more of the outstanding shares of common stock of the Company or (b) the first date on which an executive officer of the Company has actual knowledge that an Acquiring Person has become such or (2) ten business days following the commencement of a tender offer or exchange offer that would result in a person or group beneficially owning more than 20% of the outstanding shares of common stock of the Company. Each Right entitles the holder to purchase one one-thousandth of a share of Series A Junior Preferred Stock at an initial purchase price of $80.00 in cash, subject to adjustment. In the event that any person or group becomes an Acquiring Person, unless the event causing the 20% threshold to be crossed is a Permitted Offer (as defined in the Rights Agreement), each Right not owned by the Acquiring Person will entitle its holder to receive, upon exercise, that number of shares of common stock of the Company (or in certain circumstances, cash, property or other securities of the Company) which equals the exercise price of the Right divided by 50% of the current market price (as defined in the Rights Agreement) per share of such common stock at the date of the occurrence of the event. In the event that, at any time after any person or group becomes an Acquiring Person, (i) the Company is consolidated with, or merged with and into, another entity and the Company is not the surviving entity of such consolidation or merger (other than a consolidation or merger which follows a Permitted Offer) or if the Company is the surviving entity, but shares of its outstanding common stock are changed or exchanged for stock or securities (of any other person) or cash or any other property, or (ii) more than 50% of the Company s assets or earning power is sold or transferred, each holder of a Right (except Rights which previously have been voided as set forth in the Rights Agreement) shall thereafter have the right to receive, upon exercise, that number of shares of common stock of the acquiring company which equals the exercise price of the Right divided by 50% of the current market price of such common stock at the date of the occurrence of the event.

Public Offerings

In February 2012, the Company sold an aggregate of 8,625,000 shares of its common stock through an underwritten public offering at a price to the public of $10.75 per share. As a result of this offering, the Company received aggregate net proceeds of approximately $86.8 million, after deducting underwriting discounts and commissions and other estimated offering expenses of approximately $5.9 million.

In January 2013, the Company sold an aggregate of 9,200,000 shares of its common stock through an underwritten public offering at a price to the public of $20.13 per share. As a result of this offering, the Company 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.

8. STOCK INCENTIVE PLANS

Stock Plans

In June 2009, the Company s stockholders approved an amendment and restatement of the Company s 2004 Stock Incentive Plan (the Amended and Restated 2004 Plan), which replaced the Company s 2004 Stock

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ALNYLAM PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

Incentive Plan, as amended (the 2004 Plan). At December 31, 2010, the Amended and Restated 2004 Plan provided for the granting of stock options to purchase up to 12,366,485 shares of common stock. Prior to the adoption of the Amended and Restated 2004 Plan, the Company was authorized to grant both stock options and restricted stock awards under the 2004 Plan. As of the effective date of the Amended and Restated 2004 Plan, the Company may only grant stock options under the Amended and Restated 2004 Plan, provided that the terms and conditions of any restricted stock awards outstanding under the 2004 Plan will continue to be governed by the Amended and Restated 2004 Plan.

In June 2009, the Company s stockholders also approved the Company s 2009 Stock Incentive Plan (the 2009 Plan). The 2009 Plan provides for the granting of stock options, restricted stock awards and units, stock appreciation rights and other stock-based awards to purchase up to 2,200,000 shares of common stock. The 2009 Plan has a fungible share pool. Any award that is not a full value award shall be counted against the authorized share limits specified in the 2009 Plan as one share for each share of common stock subject to award, and all full value awards, defined in the 2009 Plan as restricted stock awards or other stock-based awards, shall be counted as one and a half shares for each one share of common stock subject to such full value award. In addition, the 2009 Plan includes a non-employee director stock option program under which each eligible non-employee director is entitled to (1) a grant of an option to purchase 30,000 shares of common stock upon his or her initial appointment to the Board of Directors, or such other amount as the Board of Directors deems appropriate, and (2) a subsequent annual grant of an option to purchase 15,000 shares of common stock based on continued service, made on the date of each annual meeting of stockholders, provided the non-employee director has served as a director for at least six months and is serving as a director immediately prior to and following such annual meeting. The chairman of the audit committee will receive an additional annual grant of an option to purchase 10,000 shares of common stock based on continued service and the chairman of the science and technology committee will receive an additional annual grant of an option to purchase 15,000 shares of common stock based on continued service. Stock options granted by the Company to non-employee directors upon their appointment to the Board of Directors vest as to one-third of such shares on each of the first, second and third anniversaries of the date of grant, and those granted at each year s annual meeting at which they serve as a director vest in full on the first anniversary of the date of grant.

At December 31, 2012, an aggregate of 815,916 shares of common stock were reserved for issuance under the Company s stock plans, including 541,806 shares of common stock available for equity awards and 274,110 shares available for future grant under the Company s 2004 Employee Stock Purchase Plan (the 2004 Purchase Plan). Each option shall expire within ten years of issuance. Stock options granted by the Company to employees generally vest as to 25% of the shares on the first anniversary of the grant date and 6.25% of the shares at the end of each successive three-month period until fully vested.

Stock-Based Compensation

The Company recorded $9.0 million, $14.8 million and $18.7 million of stock-based compensation expense for the years ended December 31, 2012, 2011 and 2010, respectively, related to employee stock options and the 2004 Purchase Plan.

The Company accounts for non-employee grants as an expense over the vesting period of the underlying stock options. At the end of each financial reporting period prior to vesting, the Company re-measures the value of these stock options (as calculated using the Black-Scholes option-pricing model) using the then-current fair value of the Company s common stock. The Company recognized $1.0 million, $0.4 million and $0.3 million of non-employee stock-based compensation expense for the years ended December 31, 2012, 2011 and 2010, respectively.

In connection with the establishment of Regulus, the Company granted stock options to the members of Regulus scientific advisory board and board of directors and certain Regulus employees. In addition to the total stock-based compensation expense stated above, the Company recorded $0.3 million, $0.4 million and

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

$0.3 million of stock-based compensation expense related to these stock option grants in equity in loss of joint venture (Regulus Therapeutics Inc.) in its consolidated statements of comprehensive loss for the years ended December 31, 2012, 2011 and 2010, respectively.

In October 2010, the Company granted 113,370 shares of restricted stock of the Company to certain employees. These restricted stock awards were valued at $1.4 million on the grant date. These restricted stock awards vest ratably over an approximate three-year period. In May 2011, the Company granted an aggregate of 229,806 shares of performance-based restricted stock awards to its employees, excluding the Company s leadership team. These restricted stock awards were valued at $2.3 million on the grant date and have a term of five years. The vesting of these awards is predicated on the Company s achievement of certain clinical development goals. In January 2012, as part of its post-restructuring retention program, the Company granted an aggregate of 513,082 shares of restricted stock to its retained employees, excluding the Company s chief executive officer and president and chief operating officer. These restricted stock awards were valued at $5.3 million on the grant date and vest in full on the second anniversary of the grant date. The Company recognized an aggregate of $2.4 million, $1.5 million and $0.1 million of stock-based compensation expense related to all of these restricted stock awards for the years ended December 31, 2012, 2011 and 2010, respectively.

Total compensation cost for all stock-based awards for the years ended December 31, 2012, 2011 and 2010 was $12.7 million, $17.1 million and $19.4 million, respectively. No amounts relating to the stock-based compensation have been capitalized.

Valuation Assumptions for Stock Options

The fair value of stock options at date of grant, based on the following assumptions, was estimated using the Black-Scholes option-pricing model. The Company s expected stock-price volatility assumption for 2012 and 2011 is based on the historical volatility of the Company s publicly traded stock. The expected life assumption for 2012 and 2011 is based on the Company s historical data. The Company s expected stock-price volatility assumption for 2010 is based on a combination of implied volatilities of its publicly traded stock option prices as well as the historical volatility of the Company s publicly traded stock. The expected life assumption for 2010 is based on the equal weighting of the Company s historical data and the historical data of the Company s pharmaceutical and biotechnology peers. The dividend yield assumption is based on the fact that the Company has never paid cash dividends and has no present intention to pay cash dividends. The risk-free interest rate used for each grant is equal to the zero coupon rate for instruments with a similar expected life. The Company currently expects, based on an analysis of its historical forfeitures, excluding the impact of its corporate restructurings, that approximately 67% of its stock options will actually vest, and therefore has applied an annual forfeiture rate of 9.5% to all unvested employee stock options at December 31, 2012. The Company will record additional expense if the actual forfeitures are lower than estimated and will record a recovery of prior expense if the actual forfeitures are higher than estimated.

	2012	2011	2010
Risk-free interest rate	0.8-1.0%	1.2-2.6%	1.6-2.9%
Expected dividend yield			
Expected option life	5.6-5.9 years	5.8-5.9 years	5.9-6.1 years
Expected volatility	57%	55-57%	53-55%

At December 31, 2012, there was $14.7 million of unearned compensation expense remaining related to unvested employee stock options to be recognized as expense over a weighted-average period of approximately 2.6 years.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

Stock Option Activity

The following table summarizes the activity of the Company s stock option plans:

	Number of Options	Weighted Average Exercise Price
Outstanding, December 31, 2011	9,778,539	$ 15.53
Granted	1,233,086	$ 17.02
Exercised	(661,909)	$ 9.67
Cancelled	(1,418,133)	$ 18.47
Outstanding, December 31, 2012	8,931,583	$ 15.71
Exercisable at December 31, 2010	4,983,088	$ 18.60
Exercisable at December 31, 2011	6,033,858	$ 18.13
Exercisable at December 31, 2012	5,885,363	$ 17.20

The weighted average remaining contractual life for stock options outstanding and stock options exercisable at December 31, 2012 was 6.4 years and 5.2 years, respectively.

The aggregate intrinsic value of stock options outstanding at December 31, 2012 was $41.8 million, of which $24.9 million related to exercisable stock options. The intrinsic value of stock options exercised was $4.8 million, $40,000 and $1.8 million for the years ended December 31, 2012, 2011 and 2010, respectively. The weighted average fair value of stock options granted was $8.68, $7.68 and $5.98 per share for the years ended December 31, 2012, 2011 and 2010, respectively.

The aggregate intrinsic value of stock options expected to vest at December 31, 2012 was $14.7 million. The weighted average fair value of stock options expected to vest was $5.56. The weighted average remaining contractual life for stock options expected to vest was 8.8 years and the weighted average exercise price for these stock options was $12.82 per share at December 31, 2012.

Restricted Stock Awards

The following table summarizes the activity of the Company s restricted stock awards:

	Number of Awards	Weighted Average Grant Date Fair Value
Unvested at December 31, 2011	312,482	$ 10.68
Granted	513,082	$ 10.49
Vested	(141,740)	$ 10.42
Forfeited	(80,064)	$ 5.94
Unvested at December 31, 2012	603,760	$ 9.37

The total fair value of restricted stock awards that vested during the years ended December 31, 2012, 2011 and 2010 was $1.5 million, $0.5 million and zero, respectively. At December 31, 2012, there remained $2.8 million of unearned compensation expense related to unvested restricted stock awards to be recognized as expense over a weighted-average period of approximately one year.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

Employee Stock Purchase Plan

In 2004, the Company adopted the 2004 Purchase Plan with 315,789 shares authorized for issuance. In June 2010, the Company s stockholders approved an amendment to the 2004 Purchase Plan, which increased the shares authorized for issuance from 315,789 shares to 715,789 shares. Under the 2004 Purchase Plan, each offering period is six months, at the end of which employees may purchase shares of common stock through payroll deductions made over the term of the offering. The per-share purchase price at the end of each offering period is equal to the lesser of 85% of the closing price of the common stock at the beginning or end of the offering period. The Company issued 73,590, 79,038 and 72,674 shares during the years ended December 31, 2012, 2011 and 2010, respectively, and at December 31, 2012, 274,110 shares were available for issuance under the 2004 Purchase Plan.

The weighted average fair value of stock purchase rights granted as part of the 2004 Purchase Plan was $2.82, $3.46 and $5.12 per share for the years ended December 31, 2012, 2011 and 2010, respectively. The fair value was estimated using the Black-Scholes option-pricing model. The Company used a weighted-average stock-price volatility of 57%, expected option life assumption of six months and a risk-free interest rate of 0.1%. The Company recorded $0.2 million, $0.3 million and $0.3 million of stock-based compensation expense for the years ended December 31, 2012, 2011 and 2010, respectively, related to the 2004 Purchase Plan.

9. INCOME TAXES

Deferred income taxes reflect the tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting and income tax purposes. The Company establishes a valuation allowance when uncertainty exists as to whether all or a portion of the net deferred tax assets will be realized. Components of the net deferred tax (liability) asset at December 31, 2012 and 2011 are as follows, in thousands:

	2012	2011
Deferred tax assets:		
Net operating loss carryforwards	$ 102,819	$ 46,230
Research and development credits	17,443	12,405
AMT credits	788	788
Foreign tax credits	3,196	3,196
Capitalized research and development and start-up costs	16,102	3,974
Deferred revenue	30,776	53,485
Deferred compensation	24,804	21,855
Intangible assets	2,540	4,302
Partnership interest	7,118	5,338
Other	4,173	2,850
Total deferred tax assets	209,759	154,423
Deferred tax liabilities:		
Intangible assets	(38)	(91)
Unrealized gain on available-for-sale securities	(10,572)	
Gain on issuance of stock by Regulus	(6,466)	
Deferred tax asset valuation allowance	(192,721)	(154,423)
Net deferred tax liability	$ (38)	$ (91)

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

The (benefit from) provision for income taxes for the years ended December 31, 2012, 2011 and 2010 are as follows, in thousands:

	2012	2011	2010
U.S.:			
Current	$ 52	$ 52	$ (9,928)
Deferred	(10,572)		10,494
Total U.S.	(10,520)	52	566
Foreign:			
Current			
Deferred	(52)	(52)	(52)
Total Foreign	(52)	(52)	(52)
Provision for income taxes	$ (10,572)	$	$ 514

The Company s effective income tax rate differs from the statutory federal income tax rate as follows for the years ended December 31, 2012, 2011 and 2010:

	2012	2011	2010
At U.S. federal statutory rate	35.0%	35.0%	35.0%
State taxes, net of federal effect	4.9	4.6	4.2
Stock compensation	(0.7)	(3.3)	(5.0)
Other permanent items	(1.6)	(0.2)	1.3
Valuation allowance	(28.5)	(36.1)	(36.7)
Effective income tax rate	9.1%	%	(1.2)%

The Company has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets. The Company has concluded, in accordance with the applicable accounting standards, that it is more likely than not that the Company may not realize the benefit of all of its deferred tax assets. Accordingly, the Company has recorded a valuation allowance against the deferred tax assets that management believes will not be realized. The Company reevaluates the positive and negative evidence on a quarterly basis. The valuation allowance increased by $38.3 million, $23.0 million and $15.2 million for the years ended December 31, 2012, 2011 and 2010 respectively, due primarily to additional operating losses. Increases to the valuation allowance were partially offset by decreases related to the recognition of deferred revenue.

For the year ended December 31, 2012, the Company recorded a tax benefit of $10.6 million. For the years ended December 31, 2011 and 2010, the Company recorded a provision for income taxes of zero and $0.5 million, respectively. For the year ended December 31, 2012, the Company recorded unrealized gains on its investments in available-for-sale securities in other comprehensive income. The benefit of $10.6 million for the year ended December 31, 2012 is due to the recognition of corresponding income tax expense associated with the increase in the value of the Company s investment in Regulus that the Company carried at fair market value during the same period. The corresponding income tax expense has been recorded in other comprehensive income. Intraperiod tax allocation rules require the Company to allocate its provision for income taxes between continuing operations and other categories of earnings, such as other comprehensive income. In periods in which the Company has a year-to-date pre-tax loss from continuing operations and pre-tax income in other categories of earnings, such as other comprehensive income,

the Company must allocate the tax provision to the other categories of earnings. The Company then records a related tax benefit in continuing operations.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

The deferred tax assets above exclude $10.1 million of net operating losses and $0.5 million of federal and state research and development credits related to tax deductions from the exercise of stock options subsequent to the adoption of the 2006 accounting standard on stock-based compensation. This amount represents an excess tax benefit and has not been included in the gross deferred tax assets.

At December 31, 2012, the Company had federal and state net operating loss carryforwards of $272.7 million and $337.8 million, respectively, to reduce future taxable income that will expire at various dates through 2032. At December 31, 2012, federal and state research and development credit carryforwards were $15.3 million and $5.6 million, respectively, available to reduce future tax liabilities that expire at various dates through 2032. At December 31, 2012, foreign tax credit carryforwards were $3.2 million available to reduce future tax liabilities that expire in 2017. At December 31, 2012, alternative minimum tax credits of $0.8 million are available to reduce future regular tax liabilities to the extent such regular tax less other non-refundable credits exceeds the tentative minimum tax. Ownership changes, as defined in the Internal Revenue Code, including those resulting from the issuance of common stock in connection with the Company s public offerings, may limit the amount of net operating loss that can be utilized to offset future taxable income or tax liability. The Company has determined that based on the value of the Company, in the event there was an annual limitation under Section 382, all net operating loss and tax credit carryforwards would still be available to offset taxable income.

At December 31, 2012, the Company had no unrecognized tax benefits that, if recognized, would favorably impact the Company s effective income tax rate in future periods. A reconciliation of the beginning and ending amount of unrecognized tax benefits is as follows, in thousands:

Balance at December 31, 2010	$ 428
Subtractions for tax positions related to the prior years	(300)
Balance at December 31, 2011	128
Subtractions for tax positions related to the prior years	(128)
Balance at December 31, 2012	$

The tax years 2010 through 2012 remain open to examination by major taxing jurisdictions to which the Company is subject, which are primarily in the United States, as carryforward attributes generated in years past may still be adjusted upon examination by the Internal Revenue Service or state tax authorities if they have or will be used in a future period. In July 2011, the Internal Revenue Service completed its audits of the Company s 2008 and 2009 tax years. The Company did not record any tax expense related to these audits. The Company has not recorded any interest and penalties on any unrecognized tax benefits since its inception.

10. REGULUS

In September 2007, the Company and Isis established Regulus, a company focused on the discovery, development and commercialization of microRNA therapeutics, a potential new class of drugs to treat the pathways of human disease. Regulus, which initially was established as a limited liability company, converted to a C corporation in January 2009 and changed its name to Regulus Therapeutics Inc. Regulus operates as an independent company with a separate board of directors, scientific advisory board and management team.

In consideration for the Company s and Isis initial interests in Regulus, each party granted Regulus exclusive licenses to its intellectual property for certain microRNA therapeutic applications as well as certain patents in the microRNA field. In addition, the Company made an initial cash contribution to Regulus of $10.0 million, resulting in the Company and Isis making approximately equal aggregate initial capital contributions to Regulus. In March 2009, the Company and Isis each purchased $10.0 million of Series A preferred stock of Regulus. In October 2010, in connection with its strategic alliance with Regulus formed in

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ALNYLAM PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

June 2010, Sanofi made a $10.0 million equity investment in Regulus. As a result of the $10.0 million equity investment made by Sanofi, the Company recognized a gain of $4.4 million. This amount was recorded as other income in the Company s consolidated statements of comprehensive loss for the year ended December 31, 2010.

From the formation of Regulus in September 2007 to October 2012, the Company accounted for its interest in Regulus using the equity method of accounting. The Company reviewed the consolidation guidance that defines a VIE and concluded that Regulus qualified as a VIE during such time period. The Company did not consolidate Regulus as the Company lacked the power to direct the activities that could significantly impact the economic success of this entity.

Summary results of Regulus statements of comprehensive loss for the nine months ended September 30, 2012 and the years ended December 31, 2011 and 2010 and the balance sheet at December 31, 2011 are presented in the tables below, in thousands:

	Nine months ended September 30, 2012	Year ended December 31, 2011	2010
Statements of Comprehensive Loss Data:			
Net revenues	$ 9,462	$ 13,789	$ 8,601
Operating expenses	17,733	20,926	24,099
Loss from operations	(8,271)	(7,137)	(15,498)
Other (expense) income	(2,289)	(259)	(91)
Income tax benefit (expense)	28	(206)	30
Net loss	$ (10,532)	$ (7,602)	$ (15,559)

	December 31, 2011
Balance Sheet Data:	
Cash, cash equivalents and marketable securities	$ 38,144
Current assets	38,666
Total assets	42,881
Current liabilities	12,850
Non-current liabilities	28,834
Notes payable	11,259
Net assets	1,197

Under the equity method of accounting, the Company was required to recognize losses up to the amount of Regulus debt, which was guaranteed by the Company. This resulted in a negative carrying amount. In October 2012, Regulus completed an initial public offering, resulting in the Company s ownership percentage decreasing from approximately 44% to 17% of Regulus outstanding common stock. Upon the completion of the Regulus initial public offering, the Company s debt guarantee was terminated.

Based upon the Company s new ownership percentage of 17%, as well as a review of qualitative factors, the Company does not believe that it has the ability to exercise significant influence over the operating decisions and financial policies of Regulus and has therefore discontinued the equity method of accounting for Regulus at September 30, 2012. The Company determined that the period between September 30, 2012 and the date on

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ALNYLAM PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

which Regulus closed its initial public offering was immaterial for additional equity method accounting. Accordingly, beginning October 10, 2012, the Company has accounted for its investment in Regulus as an available-for-sale marketable security due to its readily determinable fair value. At December 31, 2012, the fair value of the Regulus equity securities was $38.7 million. As a result of the issuance of additional common stock by Regulus, the Company recognized a gain of $16.1 million. This amount was recorded as other income in the Company s consolidated statements of comprehensive loss for the year ended December 31, 2012. The Company s carrying amount in Regulus increased to $12.4 million following the initial public offering, which became the initial basis of its investment in Regulus under the accounting standard for marketable securities. In addition, the Company recorded $15.7 million as an unrealized gain in other comprehensive income, net of an intraperiod tax benefit of $10.6 million.

The Company has historically classified the equity method investment amount in the financial statement caption Investment in joint venture (Regulus Therapeutics Inc.) on the Company s consolidated balance sheets. For the purposes of the 2012 balance sheet, this amount is zero and the Company has reclassified the 2011 balance of $0.6 million to the financial statement caption Other assets.

11. QUARTERLY FINANCIAL DATA (UNAUDITED)

The following information has been derived from unaudited consolidated financial statements that, in the opinion of management, include all recurring adjustments necessary for a fair statement of such information.

	Three Months Ended			
	March 31, 2012	June 30, 2012	September 30, 2012	December 31, 2012
	(In thousands, except per share data)			
Revenues	$ 20,587	$ 20,884	$ 16,759	$ 8,495
Operating expenses	31,480	32,951	34,906	96,844
Net loss	(11,368)	(12,956)	(19,502)	(62,188)
Net loss per common share basic and diluted	$ (0.25)	$ (0.25)	$ (0.38)	$ (1.20)
Weighted average common shares basic and diluted	46,210	51,280	51,542	51,821

The increase in operating expenses for the three months ended December 31, 2012 resulted from a $65.0 million charge to operating expenses in connection with the restructuring of the Company s license agreement with Tekmira in November 2012. This increase in operating expenses was offset by a gain in other income of $16.1 million and a tax benefit of $10.6 million recorded as part of the Company s accounting for the Regulus initial public offering.

	Three Months Ended			
	March 31, 2011	June 30, 2011	September 30, 2011	December 31, 2011
	(In thousands, except per share data)			
Revenues	$ 20,897	$ 20,614	$ 20,791	$ 20,455
Operating expenses	36,573	33,732	33,229	34,041
Net loss	(16,285)	(13,824)	(13,237)	(14,303)
Net loss per common share basic and diluted	$ (0.38)	$ (0.33)	$ (0.31)	$ (0.33)
Weighted average common shares basic and diluted	42,345	42,379	42,654	42,715

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ALNYLAM PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

12. SUBSEQUENT EVENT

On February 4, 2013, the Company and MedCo entered into the MedCo Agreement pursuant to which the Company 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 (collectively, Licensed Products). ALN-PCS02 is an intravenously administered RNAi therapeutic for which the Company 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 the Company an upfront cash payment of $25.0 million. In addition, MedCo is required to make payments to the Company upon the achievement of specified clinical development, regulatory approval and commercialization milestones totaling up to $180.0 million, and to pay the Company 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. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, the Company may not receive any milestone or royalty payments from MedCo.

Under the MedCo Agreement, the parties will collaborate in the further development of Licensed Products. The Company will retain responsibility for the development of Licensed Products until Phase I Completion (as defined in the MedCo Agreement) at its cost, up to an agreed upon initial development cost cap. MedCo will assume all other responsibility for the development and commercialization of Licensed Products, at its sole cost. Initially the collaboration will include the development of both ALN-PCS02 and ALN-PSCsc in parallel, provided that the parties intend to select one of ALN-PCS02 or ALN-PSCsc for ongoing development at a specified development stage, in accordance with the terms of the MedCo Agreement. The collaboration between MedCo and the Company will be governed by a joint steering committee that will be comprised of an equal number of representatives from each party.

The Company will be solely responsible for obtaining supply of finished product reasonably required for the conduct of its obligations under the initial development plan through Phase I Completion, and supplying MedCo with finished product reasonably required for the first Phase II study of a Licensed Product conducted by MedCo, at the Company s expense, provided such costs do not exceed the development costs cap, subject to certain exceptions. After such time, MedCo will have the sole right and responsibility to manufacture and supply Licensed Product for development and commercialization under the MedCo development plan, subject to the terms of the MedCo Agreement. The Company and MedCo intend to enter into a supply and technical transfer agreement to provide for supply of Licensed Products to MedCo within a specified time following the effective date of the MedCo Agreement.

Unless terminated earlier in accordance with the terms of the agreement, the MedCo Agreement expires on a Licensed Product-by-Licensed Product and country-by-country basis upon expiration of the last royalty term for any Licensed Product in any country, where a royalty term is defined as the latest to occur of (1) the expiration of the last valid claim of patent rights covering a Licensed Product, (2) the expiration of the Regulatory Exclusivity (as defined in the MedCo Agreement), and (3) the twelfth anniversary of the first commercial sale of the Licensed Product in such country. The Company estimates that its fundamental RNAi patents covering Licensed Products under the MedCo Agreement will expire both in and outside of the United States generally between 2015 and 2023. The Company also estimates that its ALN-PCS product-specific patents covering Licensed Products under the MedCo Agreement in the United States and elsewhere will expire at the end of 2033. These patent rights are subject to potential patent term extensions and/or supplemental protection certificates extending such terms in countries where such extensions may become available. In addition, more patent filings relating to the collaboration may be made in the future.

Either party may terminate the MedCo Agreement in the event the other party fails to cure a material breach or upon patent-related challenges by the other party. The Company may terminate the agreement in the event that

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ALNYLAM PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

a lead Licensed Product has not been designated by the joint steering committee within a designated time period. In addition, MedCo has the right to terminate the agreement without cause at any time upon four months prior written notice.

During the term of the MedCo Agreement, neither party will, alone or with an affiliate or third party, research, develop or commercialize, or grant a license to any third party to research, develop or commercialize, in any country, any product directed to the PCSK9 gene, other than a Licensed Product, without the prior written agreement of the other party, subject to the terms of the MedCo Agreement.

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ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A. CONTROLS AND PROCEDURES

Our management, with the participation of our chief executive officer and vice president of finance and treasurer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2012. The term disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended (the Exchange Act), means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC s rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company s management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2012, the Company s chief executive officer and vice president of finance and treasurer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Management s report on our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) and the independent registered public accounting firm s report on the effectiveness of our internal control over financial reporting are included in Item 8 of this annual report on Form 10-K and are incorporated herein by reference.

No change in our internal control over financial reporting occurred during the fiscal quarter ended December 31, 2012 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

None.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by this item is incorporated herein by reference to the information contained under the sections captioned Proposal One Election of Class III Directors, Section 16(a) Beneficial Ownership Reporting Compliance and Corporate Governance of the Proxy Statement. The information required by this item relating to executive officers is included in Part I, Item 1, Business-Executive Officers of the Registrant, of this annual report on Form 10-K.

ITEM 11. EXECUTIVE COMPENSATION

The information required by this item is incorporated herein by reference to the information contained under the sections captioned Information about Executive Officer and Director Compensation, Compensation Committee Interlocks and Insider Participation, Employment Arrangements and Compensation Committee Report of the Proxy Statement.

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ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by this item is incorporated herein by reference to the information contained under the sections captioned Security Ownership of Certain Beneficial Owners and Management, Information about Executive Officer and Director Compensation and Securities Authorized for Issuance Under Equity Compensation Plans of the Proxy Statement.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required by this item is incorporated herein by reference to the information contained under the sections captioned Corporate Governance, Employment Arrangements and Certain Relationships and Related Transactions of the Proxy Statement.

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

The information required by this item is incorporated herein by reference to the information contained under the sections captioned Corporate Governance, Principal Accountant Fees and Services and Pre-Approval Policies and Procedures of the Proxy Statement.

PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

(a) (1) Financial Statements

The following consolidated financial statements are filed as part of this report under Item 8 Financial Statements and Supplementary Data :

(a) (2) List of Schedules

All schedules to the consolidated financial statements are omitted as the required information is either inapplicable or presented in the consolidated financial statements.

(a) (3) List of Exhibits

The exhibits which are filed with this report or which are incorporated herein by reference are set forth in the Exhibit Index hereto.

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SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this Report to be signed on its behalf by the undersigned, thereunto duly authorized, on February 19, 2013.

ALNYLAM PHARMACEUTICALS, INC.

By: /s/ John M. Maraganore, Ph.D.
John M. Maraganore, Ph.D.
Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, the Report has been signed below by the following persons on behalf of the Registrant and in the capacities indicated as of February 19, 2013.

Name	Title
/s/ John M. Maraganore, Ph.D.	Director and Chief Executive Officer
John M. Maraganore, Ph.D.	(Principal Executive Officer)
/s/ Michael P. Mason	Vice President of Finance and Treasurer
Michael P. Mason	(Principal Financial and Accounting Officer)
/s/ Dennis A. Ausiello	Director
Dennis A. Ausiello	
/s/ John K. Clarke	Director
John K. Clarke	
/s/ Victor J. Dzau, M.D.	Director
Victor J. Dzau, M.D.	
/s/ Marsha H. Fanucci	Director
Marsha H. Fanucci	
/s/ Steven M. Paul, M.D.	Director
Steven M. Paul, M.D.	
/s/ Paul R. Schimmel, Ph.D.	Director
Paul R. Schimmel, Ph.D.	
/s/ Phillip A. Sharp, Ph.D.	Director

Phillip A. Sharp, Ph.D.

/s/ Kevin P. Starr Director

Kevin P. Starr

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EXHIBIT INDEX

Exhibit No.	Exhibit
3.1	Restated Certificate of Incorporation of the Registrant (filed as Exhibit 3.1 to the Registrant s Quarterly Report on Form 10-Q filed on August 11, 2005 (File No. 000-50743) for the quarterly period ended June 30, 2005 and incorporated herein by reference)
3.2	Amended and Restated Bylaws of the Registrant (filed as Exhibit 3.4 to the Registrant s Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
4.1	Specimen certificate evidencing shares of common stock (filed as Exhibit 4.1 to the Registrant s Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
4.2	Rights Agreement dated as of July 13, 2005 between the Registrant and EquiServe Trust Company, N.A., as Rights Agent, which includes as Exhibit A the Form of Certificate of Designations of Series A Junior Participating Preferred Stock, as Exhibit B the Form of Rights Certificate and as Exhibit C the Summary of Rights to Purchase Preferred Stock (filed as Exhibit 4.1 to the Registrant s Current Report on Form 8-K filed on July 14, 2005 (File No. 000-50743) and incorporated herein by reference)
10.1*	2002 Employee, Director and Consultant Stock Plan, as amended, together with forms of Incentive Stock Option Agreement, Non-qualified Stock Option Agreement and Restricted Stock Agreement (filed as Exhibit 10.1 to the Registrant s Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.2*	2003 Employee, Director and Consultant Stock Plan, as amended, together with forms of Incentive Stock Option Agreement, Non-qualified Stock Option Agreement and Restricted Stock Agreement (filed as Exhibit 10.2 to the Registrant s Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.3*	Amended and Restated 2004 Stock Incentive Plan (filed as Exhibit 10.1 to the Registrant s Quarterly Report on Form 10-Q filed on August 7, 2009 (File No. 000-50743) for the quarterly period ended June 30, 2009 and incorporated herein by reference)
10.4*	Forms of Incentive Stock Option Agreement and Nonstatutory Stock Option Agreement under 2004 Stock Incentive Plan, as amended (filed as Exhibit 10.3 to the Registrant s Quarterly Report on Form 10-Q filed on August 11, 2005 (File No. 000-50743) for the quarterly period ended June 30, 2005 and incorporated herein by reference)
10.5*	Form of Nonstatutory Stock Option Agreement under 2004 Stock Incentive Plan granted to John M. Maraganore, Ph.D., on December 21, 2004 (filed as Exhibit 10.1 to the Registrant s Current Report on Form 8-K filed on December 28, 2004 (File No. 000-50743) and incorporated herein by reference)
10.6*	2009 Stock Incentive Plan (filed as Exhibit 10.2 to the Registrant s Quarterly Report on Form 10-Q filed on August 7, 2009 (File No. 000-50743) for the quarterly period ended June 30, 2009 and incorporated herein by reference)
10.7*	Forms of Incentive Stock Option Agreement and Nonstatutory Stock Option Agreement under 2009 Stock Incentive Plan (filed as Exhibit 10.9 to the Registrant s Annual Report on Form 10-K filed on February 26, 2010 (File No. 000-50743) for the year ended December 31, 2009 and incorporated herein by reference)
10.8*	Form of Restricted Stock Agreement under 2009 Stock Incentive Plan (filed as Exhibit 10.10 to the Registrant s Annual Report on Form 10-K filed on February 18, 2011 (File No. 000-50743) for the year ended December 31, 2010 and incorporated herein by reference)
10.9*	2004 Employee Stock Purchase Plan, as amended (filed as Appendix A to the Registrant s Definitive Proxy Statement on Schedule 14A filed on April 20, 2010 (File No. 000-50743) and incorporated herein by reference)
10.10	Stock Purchase Agreement, dated as of September 6, 2005, by and between the Registrant and Novartis Pharma AG (filed as Exhibit 10.1 to the Registrant s Current Report on Form 8-K filed on September 12, 2005 (File No. 000-50743) and incorporated herein by reference)

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Exhibit No.	Exhibit
10.11	Investor Rights Agreement, dated as of September 6, 2005, by and between the Registrant. and Novartis Pharma AG (filed as Exhibit 10.2 to the Registrant s Current Report on Form 8-K filed on September 12, 2005 (File No. 000-50743) and incorporated herein by reference)
10.12	Letter Agreement dated as of September 20, 2012 by and between the Registrant and Novartis Pharma AG (filed as Exhibit 10.3 to the Registrant s Quarterly Report on Form 10-Q filed on November 5, 2012 (File No. 000-50743) for the quarterly period ended September 30, 2012 and incorporated herein by reference)
10.13*	Letter Agreement between the Registrant and John M. Maraganore, Ph.D. dated October 30, 2002 (filed as Exhibit 10.7 to the Registrant s Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.14*	Letter Agreement between the Registrant and Barry E. Greene dated September 29, 2003 (filed as Exhibit 10.10 to the Registrant s Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.15*	Separation Agreement effective as of March 21, 2011 by and between the Registrant and Patricia Allen, and related Consulting Agreement dated as of March 22, 2011 (filed as Exhibit 10.1 to the Registrant s Quarterly Report on Form 10-Q filed on May 5, 2011 (File No. 000-50743) for the quarterly period ended March 31, 2011 and incorporated herein by reference)
10.16*#	Consulting Agreement dated as of March 1, 2006 by and between the Registrant and Phillip A. Sharp, Ph.D., as amended
10.17*	Consulting Agreement dated as of April 20, 2012 by and between the Registrant and Dennis A. Ausiello, M.D. (filed as Exhibit 10.1 to the Registrant s Current Report on Form 8-K filed on April 23, 2012 (File No. 000-50743) and incorporated herein by reference)
10.18	Lease, dated as of September 26, 2003 by and between the Registrant and Three Hundred Third Street LLC (filed as Exhibit 10.15 to the Registrant s Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.19	First Amendment to Lease, dated March 16, 2006, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.1 to the Registrant s Current Report on Form 8-K filed on March 17, 2006 (File No. 000-50743) and incorporated herein by reference)
10.20	Second Amendment to Lease, dated June 26, 2009, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.4 to the Registrant s Quarterly Report on Form 10-Q filed on August 7, 2009 (File No. 000-50743) for the quarterly period ended June 30, 2009 and incorporated herein by reference)
10.21	Third Amendment to Lease, dated May 11, 2010, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.2 to the Registrant s Quarterly Report on Form 10-Q filed on August 5, 2010 (File No. 000-50743) for the quarterly period ended June 30, 2010 and incorporated herein by reference)
10.22	Fourth Amendment to Lease, dated November 4, 2011, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.19 to the Registrant s Annual Report on Form 10-K filed on February 13, 2012 (File No. 000-50743) for the year ended December 31, 2011 and incorporated herein by reference)
10.23	Sublease made as of August 3, 2010, by and between the Registrant and sanofi-aventis U.S. Inc., as amended by the First Amendment to Sublease effective as of November 4, 2011 (filed as Exhibit 10.20 to the Registrant s Annual Report on Form 10-K filed on February 13, 2012 (File No. 000-50743) for the year ended December 31, 2011 and incorporated herein by reference)
10.24	Lease entered into as of February 10, 2012 by and between BMR-Fresh Pond Research Park LLC and the Registrant (filed as Exhibit 10.2 to the Registrant s Quarterly Report on Form 10-Q filed on May 3, 2012 (File No. 000-50743) for the quarterly period ended March 31, 2012 and incorporated herein by reference)

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Exhibit No.	Exhibit
10.25	Co-exclusive License Agreement between Garching Innovation GmbH (now known as Max Planck Innovation GmbH) and Alnylam U.S., Inc. dated December 20, 2002, as amended by Amendment dated July 8, 2003 together with Indemnification Agreement by and between Garching Innovation GmbH (now known as Max Planck Innovation GmbH) and Alnylam Pharmaceuticals, Inc. effective April 1, 2004 (filed as Exhibit 10.19 to the Registrant s Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.26	Co-exclusive License Agreement between Garching Innovation GmbH (now known as Max Planck Innovation GmbH) and Alnylam Europe, AG dated July 30, 2003 (filed as Exhibit 10.20 to the Registrant s Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.27	Agreement between the Registrant, Garching Innovation GmbH (now known as Max Planck Innovation GmbH), Alnylam U.S., Inc. and Alnylam Europe AG dated June 14, 2005 (filed as Exhibit 10.8 to the Registrant s Quarterly Report on Form 10-Q filed on August 11, 2005 (File No. 000-50743) for the quarterly period ended June 30, 2005 and incorporated herein by reference)
10.28	Confidential Settlement Agreement and Mutual Release entered into as of March 14, 2011 by and between Max-Planck-Gesellschaft zur Förderung der Wissenschaften e. V., Max-Planck-Innovation GmbH and the Registrant, on the one hand, and Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, and the University of Massachusetts, on the other hand (filed as Exhibit 10.2 to the Registrant s Quarterly Report on Form 10-Q filed on May 5, 2011 (File No. 000-50743) for the quarterly period ended March 31, 2011 and incorporated herein by reference)
10.29	Exclusive License Agreement for Tuschl II United States Patents and Patent Applications dated as of March 14, 2011, by and between the Registrant and University of Massachusetts (filed as Exhibit 10.3 to the Registrant s Quarterly Report on Form 10-Q filed on May 5, 2011 (File No. 000-50743) for the quarterly period ended March 31, 2011 and incorporated herein by reference)
10.30	Amendment to Co-Exclusive License Agreement dated as of March 14, 2011, by and between the Registrant, on the one hand, and Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology and Max-Planck-Innovation GmbH (filed as Exhibit 10.4 to the Registrant s Quarterly Report on Form 10-Q filed on May 5, 2011 (File No. 000-50743) for the quarterly period ended March 31, 2011 and incorporated herein by reference)
10.31	Research Collaboration and License Agreement effective as of October 12, 2005 by and between the Registrant and Novartis Institutes for BioMedical Research, Inc. (filed as Exhibit 10.23 to the Registrant s Annual Report on Form 10-K filed on March 2, 2009 (File No. 000-50743) for the quarterly and annual period ended December 31, 2008 and incorporated herein by reference)
10.32	License and Collaboration Agreement, entered into as of July 8, 2007, by and among F. Hoffmann-La Roche, Ltd, Hoffmann-La Roche Inc., the Registrant and, for limited purposes, Alnylam Europe AG (filed as Exhibit 10.26 to the Registrant s Annual Report on Form 10-K filed on March 2, 2009 (File No. 000-50743) for the quarterly and annual period ended December 31, 2008 and incorporated herein by reference)
10.33	Share Purchase Agreement, dated as of July 8, 2007, among Alnylam Europe AG, the Registrant and Roche Pharmaceuticals GmbH (filed as Exhibit 10.3 to the Registrant s Quarterly Report on Form 10-Q filed on November 8, 2007 (File No. 000-50743) for the quarterly period ended September 30, 2007 and incorporated herein by reference)
10.34	Amended and Restated Collaboration Agreement, entered into as of July 27, 2007, by and between the Registrant and Medtronic, Inc. (filed as Exhibit 10.4 to the Registrant s Quarterly Report on Form 10-Q filed on November 8, 2007 (File No. 000-50743) for the quarterly period ended September 30, 2007 and incorporated herein by reference)

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Exhibit No.	Exhibit
10.35	Termination Agreement, dated as of September 18, 2007, by and between Merck & Co., Inc. and the Registrant (filed as Exhibit 10.7 to the Registrant s Quarterly Report on Form 10-Q filed on November 8, 2007 (File No. 000-50743) for the quarterly period ended September 30, 2007 and incorporated herein by reference)
10.36	License and Collaboration Agreement entered into as of May 27, 2008 by and among Takeda Pharmaceutical Company Limited and the Registrant (filed as Exhibit 10.1 to the Registrant s Quarterly Report on Form 10-Q filed on August 8, 2008 (File No. 000-50743) for the quarterly period ended June 30, 2008 and incorporated herein by reference)
10.37	License and Collaboration Agreement entered into as of January 9, 2009 by and between the Registrant and Cubist Pharmaceuticals, Inc. (filed as Exhibit 10.2 to the Registrant s Quarterly Report on Form 10-Q filed on May 8, 2009 (File No. 000-50743) for the quarterly period ended March 31, 2009 and incorporated herein by reference)
10.38	Amended and Restated License and Collaboration Agreement, entered into as of January 1, 2009, by and among the Registrant, Isis Pharmaceuticals, Inc. and Regulus Therapeutics Inc. (filed as Exhibit 10.3 to the Registrant s Quarterly Report on Form 10-Q filed on May 8, 2009 (File No. 000-50743) for the quarterly period ended March 31, 2009 and incorporated herein by reference)
10.39	Founding Investor Rights Agreement entered into as of January 1, 2009, by and among Regulus Therapeutics Inc., Isis Pharmaceuticals, Inc. and the Registrant (filed as Exhibit 10.4 to the Registrant s Quarterly Report on Form 10-Q filed on May 8, 2009 (File No. 000-50743) for the quarterly period ended March 31, 2009 and incorporated herein by reference)
10.40	Amended and Restated Strategic Collaboration and License Agreement effective as of April 28, 2009 between Isis Pharmaceuticals, Inc. and the Registrant (filed as Exhibit 10.3 to the Registrant s Quarterly Report on Form 10-Q filed on August 7, 2009 (File No. 000-50743) for the quarterly period ended June 30, 2009 and incorporated herein by reference)
10.41	Letter Agreement Amendment dated August 27, 2012, amending the Amended and Restated Strategic Collaboration and License Agreement effective as of April 28, 2009 between Isis Pharmaceuticals, Inc. and the Registrant (filed as Exhibit 10.2 to the Registrant s Quarterly Report on Form 10-Q filed on November 5, 2012 (File No. 000-50743) for the quarterly period ended September 30, 2012 and incorporated herein by reference)
10.42	First Amendment to License and Collaboration Agreement entered into as of November 2, 2009 by and between the Registrant and Cubist Pharmaceuticals, Inc. (filed as Exhibit 10.40 to the Registrant s Annual Report on Form 10-K filed on February 26, 2010 (File No. 000-50743) for the year ended December 31, 2009 and incorporated herein by reference)
10.43	Sublicense Agreement dated effective January 8, 2007 among the Registrant and INEX Pharmaceuticals Corporation (now Tekmira Pharmaceuticals Corporation, as successor in interest) (filed as Exhibit 10.38 to the Registrant s Annual Report on Form 10-K filed on February 18, 2011 (File No. 000-50743) for the year ended December 31, 2010 and incorporated herein by reference)
10.44	License and Collaboration Agreement effective as of June 19, 2008 by and between the Registrant and Kyowa Hakko Kirin Co., Ltd. (formerly Kyowa Hakko Kogyo Co., Ltd.), as amended as of February 1, 2010 and June 3, 2010 (filed as Exhibit 10.42 to the Registrant s Annual Report on Form 10-K filed on February 18, 2011 (File No. 000-50743) for the year ended December 31, 2010 and incorporated herein by reference)
10.45	Sponsored Research Agreement dated as of July 27, 2009 by and among the Registrant, The University of British Columbia and AlCana Technologies, Inc. (filed as Exhibit 10.1 to the Registrant s Current Report on Form 8-K filed on June 29, 2011 (File No. 000-50743) and incorporated herein by reference)

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Exhibit No.	Exhibit
10.46	Supplemental Agreement effective July 27, 2009 by and among the Registrant, Tekmira Pharmaceuticals Corporation, Protiva Biotherapeutics Inc., The University of British Columbia and AlCana Technologies, Inc. (filed as Exhibit 10.2 to the Registrant s Current Report on Form 8-K filed on June 29, 2011 (File No. 000-50743) and incorporated herein by reference)
10.47	Amendment No. 1, dated as of July 27, 2011, to the Sponsored Research Agreement dated as of July 27, 2009 by and among the Registrant, The University of British Columbia and AlCana Technologies, Inc. (filed as Exhibit 10.1 to the Registrant s Quarterly Report on Form 10-Q filed on November 3, 2011 (File No. 000-50743) for the quarterly period ended September 30, 2011 and incorporated herein by reference)
10.48	License and Collaboration Agreement dated as of August 27, 2012 by and among Monsanto Company and the Registrant (filed as Exhibit 10.1 to the Registrant s Quarterly Report on Form 10-Q filed on November 5, 2012 (File No. 000-50743) for the quarterly period ended September 30, 2012 and incorporated herein by reference)
10.49 #	License and Collaboration Agreement dated as of October 18, 2012 by and between the Registrant and Genzyme Corporation, as amended
10.50 #	Cross-License Agreement dated as of November 12, 2012 by and among the Registrant, Tekmira Pharmaceuticals Corporation and Protiva Biotherapeutics Inc.
10.51 #	Settlement Agreement and General Release entered into as of November 12, 2012 by and among Tekmira Pharmaceuticals Corporation, Protiva Biotherapeutics Inc., the Registrant and AlCana Technologies, Inc.
10.52#	Letter Agreement dated as of February 6, 2013 by and between Cubist Pharmaceuticals, Inc. and the Registrant
12#	Computation of Consolidated Ratios of Earnings/Deficiencies to Fixed Charges
21.1#	Subsidiaries of the Registrant
23.1#	Consent of PricewaterhouseCoopers LLP, an Independent Registered Public Accounting Firm
23.2#	Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm of Regulus Therapeutics Inc.
31.1#	Certification pursuant to Section 302 of the Sarbanes-Oxley Act of 2002, Rule 13(a)- 14(a)/15d-14(a), by Principal Executive Officer
31.2#	Certification pursuant to Section 302 of the Sarbanes-Oxley Act of 2002, Rule 13(a)- 14(a)/15d-14(a), by Principal Financial Officer
32.1#	Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, by Principal Executive Officer
32.2#	Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, by Principal Financial Officer
99.1#	Report of Ernst & Young LLP, Independent Registered Public Accounting Firm of Regulus Therapeutics Inc.
101#	The following materials from Registrant s Annual Report on Form 10-K for the year ended December 31, 2012, formatted in XBRL (Extensible Business Reporting Language): (i) the Consolidated Balance Sheets, (ii) the Consolidated Statements of Comprehensive Loss, (iii) the Consolidated Statements of Stockholders Equity, (iv) the Consolidated Statements of Cash Flows, and (v) Notes to Consolidated Financial Statements.

* Management contracts or compensatory plans or arrangements required to be filed as an exhibit hereto pursuant to Item 15(a) of Form 10-K.

Indicates confidential treatment requested as to certain portions, which portions were omitted and filed separately with the Securities and Exchange Commission pursuant to a Confidential Treatment Request.

Filed herewith.