ALNYLAM PHARMACEUTICALS, INC.
Form 10-K
February 13, 2012
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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, 2011

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 ¨ No þ

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, 2011, was $290,090,680. 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, 2012, the registrant had 43,208,456 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 2012 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, 2011, 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, 2011

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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 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. Our core programs currently in clinical or pre-clinical development are: ALN-TTR for the treatment of transthyretin-mediated amyloidosis, or ATTR; ALN-APC for the treatment of hemophilia; ALN-PCS for the treatment of severe hypercholesterolemia; ALN-HPN for the treatment of refractory anemia; and ALN-TMP for the treatment of hemoglobinopathies, including beta-thalassemia and sickle cell anemia. We intend to focus on developing and commercializing ALN-TTR and ALN-APC on our own in the United States and potentially certain other countries, and we intend to enter into alliances to advance our ALN-PCS, ALN-HPN and ALN-TMP 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 three partner-based programs in clinical or pre-clinical development, including ALN-RSV01 for the treatment of respiratory syncytial virus, or RSV, infection, ALN-VSP for the treatment of liver cancers and ALN-HTT for the treatment of Huntington s disease, or 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

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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 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, and Cubist Pharmaceuticals, Inc., or Cubist. We have previously entered, and in the future, we intend to enter, into contracts with government agencies, including the National Institute of Allergy and Infectious Diseases, or NIAID, a component of the National Institutes of Health, or NIH. 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. 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 intend to form additional, collaborations through this effort with third-party biopharmaceutical companies. In addition, we recently 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. In October 2011, we entered into a VaxiRNA collaboration with GlaxoSmithKline, or GSK, for influenza vaccine production. Additionally, in 2007, we and Isis established Regulus Therapeutics Inc., or Regulus, a company focused on the discovery, development and commercialization of microRNA therapeutics. Regulus has formed collaborations with GSK and Sanofi to advance its efforts. Given the broad applications for RNAi technology, in addition to our efforts on Alnylam Biotherapeutics, VaxiRNA and Regulus, we believe new ventures and opportunities will be available to us.

Recent Developments

In January 2012, our Board of Directors approved, and 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 is to align our resources to focus on what we believe to be our highest value opportunities, including a focus on ALN-TTR for the treatment of ATTR and ALN-APC for the treatment of hemophilia as our lead programs, while advancing other pipeline programs through existing alliances and new collaborations. We expect to substantially complete the workforce reduction by the end of the first quarter of 2012.

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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 diseases. Drugs based on the RNAi mechanism could offer numerous opportunities and benefits, which may include:

Ability to target proteins that cannot be targeted effectively by existing drug classes. Over the last decade, the understanding of human disease has advanced enormously, and many proteins that play fundamental roles in human disease have been identified. Paradoxically, greater than 80% of these key proteins cannot be targeted effectively with existing drug approaches like small molecules or proteins such as monoclonal antibodies. These so called undruggable targets are potentially accessible to siRNAs as they are made by mRNAs that can be targeted with RNAi.

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 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.

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.*

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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. In some tissues, including the respiratory tract and central nervous system, the direct RNAi delivery approach, which employs the direct or local application of siRNAs, achieves cellular uptake and gene silencing. For other tissues, such as the liver, systemic RNAi delivery has been employed, where tissue access comes via intravenous or subcutaneous injection of the siRNA into the bloodstream and where cellular uptake can be achieved by formulation with other biomaterials, such as lipid nanoparticles, or LNPs, or the conjugation of the siRNA with other molecules, such as small chemical groups. siRNA delivery is a key focus for our internal research team and is also the focus of numerous current academic and corporate collaborations. We have demonstrated RNAi therapeutic activity towards multiple genes, in multiple organs and in multiple species, including humans, as recently demonstrated by the preliminary results from our Phase I clinical trials for ALN-TTR01 and ALN-PCS, as well as the biopsy results from our Phase I clinical trial for ALN-VSP.

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 progress has enabled us to advance several development programs for RNAi therapeutics that are administered directly to diseased tissues, including ALN-RSV01 and ALN-HTT. Our progress in achieving delivery of RNAi therapeutics through systemic RNAi has been demonstrated by data from our Phase I clinical trial for ALN-VSP for the treatment of liver cancers, as well as by preliminary data from our Phase I clinical trials for ALN-TTR01 for the treatment of ATTR and ALN-PCS for the treatment of severe hypercholesterolemia. ALN-VSP and ALN-TTR01 both utilize a first-generation LNP delivery technology developed in collaboration with Tekmira Pharmaceuticals Corporation, or Tekmira. ALN-PCS utilizes a proprietary second-generation LNP technology with the MC3 lipid, that has demonstrated improved potency over first generation LNPs in pre-clinical and preliminary Phase I clinical trials. We expect to initiate a Phase I clinical trial for ALN-TTR02 for the treatment of ATTR in the first quarter of 2012. ALN-TTR02 also utilizes a proprietary second-generation LNP technology with the MC3 lipid.

Our Product Pipeline

Our core product strategy is focused on the development and commercialization of novel RNAi therapeutics for the treatment of genetically defined 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 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 for the treatment of ATTR; ALN-APC for the treatment of hemophilia; ALN-PCS for the treatment of severe hypercholesterolemia; ALN-HPN for the treatment of refractory anemia; and ALN-TMP for the treatment of hemoglobinopathies, including beta-thalassemia and sickle cell anemia. We intend to focus on developing and commercializing ALN-TTR and ALN-APC on our own in the United States and potentially certain other countries, and we intend to enter into alliances to advance our ALN-PCS, ALN-HPN and ALN-TMP programs.

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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 three partner-based programs in clinical or pre-clinical development, including ALN-RSV01 for the treatment of RSV, ALN-VSP for the treatment of liver cancers and ALN-HTT for the treatment of HD.

The following is a summary of our product development programs as of January 31, 2012:

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 $99.3 million in 2011, $106.4 million in 2010 and $108.7 million in 2009.

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 a hereditary, systemic disease caused by a mutation in the TTR gene, of which over 100 mutations have been identified. TTR protein is produced primarily in the liver and is normally a carrier for thyroid hormone and retinol binding protein. We believe TTR is a suitable target for an RNAi therapeutic formulated to maximize delivery to liver cells. Mutations in TTR result in the accumulation of toxic deposits of the wild-type and mutant protein in several 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 predominant 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 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 Vyndaqel® (tafamidis), a small molecule stabilizer of the TTR protein for early-stage FAP patients that was recently approved in the European Union, or EU. Despite these options, there remains a significant need for novel therapeutics to treat patients who have inherited mutations in the TTR gene.

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In November 2011, we reported preliminary data from our Phase I clinical trial for ALN-TTR01, an RNAi therapeutic that employs a first-generation LNP formulation. The Phase I clinical trial for ALN-TTR01 was conducted in Portugal, Sweden, the United Kingdom and France as a randomized, blinded, placebo-controlled, single-dose escalation study in up to 36 patients with ATTR. Patients were enrolled in seven sequential cohorts of increasing doses ranging from 0.01 to 1.0 mg/kg. Data available in November 2011 were presented from 31 patients, including eight who received placebo and 23 who received ALN-TTR01. Assessment of ALN-TTR01 clinical activity based on measurements of serum levels of circulating TTR protein was performed to demonstrate human proof of concept for the ALN-TTR program. ALN-TTR01 demonstrated a dose-dependent reduction in serum TTR levels with a statistically significant mean 41% reduction at the 1.0 mg/kg dose level (geometric mean relative to placebo, p=0.02). To date, ALN-TTR01 has been found to be well tolerated and there were no serious adverse events related to study drug administration. Mild-to-moderate acute infusion reactions were observed in three of 23 (13%) patients receiving ALN-TTR01 and were readily managed by slowing of the infusion rate where necessary. There were no drug-related discontinuations from the study and there were no significant increases in liver function test parameters. Further, pharmacokinetic analyses showed that ALN-TTR01 administration was associated with approximately dose-proportional plasma exposure.

In parallel with the completion of the ALN-TTR01 Phase I clinical trial, we are also advancing ALN-TTR02 utilizing the same siRNA as ALN-TTR01, formulated in a proprietary second-generation LNP with the MC3 lipid. We expect ALN-TTR02 to be our lead development candidate for our ALN-TTR program. In January 2012, the U.K. Medicines and Healthcare products Regulatory Agency, or MHRA, completed review of our clinical trial application, or CTA, and we expect to initiate a Phase I clinical trial for ALN-TTR02 during the first half of 2012. The ALN-TTR02 Phase I clinical trial will be conducted in the United Kingdom as a randomized, single-blind, single-ascending dose study, enrolling up to 32 healthy volunteer subjects. The primary objective of the study will be to evaluate the safety and tolerability of a single dose of ALN-TTR02. Secondary objectives include characterization of pharmacokinetics of ALN-TTR02 and assessment of clinical activity of the drug as measured by effects on serum TTR levels. Pre-clinical studies have shown that administration of ALN-TTR02 results in a greater than ten-fold improvement in potency of TTR silencing as compared to ALN-TTR01.

We also plan to advance ALN-TTRsc, which utilizes a GalNAc-conjugate delivery technology and subcutaneous dose administration, into clinical development. Pre-clinical studies have shown that once-weekly dosing with ALN-TTRsc enables robust and sustained silencing of TTR over a multi-week period. We believe that ALN-TTRsc represents an attractive opportunity for product differentiation in the ATTR clinical setting.

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. 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.

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 Vyndaqel 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.

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ALN-APC Hemophilia

ALN-APC is an RNAi therapeutic targeting protein C, a genetically defined target, for the treatment of hemophilia. Hemophilia is a hereditary disorder caused by genetic deficiencies of various blood clotting factors, resulting in recurrent bleeds into joints, muscles and other major internal organs. Protein C is expressed exclusively in the liver, circulates in plasma and is an endogenous anticoagulant, or anti-clotting, enzyme. Activated protein C, or APC, inactivates factors Va and VIIIa, both proteins in the blood coagulation, or clotting, cascade, resulting in reduced thrombin generation. Thrombin is a key enzyme that converts soluble fibrinogen to insoluble fibrin, thereby forming a clot that stops bleeding. ALN-APC provides a pharmacologic strategy to reproduce the human genetics observed with co-inheritance of prothrombotic factors in hemophilia. A variety of prothrombotic genetic mutations have been discovered that are associated with increased clotting, the most common of which is factor V Leiden, a form of factor V that confers resistance to inactivation by APC. RNAi silencing of protein C is expected to increase thrombin generation and reduce the frequency of bleeding in hemophilia patients, including those patients with inhibitors against replacement factors.

Pre-clinical studies of an siRNA targeting protein C showed dose-dependent silencing of the protein C mRNA. Further, administration of the siRNA resulted in marked reductions in protein C plasma levels. We are exploring both systemically delivered LNP and subcutaneously delivered GalNAc-conjugate approaches for ALN-APC with the goal of selecting the clinical candidate and advancing the ALN-APC program toward the clinic.

ALN-PCS Severe Hypercholesterolemia

ALN-PCS is a systemically delivered RNAi therapeutic targeting proprotein convertase subtilisin/kexin type 9, or PCSK9, for the treatment of severe hypercholesterolemia. PCSK9 is involved in the regulation of LDL receptor, or LDLR, levels on hepatocytes and the metabolism of LDL cholesterol, or LDL-c, which is commonly referred to as bad cholesterol. PCSK9 is a protein that 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 levels of LDLR. 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. Currently, in the United States, there are more than 500,000 patients with high cholesterol levels not controlled by the use of existing lipid lowering therapies. These patients are viewed as having severe hypercholesterolemia and constitute a potential target population for ALN-PCS.

We are advancing ALN-PCS using the same RNAi delivery formulation being used for ALN-TTR02, described above, a second-generation LNP technology with the MC3 lipid. In January 2012, we reported preliminary data from a Phase I clinical trial for ALN-PCS that was initiated during 2011 and is ongoing. We are conducting this clinical trial in the United Kingdom as a randomized, single-blind, placebo-controlled, single-ascending dose study in healthy volunteer subjects with elevated baseline LDL-c. The primary objective of the study is to evaluate the safety and tolerability of a single dose of ALN-PCS, with subjects being enrolled into sequential cohorts of increasing doses. Secondary objectives of the study include characterization of plasma and urine pharmacokinetics of ALN-PCS, assessment of pharmacodynamic effects of the drug on plasma PCSK9 protein levels, and evaluation of clinical efficacy as measured by serum LDL-c levels. This clinical trial is being performed in the absence of statins or other lipid lowering therapy.

The preliminary data we reported in January 2012 describe results from the initial 20 subjects enrolled in five sequential dose cohorts ranging from 0.015 to 0.250 mg/kg in a three-to-one randomization of drug to placebo. Based on the preliminary data in this clinical trial, administration of ALN-PCS resulted in a rapid, dose-dependent, and durable silencing of PCSK9 protein levels in plasma of up to 66% relative to baseline, with a

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statistically significant mean reduction of 60% at day four post-dose in the 0.250 mg/kg ($p<0.001$) dose group. In addition, administration of ALN-PCS resulted in dose-dependent reductions in LDL-c of over 50% relative to baseline, with a statistically significant mean reduction of 39% on day four post-dose ($p<0.05$) at the 0.250 mg/kg dose level. Nadir effects on PCSK9 and LDL-C were achieved rapidly and occurred approximately four days after administration of a single dose. 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 ($p<0.05$), with 100% (six out of six) of subjects in the two highest dose groups achieving target and a mean LDL-c of 84.0 mg/dL, as compared with 21.4% (three out of 14) of subjects achieving target in any other group. Moreover, the effects of a single dose were durable, possibly supporting a once-monthly dose administration regimen in future studies. Further, there was no significant decrease in high-density lipoprotein, or HDL, commonly referred to as good cholesterol levels, consistent with the phenotype observed in human loss-of-function mutations in PCSK9.

Preliminary data from the initial 20 subjects has shown ALN-PCS to be safe and well tolerated in this Phase I clinical trial and there have been no serious adverse events related to study drug administration. There have been no drug-related discontinuations from the study and no liver enzyme elevations. A mild, transient rash was observed in five subjects, including two who received placebo. The Phase I clinical trial is ongoing with planned dose escalation. We plan to partner our ALN-PCS program prior to initiating a Phase II clinical trial.

ALN-HPN Refractory Anemia

ALN-HPN is a systemically delivered RNAi therapeutic targeting the hepcidin pathway, specifically via transferrin receptor subtype 2, or TFR2, a genetically validated gene in iron homeostasis, for the treatment of refractory anemia. Anemia is the clinical manifestation of a decrease in circulating red blood cell mass and is usually detected by low blood hemoglobin concentrations. Symptoms include fatigue and dizziness, and generally have a significant impact on the patient s quality of life. Anemia of chronic disease, or ACD, occurs in patients with end-stage renal disease, cancer, chronic inflammatory disease, and in certain genetic conditions.

Pre-clinical studies with an siRNA targeting TFR2 have demonstrated the ability to silence the gene, down-regulate hepcidin and increase serum iron levels *in vivo*. In addition, pre-clinical studies have demonstrated efficacy in animal models of ACD. We are advancing ALN-HPN using an LNP formulation for systemic delivery. We plan to partner our ALN-HPN program prior to initiating a Phase I clinical trial.

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 and sickle cell anemia. 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 absorption and 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 and spleen histopathology. 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 the product development programs as described above, we also intend to continue to advance additional product development programs through existing or future alliances, including those 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

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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. 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 and Cubist 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 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, a potentially life-threatening complication in lung transplant patients. 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 February 2010, we initiated a multi-center, global, randomized, double-blind, placebo-controlled Phase IIb clinical trial to evaluate the clinical efficacy as well as safety of aerosolized ALN-RSV01 in adult lung transplant patients naturally infected with RSV. The objective of this Phase IIb clinical trial is to repeat and extend the clinical results observed in the Phase IIa clinical trial described above. The primary endpoint was designed as a reduction in the incidence of new or progressive BOS at 180 days. This clinical trial enrolled 87 patients who were randomized in a one-to-one ratio of drug to placebo. In 2011, a planned interim analysis was performed by an independent biostatistical committee to determine whether an increase in sample size up to a maximum of 120 patients was warranted. We were informed that the study should be completed with the current sample size. Because the study remains blinded to all parties, the interim analysis results cannot be interpreted to suggest either a positive or negative outcome. We expect to report the results from this clinical trial in mid-2012.

We have formed collaborations with Cubist and Kyowa Hakko Kirin for the development and commercialization of RNAi products for the treatment of RSV. Under our agreement with Cubist, we are developing ALN-RSV01 for adult transplant patients at our sole discretion and expense. Cubist has the right to opt into collaborating with us on ALN-RSV01 in the future, which right may be exercised for a specified period of time following the completion of our Phase IIb trial, subject to the payment by Cubist of an opt-in fee representing reimbursement of an agreed upon percentage of certain of our development expenses for ALN-RSV01. In December 2010, we and Cubist jointly made a portfolio decision to put the development of ALN-RSV02, a second-generation compound for the pediatric population, on hold.

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. Seven patients with either a major tumor response or prolonged stable disease went onto an extension study. As of January 2012, three patients remained in the study, including a patient with endometrial cancer and multiple liver metastases with an ongoing partial response who has had >80% tumor regression after 19 months of treatment at 0.7 mg/kg, and two additional patients, one with advanced renal cell cancer and the other with pancreatic neuroendocrine tumor, with continued stable disease after over one year of treatment at 1.0 mg/kg. 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. We plan to partner our ALN-VSP program prior to initiating a Phase II clinical trial.

ALN-HTT Huntington s Disease (HD)

In collaboration with Medtronic and CHDI, we are developing 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. HD is an inherited and progressive brain disease that results in uncontrolled movements, loss of intellectual faculties, emotional disturbance and premature death. The disease is caused by the production of an altered form of a protein known as huntingtin, the presence of which is believed to trigger the death of important cells in the brain. This autosomal dominant, neurodegenerative disease afflicts approximately 30,000 patients in the United States. An estimated 150,000 additional people in the United States carry the mutant huntingtin gene and have an approximate 50% risk of developing the disease in their lifetimes.

Alnylam scientists and collaborators have published data from our ALN-HTT program comprised of *in vitro*, rodent and non-human primate data supporting the continued development of ALN-HTT for the treatment of HD.

The ALN-HTT program is part of a 50-50 co-development/profit share relationship with Medtronic for the United States market. Outside the United States, Medtronic will be solely responsible for the development and commercialization of the drug-device product. In November 2010, we and Medtronic entered into an agreement with CHDI, under which CHDI has agreed to initially fund approximately 50% of the costs of this program up to the point at which an IND or comparable foreign regulatory application can be filed.

Discovery Programs

In addition to our core development efforts on ATTR, hemophilia, severe hypercholesterolemia, refractory anemia and hemoglobinopathies, including beta-thalassemia and sickle cell anemia, 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 with a focus on genetically defined diseases that we can partner with third parties. These include programs focused on erythropoiesis, alpha-1-antitrypsin deficiency-associated liver disease, severe hypertriglyceridemia and acute intermittent porphyria.

Our Collaboration and Licensing Strategy

Our business strategy is to develop and commercialize a pipeline of RNAi therapeutic products. 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.

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Our collaboration strategy is to form worldwide or specific geographic collaborations relating to (1) RNAi platform and/or multi-target discovery alliances, and (2) select RNAi therapeutic programs in our pipeline. 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. We have also established product alliances with Cubist and Medtronic for the development and commercialization of ALN-RSV and ALN-HTT, respectively. In addition, we have entered into a product alliance with Kyowa Hakko Kirin for the development and commercialization of ALN-RSV in territories not covered by the Cubist agreement, which include Japan and other markets in Asia. We also have a discovery and development alliance with Isis. We intend to seek partners to advance a number of our programs in development, including our ALN-PCS, ALN-HPN, ALN-TMP and ALN-VSP programs.

We also seek to form or advance new ventures and opportunities in areas outside our primary focus on RNAi therapeutics. 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 intend to 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 VaxiRNA collaboration with GSK for influenza vaccine production. Additionally, in 2007, we and Isis formed Regulus to capitalize on our technology and intellectual property in the field of microRNA therapeutics. Regulus has formed collaborations with GSK and Sanofi to advance its efforts. Given the broad applications for RNAi technology, in addition to our efforts on Alnylam Biotherapeutics, VaxiRNA and Regulus, 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, 2012, 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, the Massachusetts Institute of Technology, or MIT, The University of British Columbia, or UBC, and AlCana Technologies, Inc., or AlCana, among others, to focus on various delivery strategies. 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 Center, or UTSW, as well as a number of other entities, to obtain rights to intellectual property in the field of RNAi.

Finally, we seek funding for the development of our proprietary RNAi therapeutics pipeline from the government and foundations. For example, in 2010, we completed a contract awarded to us by NIAID to advance the development of a broad spectrum RNAi anti-viral therapeutic against hemorrhagic fever virus, including the Ebola virus.

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.

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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 now has 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 other 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 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. 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.

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.

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

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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 and commercialization milestones, totaling up to $171.0 million per product, together with royalty payments based on worldwide annual net sales, if any. 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 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, 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 program. 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 in the United States of licensed products. 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.

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.

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.

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

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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. In September 2010, Novartis declined to exercise its non-exclusive option to integrate into its operations our fundamental and chemistry intellectual property under the terms of the collaboration and license agreement. If Novartis had elected to exercise the integration option, Novartis would have been required to make additional payments to us totaling $100.0 million.

The investor rights agreement provides Novartis with the right generally to maintain its ownership percentage in Alnylam until the earlier of any sale by Novartis of shares of our common stock and the expiration or termination of the collaboration and license agreement, neither of which has yet occurred, subject to certain exceptions. At December 31, 2011, Novartis owned 13.1% of our outstanding common stock. Under the terms of the investor rights agreement, we also granted Novartis demand and piggyback registration rights under the Securities Act of 1933, as amended, for the shares of our common stock held by Novartis, which rights remain in effect.

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. The amended and restated collaboration agreement supersedes the collaboration agreement entered into by the parties in February 2005, and continues the existing collaboration between the parties focusing on the delivery of RNAi therapeutics to specific areas of the brain using implantable infusion systems.

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Under the terms of the amended and restated collaboration agreement, we and Medtronic are continuing our existing development program focused on developing a combination drug-device product for the treatment of HD. In addition, we and Medtronic may jointly agree to collaborate on additional product development programs for the treatment of other neurodegenerative diseases, which can be addressed by the delivery of siRNAs to the human nervous system through implantable infusion devices. 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, each party is funding 50% of the development efforts for the United States, subject to the funding reimbursement received from CHDI described below. Medtronic is responsible for funding development efforts outside the United States. Medtronic will commercialize any resulting products and pay royalties to us based on net sales of such products, if any, which royalties in the United States are designed to approximate 50% of the profit associated with the sale of such product and which royalties in Europe are similar to more traditional pharmaceutical royalties, in that they are intended to reflect each party s contribution.

Each party has the right to opt-out of its obligation to fund the program under the agreement at certain stages, and the agreement provides for revised economics based on the timing of any such opt-out. Other than pursuant to the initial product development program, and subject to specified exceptions, neither party may research, develop, manufacture or commercialize products that use implanted infusion devices for the direct delivery of siRNAs to the human nervous system to treat HD during the term of such program.

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 can be filed, which represents over $10.0 million in potential funding. 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.

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, subject to our agreement with Cubist, described below.

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.

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 are also continuing to develop ALN-RSV01 for adult transplant patients at our sole discretion and expense. Cubist has the right to opt into collaborating with us on ALN-RSV01 in the future, which right may be exercised for a specified period of time following the completion of our Phase IIb clinical trial for ALN-RSV01 in adult lung transplant patients infected with RSV, subject to the payment by Cubist of an opt-in fee representing reimbursement of an agreed upon percentage of certain of our development expenses for ALN-RSV01.

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. Cubist is also obligated under the agreement to pay us milestone payments, totaling up to an aggregate of $82.5 million, upon the achievement of specified development and sales events in the Royalty Territory, if any. In addition, if licensed products are successfully developed, Cubist will be required to pay us double-digit royalties on net sales of licensed products in the Royalty Territory, if any, subject to offsets under certain circumstances. Upon achievement of certain development milestones, we will have the right to convert the North American co-development and profit sharing arrangement into a royalty-bearing license and, in addition to royalties on net sales in North America, will be entitled to receive additional milestone payments totaling up to an aggregate of $130.0 million upon achievement of specified development and sales events in North America, subject to the timing of the conversion by us and the regulatory status of a licensed product at the time of conversion. If we make the conversion to a royalty-bearing license with respect to North America, then North America becomes part of the Royalty Territory. 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 Cubist.

Unless terminated earlier in accordance with the agreement, the agreement expires on a country-by-country and licensed product-by-licensed product basis, (a) with respect to the Royalty Territory, upon the latest to occur of (1) the expiration of the last-to-expire Alnylam patent covering a licensed product, (2) the expiration of the Regulatory-Based Exclusivity Period (as defined in the Cubist agreement) and (3) ten years from first

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commercial sale in such country of such licensed product by Cubist or its affiliates or sublicensees, and (b) with respect to North America, if we have not converted North America into the Royalty Territory, upon the termination of the agreement by Cubist upon specified prior written notice. We estimate that our fundamental RNAi patents covered under the Cubist agreement will expire both in and outside of the United States generally between 2016 and 2025. Certain claims covering ALN-RSV compounds in the United States would expire in 2026. 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. In addition, more patent filings relating to the collaboration may be made in the future. Cubist has the right to terminate the agreement at any time (1) upon three months prior written notice if such notice is given prior to the acceptance for filing of the first application for regulatory approval of a licensed product or (2) upon nine months prior written notice if such notice is given after the acceptance for filing of the first application for regulatory approval. Either party may terminate the agreement in the event the other party fails to cure a material breach or upon patent-related challenges by the other party.

During the term of the Cubist agreement, neither party nor its affiliates may develop, manufacture or commercialize anywhere in the world, outside of Asia, a therapeutic or prophylactic product that specifically targets RSV, except for licensed products developed, manufactured or commercialized pursuant to the agreement.

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 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 also providing funding to support the advancement of these delivery technologies. During 2011, 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

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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 and Protiva. In January 2007, we obtained an exclusive worldwide license to the liposomal delivery formulation technology of Tekmira for the discovery, development and commercialization of LNP formulations for the delivery of RNAi therapeutics and a non-exclusive worldwide license to certain liposomal delivery formulation technology of Protiva Biotherapeutics Inc., or Protiva, for the discovery, development and commercialization of certain LNP formulations for the delivery of RNAi therapeutics. In May 2008, Tekmira acquired Protiva. In connection with this acquisition, we entered into new agreements with Tekmira and Protiva, which provide us access to key existing and future technology and intellectual property for the systemic delivery of RNAi therapeutics with liposomal delivery technologies. Under these agreements, we continue to have exclusive rights to the Semple (U.S. Patent No. 6,858,225) and Wheeler (U.S. Patent Nos. 5,976,567 and 6,815,432) patents for RNAi, which we believe are critical for the use of LNP delivery technology. Under our agreements with Tekmira and Protiva, Tekmira and Protiva are eligible to receive up to an aggregate of $16.0 million in milestone payments for each RNAi therapeutic formulated using Tekmira s or Protiva s liposomal delivery formulation technologies, together with single-digit royalty payments on annual product sales. In each of 2009, 2010 and 2011, we paid to Tekmira $0.5 million in milestone payments under these license agreements.

Under our agreements with Tekmira and Protiva, we also granted Tekmira and Protiva three exclusive and five non-exclusive licenses under our InterfeRx program to develop and commercialize RNAi therapeutics directed to up to eight gene targets in which we have no direct strategic interest, including the targets apolipoprotein B and polo-like kinase 1, or PLK1, and a license in connection with Tekmira s research program directed towards the Ebola virus. We are eligible to receive up to an aggregate of $8.5 million in milestone payments for each RNAi therapeutic directed to four of these targets, together with single-digit royalties on annual sales of RNAi therapeutic products directed to all of these targets, if any. In addition, under our agreement with Protiva, we have the right to opt-in to the Tekmira research program directed to PLK1 and contribute 50% of product development costs and share equally in any future product revenues. We have until the start of a Phase II clinical trial in this PLK1 research program to exercise our opt-in right.

The terms of our agreements with Tekmira and Protiva generally end upon the expiration of the last-to-expire patent licensed thereunder, whether such patent is a patent licensed by Tekmira or Protiva to us, or vice versa. As the licenses from Tekmira and Protiva will include additional patents, if any, filed to cover future inventions, if any, the dates of expiration cannot be determined at this time. Either we or Protiva may terminate a license it granted to the other in the event that the other party materially breaches its obligations relating to that license. Furthermore, either we or Tekmira may terminate our agreements with each other in the event the other party materially breaches an obligation under those agreements, but such termination will be limited to a particular product and/or region in the event of a material breach by the other party that has a material adverse effect only on that particular product in that region.

The subject matter of these agreements is the subject of ongoing litigation between us and Tekmira and Protiva, a description of which is set forth below under Part I, Item 3, Legal Proceedings, of this annual report on Form 10-K.

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UBC and AlCana. Our research agreement with UBC and AlCana, which we entered into in July 2009, is 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 over an initial two-year period, and in July 2011, we exercised our right to extend the collaborative research and our funding for a third year, through July 2012. The collaborative research is being conducted by our scientists, together with scientists at UBC and AlCana.

Under the research agreement, we have exclusive rights to all new inventions relating to the delivery of oligonucleotides and other nucleic acid constructs, as well as sole rights to sublicense any resulting intellectual property to our current and future collaborators. 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 Tekmira, Protiva, UBC and AlCana, which contains additional terms regarding the intellectual property rights arising out of the research agreement. Pursuant to the terms of the supplemental agreement, each of Tekmira and Protiva has the right to use new inventions under the research agreement for its own RNAi therapeutic programs that are licensed under our InterfeRx program and would be required to pay milestones and royalties to UBC and AlCana in connection with such use.

Pursuant to the terms of the supplemental agreement, each of Tekmira and Protiva waived all prohibitions and restrictions on certain former Tekmira employees who are now working at UBC and AlCana in connection with their performance of the collaborative research under the research agreement and agreed not to sue us, AlCana, UBC and such former Tekmira employees for any cause of action relating to such activities that arose out of their former employment with Tekmira.

The subject matter of these agreements is the subject of ongoing litigation between Tekmira and Protiva, on the one hand, and us and AlCana, on the other hand, a description of which is set forth below under Part I, Item 3, Legal Proceedings, of this annual report on Form 10-K.

We are pursuing additional approaches for delivery that include other LNP 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 government, academic and corporate third parties 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. At December 31, 2011, we, Isis and Sanofi owned approximately 45%, 46% and 9%, respectively, of Regulus. Regulus continues to operate 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 are not eligible to receive options to purchase Regulus 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. There are approximately 700 microRNAs that have been identified in the human genome, and these are believed to regulate the expression of up to 30% of all human

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genes. 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 is advancing microRNA therapeutics in several areas including fibrosis, hepatitis C virus, or HCV, infection, immuno-inflammatory diseases, metabolic and cardiovascular diseases, and oncology.

In April 2008, Regulus entered into a worldwide strategic alliance with GSK to discover, develop and market novel microRNA-targeted therapeutics to treat inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. In connection with this alliance, Regulus received $20.0 million in upfront payments from GSK, including a $15.0 million option fee and a loan of $5.0 million (guaranteed by us and Isis) that will convert into Regulus common stock under certain specified circumstances. Regulus is eligible to receive development, regulatory and sales milestone payments for each of the four microRNA-targeted therapeutics discovered and developed as part of the alliance, and would also receive royalty payments on worldwide sales of products resulting from the alliance, if any.

In February 2010, Regulus and GSK established a new collaboration to develop and commercialize microRNA therapeutics targeting miR-122 in all fields, with the treatment of HCV infection as the lead indication. Under the terms of this collaboration, Regulus received $8.0 million in upfront payments from GSK, including a $3.0 million license fee and a loan of $5.0 million (guaranteed by us and Isis) that will convert into Regulus common stock under certain specified circumstances. Consistent with the original GSK alliance, Regulus is eligible to receive development, regulatory and sales milestone payments, as well as royalty payments on worldwide sales of products resulting from the alliance, if any, as Regulus and GSK advance microRNA therapeutics targeting miR-122.

In June 2010, Regulus entered into a global, strategic alliance with Sanofi to discover, develop and commercialize microRNA therapeutics on up to four microRNA targets. Under the terms of this alliance, Regulus received $25.0 million in upfront fees and is entitled to annual research support for three years with the option to extend research support for two additional years. In addition, Regulus is eligible to receive royalties on microRNA therapeutic products commercialized by Sanofi, if any. Sanofi will support 100% of the costs of clinical development and commercialization of each program. Regulus and Sanofi will collaborate on up to four microRNA targets, including Regulus lead fibrosis program targeting miR-21. Sanofi also received an option for a broader technology alliance with Regulus that provides Regulus certain rights to participate in development and commercialization of resulting products. If exercised, this option is worth up to an additional $50.0 million to Regulus. We and Isis are each eligible to receive 7.5% of all potential upfront and milestone payments, in addition to single-digit royalties on product sales, if any. We received $1.9 million from Regulus in connection with this alliance, representing 7.5% of the $25.0 million upfront payment from Sanofi to Regulus. In addition, in October 2010, Sanofi made a $10.0 million equity investment in Regulus.

We, Isis and Regulus have also entered into a license and collaboration agreement to pursue the discovery, development and commercialization of therapeutic products directed to microRNAs. Under the terms of the license and collaboration agreement, we and Isis assigned to Regulus specified patents and contracts covering microRNA-specific technology. In addition, each of us granted to Regulus an exclusive, worldwide license under our rights to other microRNA-related patents and know-how to develop and commercialize therapeutic products containing compounds that are designed to interfere with or inhibit a particular microRNA, subject to our and Isis existing contractual obligations to third parties. Regulus also has the right to request a license from us and Isis to develop and commercialize therapeutic products directed to other microRNA compounds, which such license is subject to our and Isis approval and to each party s existing contractual obligations to third parties. Regulus granted to us and Isis an exclusive license to technology developed or acquired by Regulus for use solely within our respective fields (as defined in the license and collaboration agreement), but specifically excluding the right to develop, manufacture or commercialize the therapeutic products for which we and Isis granted rights to Regulus.

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

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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 two collaborations around our Alnylam Biotherapeutics initiative with leading biotechnology and pharmaceutical companies and plan to 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.

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 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, AlCana 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 20 gene targets and, as of January 31, 2012, only ten 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.

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Government Funding

Although we do not currently have any government contracts, we have had government contracts awarded to us in the past and intend to seek additional government contracts and funding in the future.

NIH. In September 2006, the NIAID, a component of the NIH, awarded us a contract for up to $23.0 million over four years to advance the development of a broad spectrum RNAi anti-viral therapeutic for hemorrhagic fever virus, including the Ebola virus. The NIAID appropriated and we received the entire $23.0 million under the contract.

Department of Defense. In August 2007, the Defense Threat Reduction Agency, or DTRA, an agency of the United States Department of Defense, awarded us a contract to advance the development of a broad spectrum RNAi anti-viral therapeutic for hemorrhagic fever virus. The government initially committed to pay us up to $10.9 million through February 2009. Following a program review in early 2009, we and DTRA determined not to continue this program and accordingly, the remaining funds of up to $27.7 million were not accessed.

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	Patent Subject Matter	First Priority Date	Inventors	Status	Expiration Date*	Alnylam Rights
Isis	Inactivation of target mRNA	6/6/1996 and 6/6/1997	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 (granted/opposed), EP 1352061 (maintained/under appeal) & EP 1349927 (granted/opposed), 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	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	11/19/1999	M. Zernicka-Goetz, M.J. Evans, D.M. Glover	EP 1230375 (revoked/under appeal), SG 89569 (Singapore), AU 774285 (Australia)	11/17/2020	Exclusive rights for therapeutic purposes

	cells					
				Additional applications pending in the U.S. and several foreign jurisdictions		
Massachusetts Institute of Technology, Whitehead Institute, University of Massachusetts, Max Planck Gesellschaft***	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	EP 1309726 (granted/opposed), AU 2001249622 (Australia) , NZ 522045 (New Zealand), KR 08724437 & KR 10-0909681 (Korea)	3/30/2020	Non-exclusive rights for therapeutic purposes***
				Additional applications pending in the U.S. and several foreign jurisdictions		
Massachusetts Institute of Technology, Whitehead Institute, University of Massachusetts, Max Planck Gesellschaft (U.S.)****	Synthetic and chemically modified siRNAs as therapeutic products	12/1/2000	T. Tuschl, S. Elbashir, W. Lendeckel, M. Wilm, R. Lührmann	U.S. 7,056,704 & U.S. 7,078,196 EP 1407044 (maintained/under appeal), EP 1873259, AU 2002235744 (Australia), ZA 2003/3929 (South Africa), SG 96891 (Singapore), NZ 52588 (New Zealand), JP 4 095 895 (Japan Invalidation Trial Proceedings), JP 4 494 392 (Japan), RU 2322500 (Russia), CN 1568373 (China)	11/29/2021	Exclusive rights for therapeutic purposes****
Max Planck Gesellschaft (ex-U.S.)				Additional applications pending in the U.S. and several foreign jurisdictions		

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Licensor/Owner	Subject Matter	First Priority Date	Inventors	Status	Expiration Date*	Alnylam Rights
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		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.

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 European Kreutzer-Limmer patent (EP 1214945) to issue in the series was granted in Europe in 2005. This patent covers 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 has been opposed. In March 2010, the EPO issued a fourth patent in the Kreutzer-Limmer series (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 has also been opposed. 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.

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The Glover patent series has resulted in several patent grants, including in Europe (EP 1230375). The European Glover patent was revoked in June 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 Forderung 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. 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 Forderung 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 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 upholding the validity of this patent. All of the opponents have appealed the decision of the Opposition 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 is the subject of an Invalidation Trial which was requested by a Japanese company. 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.

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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 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, we recently reported receipt of a notice of allowance from the USPTO for patent application number 12/813,448, covering our proprietary second-generation LNP platform, including the MC3 lipid. This second-generation LNP delivery platform is being utilized in our ALN-TTR02 and ALN-PCS development programs and may potentially be utilized in other development programs. The newly allowed patent application includes 30 claims covering composition of matter and formulations of MC3, as well as methods of using these compositions and formulations. The patent application lists inventors from our company and AlCana. Tekmira is seeking relinquishment and transfer of this patent pursuant to its ongoing litigation against us. A description of this legal matter is set forth in Part I, Item 3, Legal Proceedings, of this annual report on Form 10-K.

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

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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, the effect of which called into question the validity and/or enforceability of our patent. The interference proceedings are ongoing. If Protiva is successful in obtaining a dominating claim, we would require a license to Protiva s patent to commercialize ALN-VSP in the United States.

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.

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

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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 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 is currently on the market, and has several ASO product candidates in clinical trials, including Kynamro (mipomersen sodium), which is a lipid-lowering drug being developed by Isis in collaboration with Genzyme Corporation, or Genzyme, which was acquired by Sanofi in 2011. 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 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 Vyndaqel for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. Vyndaqel has orphan drug status in the EU for the treatment of FAP associated with ATTR. Vyndaqel 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

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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.

Severe 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 Lipitor® (atorvastatin), Zocor® (simvastatin), Crestor® (rosuvastatin) and Pravachol® (pravastatin). A different class of compounds, which includes Zetia® (ezetimibe) and Vytorin® (ezetimibe/simvastatin), function by blocking cholesterol uptake from the diet and are utilized on their own or in combination with statins.

With regard to future therapies in clinical development, Kynamro is a lipid-lowering drug targeting apolipoprotein B-100 being developed by Isis in collaboration with Genzyme. In July 2011, Genzyme submitted a marketing application for Kynamro in Europe and plans to file for marketing approval for Kynamro in the United States in the first quarter of 2012. Isis and Genzyme have evaluated Kynamro in four positive Phase III clinical trials in which its primary endpoints were met. In all four Phase III clinical trials, treatment with Kynamro lowered LDL-c and had a beneficial impact on other atherogenic lipids. A weekly injectable therapeutic, Kynamro 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. in collaboration with Sanofi, and which is currently in Phase II clinical trials. Preliminary 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 REGN127/SAR236553 compared to a mean reduction of 10% with placebo ($p<0.05$ for all dose groups). Amgen Inc. and Pfizer also have anti-PCSK9 antibodies in Phase I 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 as Virazole® 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 Synagis® (palivizumab), which is marketed by MedImmune, LLC, the worldwide biologics unit for AstraZeneca PLC. Synagis is a neutralizing monoclonal antibody that prevents the virus from infecting the cell by blocking the RSV F protein. Synagis 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

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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, also called Nexavar®, for the treatment of un-resectable liver cancer. Nexavar 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.

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-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.

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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 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 U.S. 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 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, severe hypercholesterolemia, refractory anemia, hemoglobinopathies, including beta-thalassemia and sickle cell anemia, 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.

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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 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 inspection 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, a drug or biologic may not be promoted for uses that are not approved by the FDA as reflected in the product s approved labeling. 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

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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.

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 relevant patents 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.

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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 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 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

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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.

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 study 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.

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.

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 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

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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.

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, an increasing emphasis on managed care in the United States has increased and we expect will continue to increase the 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

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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.

Manufacturing

We have no commercial manufacturing capabilities. We have manufactured only limited supplies of drug substance for use in IND-enabling toxicology studies in animals at our own facility. We 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. In the future, we expect to develop our own capabilities to manufacture drug substance, including siRNAs and siRNA conjugates, and/or finished drug product, including LNP formulations, as permitted under our manufacturing agreement with Tekmira described below, 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 currently plan to rely on third parties to manufacture commercial quantities of drug substance and finished product for any product candidate that we successfully develop.

Under our agreements with Tekmira, we are obligated to utilize Tekmira for the manufacture of all LNP-formulated product candidates covered by Tekmira s intellectual property beginning during pre-clinical development and continuing through Phase II clinical trials. During 2009, we and Tekmira entered into a manufacturing and supply agreement under which we were committed to pay Tekmira a minimum of CAD$11.2 million (representing U.S.$9.2 million at the time of execution) through December 2011 for manufacturing services. Tekmira has manufactured the clinical drug supply for our Phase I clinical trials for ALN-VSP, ALN-TTR01, ALN-TTR02 and ALN-PCS, as well as drug supply expected to be used in our planned Phase II clinical trial for ALN-TTR02. Both we and Tekmira have the right to terminate the manufacturing and supply agreement for a material breach by the other party of its obligations under this agreement. We also have the right to terminate our obligation to use Tekmira for manufacturing on a product-by-product basis for a failure by Tekmira to meet certain specific requirements with respect to a product.

We believe we have sufficient manufacturing capacity through our third-party contract manufacturers to meet our current research and clinical needs. We believe that the supply capacity we have established externally, together with the internal capacity we expect to develop to support clinical trials in the future, 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
David P. Bartel, Ph.D.	Member/Whitehead Institute for Biomedical Research; Professor/Massachusetts Institute of Technology; Investigator/Howard Hughes Medical Institute
Fritz Eckstein, Ph.D.	Professor/Max Planck Institute for Experimental Medicine
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
Stephen N. Oesterle, M.D.*	Senior Vice President for Medicine and Technology/Medtronic, Inc.
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
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

* Dr. Oesterle participates as an observer on our scientific advisory board.

Employees

At January 31, 2012, taking into account the effects of our January 2012 strategic corporate restructuring and workforce reduction, we had 116 employees, 94 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 five entities, Alnylam Pharmaceuticals, Inc. and four wholly owned subsidiaries (Alnylam U.S., Inc., Alnylam Europe AG, Alnylam Securities Corporation and Meltemi Biotherapeutics, Inc). 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. Meltemi Biotherapeutics, Inc. is a Delaware corporation that was formed in September 2011. 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

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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 otherwise furnished to, the Securities and Exchange Commission, or 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

Name	Age	Position
John M. Maraganore, Ph.D.	49	Chief Executive Officer and Director
Barry E. Greene	48	President and Chief Operating Officer
Laurence E. Reid, Ph.D.	48	Senior Vice President and Chief Business Officer
Akshay K. Vaishnaw, M.D., Ph.D.	49	Senior Vice President and Chief Medical Officer
Michael P. Mason	37	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.

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.

Akshay K. Vaishnaw, M.D., Ph.D. has served as our Senior Vice President and Chief Medical Officer since June 2011. 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.

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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 an early stage development stage company, there is limited information about our ability to successfully overcome many of the risks and uncertainties encountered by companies in the biopharmaceutical industry.

As an early-stage development stage company, 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, 2011, we had an accumulated deficit of $401.0 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 current and 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. Moreover, our investor rights agreement with Novartis provides Novartis with the right generally to maintain its ownership percentage in us, subject to certain exceptions. These rights continue until the earlier of any sale by Novartis of shares of our common stock and the expiration or termination of our license agreement with Novartis, subject to certain exceptions. Pursuant to the terms of its investor rights agreement with us, over the past five years, Novartis purchased an aggregate of 335,033 shares of our common stock, resulting in aggregate payments to us of $7.6 million. At December 31, 2011, Novartis held 13.1% of our outstanding common stock. While the exercise of these rights by Novartis has provided us with funding, and the exercise in the future by Novartis may provide us with additional funding under some circumstances, these exercises have caused, and any future exercise of these rights by Novartis will also cause further, dilution to our stockholders. Debt financing, if

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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.

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 marketable securities is subject to risks which may cause losses and affect the liquidity of these investments.

At December 31, 2011, we had $260.8 million in cash, cash equivalents and 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

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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 milestones, totaling up to $171.0 million per product, together with royalty 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. For example, we intend to enter into worldwide or specific geographic collaborations relating to (1) RNAi platform and/or multi-target discovery alliances, and (2) select RNAi therapeutic programs in our pipeline, including ALN-PCS, ALN-HPN, ALN-TMP and ALN-VSP. 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 our collaboration with Medtronic, we are jointly developing ALN-HTT, an RNAi therapeutic for HD, which would be delivered using an implanted infusion device developed by Medtronic. The success of this collaboration will depend, in part, on Medtronic s expertise in the

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area of delivery of drugs by infusion device, something that they have never done before with our product candidates. In 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 Kyowa Hakko Kirin for development and commercialization of any RNAi products for the treatment of RSV in Asia. If Kyowa Hakko Kirin is not successful in its commercialization efforts, our future revenues from RNAi therapeutics for the treatment of RSV may be adversely affected.

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. 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, Cubist and Medtronic. We may not, however, be able to enter into additional collaborations for ALN-PCS, ALN-HPN, ALN-TMP or ALN-VSP, 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 Cubist relating to the development and commercialization of certain RSV therapeutics in territories outside of Asia may be terminated by Cubist at any time upon as little as three months prior written notice, if such notice is given prior to the acceptance for filing of the first application for regulatory approval of a licensed product. 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

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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. For example, in March 2011, Tekmira filed a civil complaint against us claiming misappropriation of its confidential and proprietary information and trade secrets, civil conspiracy and tortious interference with contractual relationships, unjust enrichment, contractual breach, breach of the implied covenant of good faith and fair dealing, unfair competition, false advertising, and unfair and deceptive trade practices by us. As a result of the litigation, we have been required to expend additional resources and management attention that would otherwise be 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.

Regulus is important to our business. If Regulus does not successfully develop drugs pursuant to our license and collaboration agreement, our business could be adversely affected. In addition, disagreements between us and Isis regarding the development of microRNA technology may cause significant delays and other impediments in the development of this technology, which could negatively affect the value of the technology and our investment in Regulus.

In September 2007, we and Isis formed Regulus, of which we owned approximately 45% at December 31, 2011, to discover, develop and commercialize microRNA therapeutics. Regulus is exploring therapeutic opportunities that arise from dysregulation of microRNAs. Neither Regulus nor any other company has received regulatory approval to market therapeutics utilizing microRNA technology. In connection with the establishment of Regulus, we exclusively licensed to Regulus our intellectual property rights covering microRNA technology. Generally, we do not have rights to pursue microRNA therapeutics independently of Regulus. If Regulus is unable to discover, develop and commercialize microRNA therapeutics, our business could be adversely affected.

In April 2008, Regulus formed a collaboration with GSK pursuant to which GSK provided Regulus with a loan for $5.0 million, plus interest. In February 2010, Regulus formed an additional collaboration with GSK pursuant to which GSK provided Regulus with an additional $5.0 million loan, plus interest. These loans are guaranteed equally by us and Isis. If Regulus is unable to repay GSK or convert the loans into Regulus common stock, we could be liable for our share of these obligations, and our business could be adversely affected.

In addition, Regulus operates as an independent company, governed by a board of directors. We and Isis each can elect an equal number of directors to serve on the Regulus board. Regulus researches and develops microRNA projects and programs pursuant to an operating plan that is approved by its board. Any disagreements between Isis and us regarding a development decision or any other decision submitted to Regulus board may cause significant delays in the development and commercialization of microRNA technology and could negatively affect the value of our investment in Regulus.

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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 or rely on third parties to manufacture our products.

We have very limited manufacturing experience. Our internal manufacturing capabilities are limited to small-scale production of non-cGMP, material for use in *in vitro* and *in vivo* experiments. Some of our product candidates utilize specialized formulations, such as liposomes or LNPs, 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. 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.

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. For example, under our agreements with Tekmira, we are obligated, subject to certain exceptions specified in our contract with Tekmira, to utilize Tekmira for the manufacture of all LNP-formulated product candidates covered by Tekmira s intellectual property beginning during pre-clinical development and continuing through Phase II clinical trials. 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, in the future, we expect to develop our own capabilities to manufacture drug substance, including siRNAs and siRNA conjugates, and/or finished drug product, including LNP formulations, as permitted under our manufacturing agreement with Tekmira, for human clinical use. If we develop these manufacturing capabilities by building our own manufacturing facility, it will require substantial expenditures. Also, we will likely need to hire and train employees to staff a new facility.

The manufacturing process for any products that we may develop is subject to the 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

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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, if we elect to 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.

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.

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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, particularly given our recent workforce reduction, 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 intend to reduce our workforce by approximately 33%. We are taking these actions in order to reduce costs, streamline operations and improve our cost structure, and we expect that this restructuring plan will result in significant savings in 2012 operating expenses. The workforce reduction is expected to be substantially completed by the end of the first quarter of 2012.

As a result of the reduction in workforce, we expect to record restructuring charges and make future payments of approximately $4.0 million, a substantial portion of which we anticipate will be recorded in the first quarter of 2012. These estimated restructuring charges are 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, 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 may 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.

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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 recent 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. We are developing ALN-RSV01 for the treatment of RSV infection. In February 2010, we initiated a Phase IIb clinical trial to evaluate the clinical efficacy endpoints as well as safety of aerosolized ALN-RSV01 in adult lung transplant patients naturally infected with RSV. The objective of this Phase IIb clinical trial is to repeat and extend the clinical results observed in a Phase IIa clinical trial. In addition, in August 2011, we completed a Phase I clinical trial for ALN-VSP, our first systemically delivered RNAi therapeutic. We are developing ALN-VSP for the treatment of primary and secondary liver cancer. In July 2010, we also initiated a Phase I clinical trial for ALN-TTR01, our second systemically delivered RNAi therapeutic, which targets the TTR gene for the treatment of ATTR. In September 2011, we initiated a Phase I clinical trial for ALN-PCS for the treatment of severe hypercholesteremia. ALN-PCS is formulated in a proprietary second-generation LNP formulation. However, we may not be able to further advance these or any other product candidate through clinical trials.

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-RSV01 may not demonstrate the same results in the Phase IIb clinical trial as it did in our Phase IIa clinical trial. In addition, ALN-VSP, ALN-TTR01 and ALN-PCS employ novel delivery formulations that have yet to be extensively evaluated in human clinical trials and proven

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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. 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. Six additional patients treated at the same dose did not exhibit any evidence of hepatotoxicity. In August 2011, we announced the completion of the ALN-VSP clinical trial. In our ALN-PCS clinical trial, we reported preliminary safety data that a mild, transient rash was observed in five subjects, including two who received placebo. In addition, our ALN-TTR01 trial targets a small population of patients suffering from ATTR. Delays or difficulties in patient enrollment or difficulties retaining trial participants 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;
- 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;

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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. For example, we believe that product candidates we develop for HD or other central nervous system diseases may need to be administered using such a device. For neurodegenerative diseases, we have entered into a collaboration agreement with Medtronic to pursue potential development of drug-device combinations incorporating RNAi therapeutics. We may not achieve successful development results under this collaboration and may need to seek other collaborations to develop alternative drug delivery systems, or utilize existing drug delivery systems, for the direct delivery of RNAi therapeutics for these diseases. 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 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.

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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 REMS plan as part of an NDA 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.

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.

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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 post-marketing 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 do not have, and currently do not intend to develop, the ability to manufacture material for our clinical trials or on a 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 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;

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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 coverage and 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.

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; 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.

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;

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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 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, 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 for pharmaceutical products. If the price we are able to charge for any products we develop is inadequate in light of our development and other costs, our profitability could be adversely affected.

We currently expect that any drugs we develop may need to be administered under the supervision of a physician. Under currently applicable U.S. law, drugs that are not usually self-administered may be eligible for coverage by the Medicare 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;

they are not excluded as immunizations; and

they have been approved by the FDA.

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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.

- 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 prior 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 the company s profitability.

The full effects of the U.S. healthcare reform legislation cannot be known until the new law is implemented through regulations or guidance issued by the Centers for Medicare & Medicaid Services and other federal and

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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.

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 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 facility comply with the relevant guidelines of the City of Cambridge and the Commonwealth of Massachusetts. 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.

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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.

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 USPTO may commence interference proceedings involving our patents or patent applications. For example, 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 (which was acquired by Tekmira in 2008), the effect of which called into question the validity and/or enforceability of our patent. The interference proceedings are ongoing. If Protiva is successful in obtaining a dominating claim, we would require a license to Protiva s patent to commercialize ALN-VSP in the United States. 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 was recently enacted into law and 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

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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, 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 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 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

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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 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. For example, on January 17, 2012, we filed a complaint in the U.S. District Court for the District of Massachusetts against Tekmira for patent infringement arising from Tekmira s research activities providing LNP-formulated siRNA molecules to a pharmaceutical collaborator. As alleged in the complaint, we do not believe Tekmira s activities are protected under the exemption from patent infringement for drug development. Pursuant to the complaint, we believe Tekmira has infringed a number of issued patents related to siRNA and LNP technologies, including: U.S. Patent No. 7,695,902; U.S. Patent No. 6,858,225; U.S. Patent No. 6,815,432; U.S. Patent No. 6,534,484; U.S. Patent No. 6,586,410; and U.S. Patent No. 6,858,224. Under our contractual right to enforce U.S. Patent No. 7,695,902 owned by Isis, we joined Isis to the suit as a co-plaintiff. We and Isis are seeking judgment that Tekmira has infringed the patents at issue, a permanent injunction enjoining the infringing activities, damages, and costs and expenses, including attorneys fees.

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 and Protiva filed a civil complaint against us in the Business Litigation Section of the Suffolk County Superior Court, in Boston, Massachusetts, and in June 2011, the plaintiffs filed an amended complaint adding AlCana, a research collaborator of ours, as a defendant. The amended complaint alleges misappropriation of the plaintiffs confidential and proprietary information and trade secrets, civil conspiracy and tortious interference with contractual relationships by us and AlCana, and unjust enrichment, contractual breach, breach of the implied covenant of good faith and fair dealing, unfair competition, false advertising, unfair and deceptive trade practices by us. The plaintiffs seek, among other relief, injunctive relief, unspecified compensatory and punitive damages, attorneys fees, the termination of licenses that the plaintiffs provided to us and the relinquishment and transfer of certain of our intellectual property rights, including patents covering our MC3 technology. In April 2011, we served and filed an answer to the plaintiffs original complaint denying the plaintiffs claims and asserted counterclaims against the plaintiffs. In June 2011, we served and filed an answer to the plaintiffs amended complaint denying the plaintiffs claims and asserted counterclaims against the plaintiffs for breach of contract, defamation, breach of covenant not to sue, breach of patent prosecution and non-use provisions, misappropriation of confidential and proprietary information and trade secrets, unjust enrichment, breach of the implied covenant of good faith and fair dealing, as well as violations of Massachusetts statutes. We are seeking monetary damages, attorneys fees and equitable relief on our counterclaims. In September 2011, the Court granted the plaintiffs motion to dismiss our counterclaim for defamation. The plaintiffs did not move to dismiss any of our other counterclaims, all of which remain pending. The case is currently in discovery and we expect a trial to start in October 2012. We intend to vigorously defend ourselves in this matter. However, litigation is subject to inherent uncertainty and this matter could ultimately be decided against us and we could be required to pay substantial damages. We have also incurred, and will continue to incur during the pendency of the litigation, significant costs, and the defense of this litigation has diverted, and until resolved will continue to divert, the attention of our management and other resources that would otherwise be engaged in other activities.

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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 Forderung 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. 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 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, 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. For example, in connection with its lawsuit against us, Tekmira has alleged that we breached our license agreements with it and Protiva and is seeking that the court terminate such license agreements. If this matter is decided in Tekmira s favor, we could lose access to certain aspects of our LNP delivery technology, including MC3, which would adversely impact certain of our clinical development programs, or be required to pay additional milestones and royalties to Tekmira. In addition, while we cannot currently determine the amount of the royalty obligations we will be required to pay on sales of future products,

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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, severe hypercholesterolemia, refractory anemia, hemoglobinopathies, including beta-thalassemia and sickle-cell anemia, 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.

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;

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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, Arrowhead and its subsidiary, Calando, Tekmira, Quark, Sylentis 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 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 messenger RNAs, or 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 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

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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.

Our Alnylam Biotherapeutics efforts will also face competition from established companies developing and commercializing technology applications to improve the manufacturing processes for drugs. If these companies advance and market their technologies more rapidly than Alnylam Biotherapeutics, we may be unable to establish collaborations for Alnylam Biotherapeutics with established biologic manufacturers, selling licenses, products and services.

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 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.

Novartis ownership of our common stock could delay or prevent a change in corporate control.

At December 31, 2011, Novartis held 13.1% of our outstanding common stock and has the right to maintain its ownership percentage until the earlier of any sale by Novartis of shares of our common stock and the expiration or termination of our collaboration and license agreement, subject to certain exceptions. This concentration of ownership may harm the market price of our common stock by:

- delaying, deferring or preventing a change in control of our company;
- impeding a merger, consolidation, takeover or other business combination involving our company; or
- discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of our company.

Sales of additional shares of our common stock could result in dilution to existing stockholders and 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 others could adversely affect the price of our common stock. Novartis has rights, subject to certain conditions, to require us to file registration statements covering its shares or to include its shares in registration statements that we file. In addition, if Novartis decides to sell a portion of its shares in a rapid or disorderly manner, our stock price could be negatively impacted.

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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
- 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, 2012, 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. 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

Tekmira Litigation

On March 16, 2011, Tekmira and Protiva filed a civil complaint against us in the Business Litigation Section of the Suffolk County Superior Court, in Boston, Massachusetts, and in June 2011, the plaintiffs filed an amended complaint adding AlCana, a research collaborator of ours, as a defendant. The amended complaint alleges misappropriation of the plaintiffs confidential and proprietary information and trade secrets, civil conspiracy, and tortious interference with contractual relationships by us and AlCana, and unjust enrichment, contractual breach, breach of the implied covenant of good faith and fair dealing, unfair competition, false advertising, and unfair and deceptive trade practices by us. The plaintiffs seek, among other relief, injunctive relief, unspecified compensatory and punitive damages, attorneys fees, the termination of licenses that the plaintiffs provided to us and the relinquishment and transfer of certain of our intellectual property, including patents covering our MC3 technology.

On April 6, 2011, we timely served and filed an answer to the plaintiffs original complaint denying the plaintiffs claims, and asserted counterclaims against the plaintiffs. On June 28, 2011, we timely served and filed an answer to the plaintiffs amended complaint denying the plaintiffs claims and asserted counterclaims against the plaintiffs for breach of contract, defamation, breach of covenant not to sue, breach of patent prosecution and non-use provisions, misappropriation of confidential and proprietary information and trade secrets, unjust enrichment, breach of the implied covenant of good faith and fair dealing, as well as violations of Massachusetts statutes. We are seeking monetary damages, attorneys fees and equitable relief on our counterclaims. In September 2011, the Court granted the plaintiffs motion to dismiss our counterclaim for defamation. The plaintiffs did not move to dismiss any of our other counterclaims, all of which remain pending. The case is currently in discovery and we expect a trial to start in October 2012. We intend to vigorously defend ourselves in this matter. However, litigation is subject to inherent uncertainty and this matter could be decided against us and we could be required to pay substantial damages.

We have also incurred, and will continue to incur during the pendency of the litigation, significant costs, and the defense of this litigation has diverted, and until resolved will continue to divert, the attention of our management and other resources that would otherwise be engaged in other activities.

University of Utah Litigation

On March 22, 2011, The University of Utah, or 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

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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, Utah filed a second amended complaint dropping UMass as a defendant and adding as defendants several UMass officials. Although we believe we have meritorious defenses and intend to vigorously defend ourselves 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.

Tekmira Infringement Litigation

On January 17, 2012, we filed a complaint in the United States District Court for the District of Massachusetts against Tekmira for patent infringement arising from Tekmira s research activities providing LNP-formulated siRNA molecules to a pharmaceutical collaborator. As alleged in the complaint, we do not believe Tekmira s activities are protected under the exemption from patent infringement for drug development. Pursuant to the complaint, we believe Tekmira has infringed a number of issued patents related to siRNA and LNP technologies, including: U.S. Patent No. 7,695,902; U.S. Patent No. 6,858,225; U.S. Patent No. 6,815,432; U.S. Patent No. 6,534,484; U.S. Patent No. 6,586,410; and U.S. Patent No. 6,858,224. Under our contractual right to enforce U.S. Patent No. 7,695,902 owned by Isis, we joined Isis to the suit as a co-plaintiff.

We and Isis are seeking judgment that Tekmira has infringed the patents at issue, a permanent injunction enjoining the infringing activities, damages, and costs and expenses, including attorneys fees.

Although we are vigorously asserting our rights in this case, litigation is subject to inherent uncertainty and a court could ultimately rule against us. In addition, litigation is costly and may divert the attention of our management and other resources that would otherwise be engaged in other activities.

Tuschl Settlement

On March 14, 2011, we, Max Planck, Whitehead and UMass entered into a global settlement agreement resolving the ongoing litigation regarding the Tuschl patents. MIT, formerly a party to the litigation, also agreed to the terms of the settlement agreement.

We initiated the litigation against Max Planck, Whitehead, UMass and MIT in June 2009 and the case was scheduled for trial in March 2011 in the United States District Court for the District of Massachusetts in Boston, Massachusetts. The claims related to, among other things, the prosecution of the Tuschl I and Tuschl II patent applications. In the field of RNAi therapeutics, we are the exclusive licensee of the Tuschl I patent applications from Max Planck, MIT and Whitehead, and of the Tuschl II patent applications from Max Planck. The terms of the settlement agreement included mutual releases and dismissal with prejudice of all claims and counterclaims in the litigation between the parties.

As part of the settlement agreement, Max Planck, Whitehead, UMass and MIT agreed that future prosecution of the Tuschl I and Tuschl II patent families in the United States should be coordinated and led by a single party. Max Planck has assumed that role, in addition to their ongoing leadership in the continued prosecution of the Tuschl II patent family outside the United States. UMass will lead future prosecution of the Tuschl I patent family outside the United States. In addition, under the terms of the settlement agreement, we granted UMass the right to sublicense the U.S. Tuschl II patent family to Merck, subject to certain third-party obligations of us and other limitations, in exchange for a share of certain future sublicense income.

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 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 Market for the periods indicated:

Year Ended December 31, 2010:	High	Low
First Quarter	$ 19.29	$ 16.41
Second Quarter	$ 17.59	$ 14.88
Third Quarter	$ 16.36	$ 12.24
Fourth Quarter	$ 13.98	$ 8.79

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

Holders of record

At January 31, 2012, there were 44 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 individual stockholders 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, 2011. 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, 2006, to the close of the last trading day of 2011, 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 Pharmaceuticals Index

	12/29/2006	12/31/2007	12/31/2008	12/31/2009	12/31/2010	12/31/2011
Alnylam Pharmaceuticals, Inc.	$ 100.00	$ 135.89	$ 115.56	$ 82.34	$ 46.07	$ 38.08
NASDAQ Stock Market (U.S.) Index	$ 100.00	$ 108.46	$ 52.27	$ 75.13	$ 89.18	$ 113.82
NASDAQ Pharmaceutical Index	$ 100.00	$ 105.17	$ 97.85	$ 109.95	$ 119.18	$ 127.72

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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, 2011 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,				
	2011	2010	2009	2008	2007
Statement of Operations Data:					
Net revenues from research collaborators	$ 82,757	$ 100,041	$ 100,533	$ 96,163	$ 50,897
Operating expenses(1)	137,575	144,111	148,644	123,998	144,074
Loss from operations	(54,818)	(44,070)	(48,111)	(27,835)	(93,177)
Net loss	(57,649)	(43,515)	(47,590)	(26,249)	(85,466)
Net loss per common share basic and diluted	$ (1.36)	$ (1.04)	$ (1.14)	$ (0.64)	$ (2.21)
Weighted average common shares outstanding basic and diluted	42,410	42,040	41,633	41,077	38,657
(1) Non-cash stock-based compensation expenses included in operating expenses	$ 16,676	$ 19,118	$ 19,727	$ 16,382	$ 14,472

	December 31,				
	2011	2010	2009	2008	2007
Balance Sheet Data:					
Cash, cash equivalents and marketable securities	$ 260,809	$ 349,904	$ 435,316	$ 512,709	$ 455,602
Working capital	71,038	152,093	182,801	343,672	314,427
Total assets	281,917	393,265	481,385	554,676	493,791
Notes payable					6,758
Total stockholders equity	117,997	158,233	177,965	202,125	199,168

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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 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 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 for the treatment of ATTR; ALN-APC for the treatment of hemophilia; ALN-PCS for the treatment of severe hypercholesterolemia; ALN-HPN for the treatment of refractory anemia; and ALN-TMP for the treatment of hemoglobinopathies, including beta-thalassemia and sickle cell anemia. We intend to focus on developing and commercializing ALN-TTR and ALN-APC on our own in the United States and potentially certain other countries, and we intend to enter into alliances to advance our ALN-PCS, ALN-HPN and ALN-TMP 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 three partner-based programs in clinical or pre-clinical development, including ALN-RSV01 for the treatment of RSV, ALN-VSP for the treatment of liver cancers and 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, our Board of Directors approved, and 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 is to align our resources to focus on what we believe to be our highest value opportunities, including a focus on ALN-TTR for the treatment of ATTR and ALN-APC for the treatment of hemophilia as our lead programs, while advancing other pipeline programs through existing alliances and new collaborations. We expect the reduction in personnel costs, along with other external costs, to result in savings of approximately $20.0 million in our 2012 operating expenses. In addition, we estimate that we will incur one-time restructuring charges of approximately $4.0 million, including employee severance, benefits and related costs, the majority of which we expect to incur in the first quarter of 2012. We expect to pay substantially all of the restructuring costs during 2012, and we expect to substantially complete the workforce reduction by the end of the first quarter of 2012.

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

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revenues to continue to be derived primarily from existing alliances, new strategic alliances, new government and foundation funding, and existing and new license fee revenues.

We have incurred significant losses since we commenced operations in 2002 and expect such losses to continue for the foreseeable future. At December 31, 2011, we had an accumulated deficit of $401.0 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. Our sources of potential funding for the next several years are expected 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 July 2011, we filed a shelf registration statement with the SEC for an indeterminate number of shares of common stock and/or other securities, up to an aggregate of $150.0 million, for future issuance.

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.

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;

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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 pharmaceutical and biotechnology 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 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, 2012, 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 seek funding for the development of our proprietary RNAi therapeutics pipeline from the government and foundations. For example, in 2010, we completed a contract awarded to us by the NIAID to advance the development of a broad spectrum RNAi anti-viral therapeutic against hemorrhagic fever virus, including the Ebola virus.

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

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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 biotechnology and pharmaceutical companies for the development and commercialization of our product candidates. 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, 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 stand-alone 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. We did not enter into any significant multiple element arrangements or materially modify any of our existing multiple element arrangements during the year ended December 31, 2011. Our existing license and collaboration agreements continue to be accounted for 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 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 stand-alone 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 stand-alone value or have stand-alone 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 substantive 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.

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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. 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 involve substantial effort on our part and the achievement of which are not considered probable at the inception of the collaboration are considered substantive milestones. Substantive milestones are included in our revenue model when achievement of the milestone is considered probable. As future substantive milestones are achieved, 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, will be recognized as revenue upon achievement of such milestone. The remaining portion of the milestone will be recognized over the remaining performance period using the proportional performance or straight-line method. 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.

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 operations based on the nature of the underlying activity. Transactions between collaborators recorded in our consolidated statements of operations 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

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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, 2011, we had short-term and long-term deferred revenue of $62.4 million and $78.5 million, respectively, related to our collaborations.

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

Novartis. In consideration for rights granted to Novartis under the collaboration and license agreement, Novartis made an upfront payment of $10.0 million to us in October 2005. The collaboration and license agreement also included terms under which Novartis provided us with research funding. In addition, for RNAi therapeutic products developed under the agreement, if any, 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. We initially recorded as deferred revenue the non-refundable $10.0 million upfront payment and the $6.4 million premium paid on our common stock initially purchased by Novartis. These payments, in addition to research funding and certain milestone payments, together total approximately $64.0 million, and are being amortized into revenue using the proportional performance method over ten years. Under this method, we estimate the level of effort to be expended over the term of the agreement and recognize revenue based on the lesser of the amount calculated based on the proportional performance of total expected revenue or the amount of non-refundable payments earned.

We believe our estimated period of performance under the Novartis 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. We continue to use an expected term of ten years in our proportional performance model. We reevaluate the expected term when new information is known that could affect our estimate. In the event our period of performance is different than we estimated, we will adjust the amount of revenue recognized on a prospective basis. At December 31, 2011, deferred revenue under the Novartis collaboration and license agreement was $0.2 million.

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. In November 2010, Roche announced the discontinuation of certain activities in research and early development, including its RNAi research efforts. The remaining deliverables under the license and collaboration agreement currently remain in effect. 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 now has all of the rights and obligations of Roche under that agreement. 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. The license is initially limited to four therapeutic areas, and may be expanded to include other therapeutic areas upon payment to us by Arrowhead of an additional $50.0 million for each additional therapeutic area, if any. 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.

We have determined that the deliverables under our agreements with Arrowhead include 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 have 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

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collaboration) and, accordingly, the license and the 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 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 will end, contractually, five years from the effective date of the license and collaboration agreement. We are recognizing the Arrowhead-related revenue on a straight-line basis over five years because we cannot reasonably estimate the total level of effort required to complete our service obligations under the license and collaboration agreement and therefore, cannot utilize a proportional performance model. At December 31, 2011, deferred revenue under the Arrowhead license and collaboration agreement was $37.3 million.

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 and commercialization milestones, totaling up to $171.0 million per product, together with royalty payments based on worldwide annual net sales, if any.

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. 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, 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 program. 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 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 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. At December 31, 2011, deferred revenue under the Takeda agreement was $74.8 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 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.

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. 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

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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.

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, 2011, deferred revenue under the Kyowa Hakko Kirin agreement was $15.5 million.

Cubist. Under the terms of the Cubist agreement, we and Cubist share responsibility for developing licensed products in North America and each bears 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 is governed by a joint steering committee comprised of an equal number of representatives from each party. Cubist will have 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. Throughout the rest of the world, referred to as the Royalty Territory, excluding Asia, where we have previously partnered our ALN-RSV program with Kyowa Hakko Kirin, Cubist has an exclusive, royalty-bearing license to develop and commercialize licensed products.

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. Cubist also has an obligation under the agreement to pay us milestone payments, totaling up to an aggregate of $82.5 million, upon the achievement of specified development and sales events in the Royalty Territory. In addition, if licensed products are successfully developed, Cubist will be required to pay us double digit royalties on net sales of licensed products in the Royalty Territory, if any, subject to offsets under certain circumstances. Upon achievement of certain development milestones, we will have the right to convert the North American co-development and profit sharing arrangement into a royalty-bearing license and, in addition to royalties on net sales in North America, if any, will be entitled to receive additional milestone payments totaling up to an aggregate of $130.0 million upon achievement of specified development and sales events in North America, subject to the timing of the conversion by us and the regulatory status of a licensed product at the time of conversion. If we make the conversion to a royalty-bearing license with respect to North America, then North America becomes part of the Royalty Territory.

We have determined that the deliverables under the Cubist agreement include the licenses, technology transfer related to the ALN-RSV program, the joint steering committee and the development and manufacturing services that we are obligated to perform during the development period. We have determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the licenses and undelivered services are not separable and, accordingly, the licenses and services are being treated as a single unit of accounting. Under the Cubist agreement, the last element to be delivered is the development and manufacturing services, which have an expected life of approximately eight years. We are recognizing the upfront payment of $20.0 million on a straight-line basis over approximately eight years because we are unable to reasonably estimate the level of effort to fulfill our performance obligations and therefore, cannot utilize a proportional performance model. As future substantive 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. We will recognize the remaining portion of the milestone over the remaining performance period on a straight-line basis. At December 31, 2011, deferred revenue under the Cubist agreement was $12.5 million.

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Under the terms of the Cubist agreement, we and Cubist share responsibility for developing licensed products in North America and each bears one-half of the related development costs, provided that under the terms of the November 2009 amendment, we are funding the advancement of ALN-RSV01 for adult lung transplant patients and Cubist retains an opt-in right. In December 2010, we and Cubist jointly made a portfolio decision to put the development of ALN-RSV02 on hold.

For revenue generating arrangements that involve cost sharing between both parties, we present the results of activities for which we act as the principal on a gross basis and report any payments received from, or made to, other collaborators based on other applicable GAAP, or, in the absence of other applicable GAAP, analogy to authoritative accounting literature or a reasonable, rational and consistently applied accounting policy election. As we are not considered the principal under the Cubist agreement, we record any amounts due from Cubist as a reduction of research and development expense.

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

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, 2011, 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, 2011, we had $0.1 million of total gross 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 operations, 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 years ended December 31, 2011, 2010 and 2009, we recorded a provision for income taxes of zero, $0.5 million and $0.6 million, respectively. We were subject to federal alternative minimum tax and state income taxes in 2009 and 2008. We generated U.S. taxable income during 2009 and 2008 due to the recognition of certain proceeds received from the Roche and Takeda alliances. During 2010, we generated sufficient net operating losses to carry back to 2008 and 2009 to obtain a refund of taxes paid in those years, resulting in a realization of our net deferred tax asset. As a result, we received an income tax refund of $10.7 million in 2011.

At December 31, 2011, 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, 2011, we had federal and state net operating loss carryforwards of $129.8 million and $194.9 million, respectively, to reduce future taxable income that will expire at various dates through 2031. At December 31, 2011, we had federal and state research and development credit carryforwards of $11.1 million and $4.3 million, respectively, available to reduce future tax liabilities that expire at various dates through 2031. At December 31, 2011, we had foreign tax credit carryforwards of $3.2 million available to reduce future tax liabilities that expire in 2017. At December 31, 2011, 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

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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 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 there is no limitation on the utilization of net operating loss and tax credit carryforwards in accordance with Section 382 of the Internal Revenue Code in 2011.

Accounting for Stock-Based Compensation

We account for all stock-based awards granted to non-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, 2011, we used a weighted-average expected stock-price volatility assumption of 56%. Our expected life assumption is based on our historical data. Our weighted average expected term was 5.9 years for the year ended December 31, 2011. 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.

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, 2011, the estimated fair value of unvested employee awards was $18.3 million, net of estimated forfeitures. We will recognize this amount over the weighted average remaining vesting period of approximately 2.6 years for these awards. Stock-based employee compensation expense was $16.3 million for the year ended December 31, 2011. 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 71% of our stock options will actually vest, and therefore have applied an annual forfeiture rate of 8.1% to all unvested stock options at December 31, 2011. Ultimately, the actual expense recognized over the vesting period will only be for those shares that vest.

Accounting for Joint Venture

We account 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 currently qualifies as a VIE. We record any gain or loss recognized from the issuance of stock by our equity method investee as other income (expense) in our consolidated statements of operations. We do not consolidate Regulus financial results as we lack the power to direct the activities that could significantly impact the economic success of Regulus. Under equity method accounting, because we have guaranteed the debt of Regulus, we will be required to continue to recognize our share of any future losses which could result in the carrying value of our investment in Regulus being reduced below zero, up to a maximum negative carrying value equivalent to the amount of debt we have guaranteed. We would suspend recording our portion of Regulus losses at such time and would resume equity method accounting only after our share of net income, if any, equals the share of net losses not recognized.

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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 amounts.

Results of Operations

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

	Year Ended December 31,		
	2011	**2010**	**2009**
Net revenues from research collaborators	$ 82,757	$ 100,041	$ 100,533
Operating expenses	137,575	144,111	148,644
Loss from operations	(54,818)	(44,070)	(48,111)
Net loss	$ (57,649)	$ (43,515)	$ (47,590)

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

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 NIAID 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.

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We also had $140.9 million of deferred revenue at December 31, 2011, which consists of payments we have received from collaborators, primarily Roche/Arrowhead, Takeda, Kyowa Hakko Kirin and Cubist, 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 Roche/Arrowhead, Takeda and Cubist, and other strategic alliances, as well as new collaborations, foundation funding, government contracts and licensing activities. We expect our Roche/Arrowhead revenues to decrease during 2012 to $37.3 million, as we complete our remaining performance obligations under this agreement in 2012.

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 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.

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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. However, we expect that research and development expenses will decrease in 2012 primarily as a result of our January 2012 strategic corporate restructuring.

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 in the early stages of 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:

	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. We expect that general and administrative expenses will decrease slightly in 2012.

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 marketable securities balances.

Other expense was $0.5 million in 2011 and was due primarily to an impairment charge related to our investment in Tekmira equity securities, as the decrease in the fair value of this investment was deemed to be

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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.

Discussion of Results of Operations for 2010 and 2009

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,	
	2010	2009
Roche	$ 55,978	$ 56,884
Takeda	22,250	21,732
Novartis	9,313	9,811
Government contract	4,335	7,471
Other research collaborator	5,159	3,593
InterfeRx program, research reagent license and other	3,006	1,042
Total net revenues from research collaborators	$ 100,041	$ 100,533

Revenues remained relatively consistent for the year ended December 31, 2010 as compared to the year ended December 31, 2009. Under the Roche alliance, we are recognizing revenue on a straight-line basis over five years, which equates to approximately $14.0 million per quarter. Revenues under the Roche alliance in 2009 also included the achievement of a development milestone. Under the Takeda alliance, we are recognizing revenue on a straight-line basis over seven years, which equates to approximately $5.4 million per quarter.

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. Novartis declined to exercise its non-exclusive option to integrate into its operations our fundamental and chemistry intellectual property under the terms of the collaboration and license agreement. If Novartis had elected to exercise this option, Novartis would have been required to make additional payments to us totaling $100.0 million. At December 31, 2010, deferred revenue under the Novartis collaboration and license agreement was $0.4 million.

For the year ended December 31, 2010 as compared to the year ended December 31, 2009, government contract revenues decreased primarily as a result of a decrease in the research and development activities related to our contract with the NIAID. This contract was originally expected to be completed in September 2010. We and the NIAID agreed to a no-cost extension of the contract through December 2010 during which time we utilized the funds remaining under the contract.

Other research collaborator revenues increased in the year ended December 31, 2010 as compared to the year ended December 31, 2009 primarily as a result of the $1.9 million sublicense fee recognized in connection with Regulus June 2010 alliance with Sanofi, representing 7.5% of the $25.0 million upfront payment from Sanofi to Regulus.

The increase in InterfeRx program, research reagent license and other revenues for the year ended December 31, 2010 as compared to the year ended December 31, 2009 was primarily a result of progress and milestones achieved related to our InterfeRx and other programs.

We had $211.1 million of deferred revenue at December 31, 2010, which consisted of payments we had received from collaborators, primarily Roche, Takeda, Kyowa Hakko Kirin and Cubist, that we had yet to recognize pursuant to our revenue recognition policies.

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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:

	2010	% of Total Operating Expenses	2009	% of Total Operating Expenses	Decrease $	Decrease %
Research and development	$ 106,384	74%	$ 108,730	73%	$ (2,346)	(2)%
General and administrative	37,727	26%	39,914	27%	(2,187)	(5)%
Total operating expenses	$ 144,111	100%	$ 148,644	100%	$ (4,533)	(3)%

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:

	2010	% of Expense Category	2009	% of Expense Category	Increase (Decrease) $	Increase (Decrease) %
Research and development						
Compensation and related	$ 24,053	23%	$ 21,632	20%	$ 2,421	11%
External services	22,471	21%	20,642	19%	1,829	9%
Clinical trial and manufacturing	20,607	20%	18,880	17%	1,727	9%
Facilities-related	12,051	11%	11,612	11%	439	4%
Non-cash stock-based compensation	11,689	11%	11,415	10%	274	2%
Lab supplies and materials	7,775	7%	8,106	7%	(331)	(4)%
License fees	2,407	2%	13,632	13%	(11,225)	(82)%
Restructuring	1,863	2%			1,863	100%
Other	3,468	3%	2,811	3%	657	23%
Total research and development expenses	$ 106,384	100%	$ 108,730	100%	$ (2,346)	(2)%

Research and development expenses decreased slightly during the year ended December 31, 2010 as compared to the year ended December 31, 2009 due primarily to license fees paid to Isis in April 2009 in connection with the ssRNAi collaborative effort with Isis, which we terminated in November 2010. This decrease was partially offset by restructuring expenses related to employee severance, benefits and related costs incurred in connection with our corporate restructuring, which was implemented at the end of September 2010 and included an approximate 25% workforce reduction. In addition, prior to our corporate restructuring, there were higher compensation and related expenses during 2010 as compared to 2009 due to higher average research and development headcount to support our technology platform and expanding product pipeline.

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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:

	2010	% of Expense Category	2009	% of Expense Category	Increase (Decrease) $	Increase (Decrease) %
General and administrative						
Consulting and professional services	$ 18,753	50%	$ 19,903	50%	$ (1,150)	(6)%
Non-cash stock-based compensation	7,429	20%	8,312	21%	(883)	(11)%
Compensation and related	6,202	16%	6,383	16%	(181)	(3)%
Facilities-related	2,379	6%	2,634	7%	(255)	(10)%
Insurance	759	2%	747	2%	12	2%
Restructuring	330	1%			330	100%
Other	1,875	5%	1,935	4%	(60)	(3)%
Total general and administrative expenses	$ 37,727	100%	$ 39,914	100%	$ (2,187)	(5)%

The decrease in general and administrative expenses during the year ended December 31, 2010 as compared to the year ended December 31, 2009 was due primarily to lower 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 $7.6 million equity in loss of joint venture (Regulus Therapeutics Inc.) for the year ended December 31, 2010 as compared to $4.9 million for the year ended December 31, 2009 related to our share of the net losses incurred by Regulus. The increase in equity in loss of joint venture (Regulus Therapeutics Inc.) for the year ended December 31, 2010 was due primarily to sublicense fees paid in connection with the strategic alliance formed by Regulus with Sanofi in June 2010.

Interest income was $2.3 million in 2010 as compared to $5.4 million in 2009. The decrease in 2010 was due primarily to lower average interest rates as well as lower average cash, cash equivalent and marketable securities balances.

Other income was $6.4 million in 2010 as compared to $0.6 million in 2009. Other income in 2010 consisted of 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. Other income in 2009 consisted primarily of realized gains on sales of marketable securities.

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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,		
	2011	2010	2009
Net loss	$ (57,649)	$ (43,515)	$ (47,590)
Adjustments to reconcile net loss to net cash provided by operating activities	26,509	38,734	25,857
Changes in operating assets and liabilities	(55,928)	(79,560)	(50,412)
Net cash used in operating activities	(87,068)	(84,341)	(72,145)
Net cash provided by investing activities	81,959	17,838	14,433
Net cash provided by financing activities	738	3,663	3,509
Effect of exchange rate on cash		(29)	(121)
Net decrease in cash and cash equivalents	(4,371)	(62,869)	(54,324)
Cash and cash equivalents, beginning of period	74,599	137,468	191,792
Cash and cash equivalents, end of period	$ 70,228	$ 74,599	$ 137,468

Since we commenced operations in 2002, we have generated significant losses. At December 31, 2011, we had an accumulated deficit of $401.0 million. At December 31, 2011, we had cash, cash equivalents and marketable securities of $260.8 million, compared to cash, cash equivalents and marketable securities of $349.9 million at December 31, 2010. 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, 2011. During 2011, we recorded an impairment charge of $0.6 million related to our investment in Tekmira equity securities, as the decrease in the fair value of this investment was deemed to be other than temporary.

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, 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 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. We had a decrease in deferred revenue of $58.2 million for year ended December 31, 2009, partially offset by an increase in accounts payable of $9.9 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.

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Investing activities

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 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 marketable securities of $22.5 million, offset by purchases of property and equipment of $4.7 million. For the year ended December 31, 2009, net cash provided by investing activities of $14.4 million resulted primarily from net sales and maturities of marketable securities of $23.2 million and a decrease in restricted cash of $6.2 million resulting from the release of letters of credit in connection with the amendment of our facility lease and the termination of our sublease agreement. Offsetting these amounts was a $10.0 million investment in Regulus and purchases of property and equipment of $4.9 million.

Financing activities

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, primarily to employees. 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, primarily to employees. For the year ended December 31, 2009, net cash provided by financing activities of $3.5 million was due to proceeds of $1.2 million from our issuance of common stock to Novartis in May 2009, as well as proceeds of $2.4 million from the issuance of common stock, primarily to employees.

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. Based on our current operating plan, we believe that our existing cash, cash equivalents and fixed income marketable securities, for which we have not recognized any impairment charges, 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 2013. 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 July 2011, we filed a shelf registration statement with the SEC for an indeterminate number of shares of common stock and/or other securities, for up to an aggregate of $150.0 million, for future issuance. During the current downturn in global financial markets, some companies have experienced difficulties accessing their cash equivalents and investment securities and raising capital generally, which have had a material adverse impact on their liquidity. The current 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 financing may 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.

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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 current and 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 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 these indemnification agreements 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. 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 Tuschl and 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.

In April 2008, Regulus formed a collaboration with GSK pursuant to which GSK provided Regulus with a loan for $5.0 million, plus interest. In February 2010, Regulus formed an additional collaboration with GSK pursuant to which GSK provided Regulus with an additional $5.0 million loan, plus interest. These loans are guaranteed equally by us and Isis. If Regulus is unable to repay GSK or convert the loans into Regulus common stock, we could be liable for our share of these obligations.

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See Notes 7 and 12 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, 2011, as well as obligations related to contracts that we are likely to continue, regardless of the fact that they were cancelable at December 31, 2011. 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	**2012**	**2013 and 2014**	**2015 and 2016**	**After 2016**	**Total**
Operating lease obligations(1)	$ 5,361	$ 11,374	$ 10,687	$	$ 27,422
Purchase commitments(2)	$ 12,153	$ 468	$ 36	$	$ 12,657
Technology license commitments(3)	$ 2,599	$ 2,186	$ 1,446	$ 7,953	$ 14,184
Total contractual cash obligations	$ 20,113	$ 14,028	$ 12,169	$ 7,953	$ 54,263

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

(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 and regulatory 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 new standard is effective on a prospective basis for annual and interim reporting periods beginning on or after December 15, 2011. We do not expect that adoption of this new standard will 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 is not expected to 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 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, 2011, the net fair value of our interest-sensitive financial instruments would have resulted in a hypothetical decline of $1.0 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, 2011.

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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, 2011. 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, 2011, 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, 2011 has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in their report. This report appears on page 98.

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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, 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, 2011 and 2010, and the results of their operations and their cash flows for each of the three years in the period ended December 31, 2011 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, 2011, 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 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 financial statements of Regulus Therapeutics Inc., an approximate 45 percent-owned equity investment, which were audited by other auditors whose report thereon has been furnished to us. Our opinion expressed herein, insofar as it relates to the Company s net investment in (approximately $0.6 million and $3.6 million at December 31, 2011 and 2010, respectively) and equity in the net loss (approximately $3.5 million, $7.6 million and $4.9 million for the years ended December 31, 2011, 2010 and 2009, respectively) of 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 10, 2012

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ALNYLAM PHARMACEUTICALS, INC.

CONSOLIDATED BALANCE SHEETS

(In thousands, except share and per share amounts)

	December 31, 2011	2010
ASSETS		
Current assets:		
Cash and cash equivalents	$ 70,228	$ 74,599
Marketable securities	76,174	158,532
Billed and unbilled collaboration receivables	1,468	3,450
Income taxes receivable		10,669
Prepaid expenses and other current assets	4,158	6,889
Total current assets	152,028	254,139
Marketable securities	114,407	116,773
Property and equipment, net	14,643	18,289
Investment in joint venture (Regulus Therapeutics Inc.)	564	3,616
Intangible assets, net	275	448
Total assets	$ 281,917	$ 393,265
LIABILITIES AND STOCKHOLDERS EQUITY		
Current liabilities:		
Accounts payable	$ 5,800	$ 9,312
Accrued expenses	12,340	11,116
Deferred rent	484	484
Deferred revenue	62,366	81,134
Total current liabilities	80,990	102,046
Deferred rent, net of current portion	3,727	2,869
Deferred revenue, net of current portion	78,487	129,974
Other long-term liabilities	716	143
Total liabilities	163,920	235,032
Commitments and contingencies (Notes 7, 10, 12 and 14)		
Stockholders equity:		
Preferred stock, $0.01 par value per share, 5,000,000 shares authorized and no shares issued and outstanding at December 31, 2011 and 2010		
Common stock, $0.01 par value per share, 125,000,000 shares authorized; 42,721,942 shares issued and outstanding at December 31, 2011; 42,343,423 shares issued and outstanding at December 31, 2010	427	423
Additional paid-in capital	518,731	500,443
Accumulated other comprehensive (loss) income	(165)	714
Accumulated deficit	(400,996)	(343,347)
Total stockholders equity	117,997	158,233
Total liabilities and stockholders equity	$ 281,917	$ 393,265

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

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ALNYLAM PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

(In thousands, except per share amounts)

	Year Ended December 31,		
	2011	**2010**	**2009**
Net revenues from research collaborators	$ 82,757	$ 100,041	$ 100,533
Operating expenses:			
Research and development(1)	99,295	106,384	108,730
General and administrative(1)	38,280	37,727	39,914
Total operating expenses	137,575	144,111	148,644
Loss from operations	(54,818)	(44,070)	(48,111)
Other income (expense):			
Equity in loss of joint venture (Regulus Therapeutics Inc.)	(3,505)	(7,639)	(4,910)
Interest income	1,205	2,305	5,385
Other (expense) income	(531)	6,403	628
Total other income (expense)	(2,831)	1,069	1,103
Loss before income taxes	(57,649)	(43,001)	(47,008)
Provision for income taxes		(514)	(582)
Net loss	$ (57,649)	$ (43,515)	$ (47,590)
Net loss per common share basic and diluted	$ (1.36)	$ (1.04)	$ (1.14)
Weighted average common shares used to compute basic and diluted net loss per common share	42,410	42,040	41,633
Comprehensive loss:			
Net loss	$ (57,649)	$ (43,515)	$ (47,590)
Foreign currency translation		(29)	(121)
Unrealized (loss) gain on marketable securities	(879)	27	(349)
Comprehensive loss	$ (58,528)	$ (43,517)	$ (48,060)

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

Research and development	$ 10,921	$ 11,689	$ 11,415
General and administrative	5,755	7,429	8,312

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, 2008	41,413,828	$ 414	$ 452,767	$ 1,186	$ (252,242)	$ 202,125
Exercise of common stock options	275,908	3	1,459			1,462
Issuance of common stock	147,691	1	2,507			2,508
Stock-based compensation expense			19,727			19,727
Foreign currency translation				(121)		(121)
Joint venture stock-based compensation (Regulus Therapeutics Inc.)			(238)			(238)
Tax benefit from stock-based compensation			441			441
Unrealized loss on marketable securities				(349)		(349)
Net loss					(47,590)	(47,590)
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	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
Unrealized gain on marketable securities				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	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
Unrealized loss on marketable securities				(879)		(879)
Net loss					(57,649)	(57,649)
Balance at December 31, 2011	42,721,942	$ 427	$ 518,731	$ (165)	$ (400,996)	$ 117,997

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,		
	2011	**2010**	**2009**
Cash flows from operating activities:			
Net loss	$ (57,649)	$ (43,515)	$ (47,590)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:			
Depreciation and amortization	5,125	4,941	5,992
Deferred income taxes		10,742	(5,163)
Non-cash stock-based compensation	16,676	19,118	19,727
Charge for 401(k) company stock match	488	495	461
Equity in loss of joint venture (Regulus Therapeutics Inc.)	3,505	7,639	4,910
Tax benefit from stock-based compensation	120	220	441
Other than temporary impairment on equity securities	595		
Realized gain on sale of marketable securities			(511)
Gain on issuance of stock by joint venture		(4,421)	
Changes in operating assets and liabilities:			
Billed and unbilled collaboration receivables	1,982	2,594	(1,856)
Income taxes receivable	10,669	(10,669)	
Prepaid expenses and other assets	2,731	(2,738)	523
Accounts payable	(3,512)	(3,177)	9,901
Income taxes payable		(5,516)	(467)
Accrued expenses and other	2,457	651	(341)
Deferred revenue	(70,255)	(60,705)	(58,172)
Net cash used in operating activities	(87,068)	(84,341)	(72,145)
Cash flows from investing activities:			
Purchases of property and equipment	(1,291)	(4,732)	(4,949)
Decrease in restricted cash			6,151
Purchases of marketable securities	(293,115)	(390,473)	(481,339)
Sales and maturities of marketable securities	376,365	413,043	504,570
Investment in joint venture (Regulus Therapeutics Inc.)			(10,000)
Net cash provided by investing activities	81,959	17,838	14,433
Cash flows from financing activities:			
Proceeds from issuance of common stock	738	2,670	2,355
Proceeds from issuance of shares to Novartis		993	1,154
Net cash provided by financing activities	738	3,663	3,509
Effect of exchange rate on cash		(29)	(121)
Net decrease in cash and cash equivalents	(4,371)	(62,869)	(54,324)
Cash and cash equivalents, beginning of period	74,599	137,468	191,792
Cash and cash equivalents, end of period	$ 70,228	$ 74,599	$ 137,468
Supplemental disclosure of cash flows:			
Net proceeds from income tax refunds (cash paid for income taxes)	$ 10,657	$ (5,767)	$ (5,836)

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 biotechnology 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 five entities, Alnylam Pharmaceuticals, Inc. (the parent company) and four wholly-owned subsidiaries (Alnylam U.S., Inc., Alnylam Europe AG (Alnylam Europe), Alnylam Securities Corporation and Meltemi Biotherapeutics, Inc.). 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. Meltemi Biotherapeutics, Inc. is a Delaware corporation that was formed on September 27, 2011. 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. The Company uses the equity method of accounting to account for its investment in Regulus Therapeutics Inc., formerly Regulus Therapeutics LLC (Regulus).

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 marketable securities. At December 31, 2011 and 2010, substantially all of the Company s cash, cash equivalents and 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). Novartis owned approximately 13.1% of the Company s outstanding common stock at December 31, 2011. The Company has also generated revenues from Cubist Pharmaceuticals, Inc. (Cubist). In addition, the Company and Medtronic,

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ALNYLAM PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

Inc. (Medtronic) have 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 has agreed to initially fund approximately 50% of the costs of this program up to the point at which an investigational new drug application can be filed with the United States Food and Drug Administration or a comparable foreign regulatory filing can be made. The Company is recording this funding as a reduction to research and development expense.

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,		
	2011	2010	2009
Roche/Arrowhead	68%	56%	57%
Takeda	27%	22%	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 December 31,	
	2011	2010
CHDI	51%	44%
GSK	20%	*
Medtronic	13%	*
Takeda	*	27%

* Represents 10% or less

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, 2011 and 2010, 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:

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ALNYLAM PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

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	$

Description	At December 31, 2010	Quoted Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents	$ 59,702	$ 40,686	$ 19,016	$
Marketable securities (fixed income):				
Corporate notes	133,341		133,341	
U.S. Government obligations	122,273		122,273	
Commercial paper	17,733		17,733	
Marketable securities (equity holdings)	1,958		1,958	
Total	$ 335,007	$ 40,686	$ 294,321	$

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 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 operations. The Company did not record any impairment charges related to its fixed income marketable securities during the years ended December 31, 2011, 2010 or 2009. During 2011, the Company recorded an impairment charge of $0.6 million related to its investment in equity securities of Tekmira Pharmaceuticals Corporation (Tekmira), 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

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ALNYLAM PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

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.

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.

The following tables summarize the Company s marketable securities at December 31, 2011 and 2010, in thousands:

	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

	December 31, 2010
	Amortized Cost