

ALNYLAM PHARMACEUTICALS, INC.

Form 10-K

February 13, 2015

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UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2014

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 001-36407

ALNYLAM PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware

(State or Other Jurisdiction of

Incorporation or Organization)

77-0602661

(I.R.S.

Employer

*Identification
No.)*

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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 Select 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 ☒

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 ☒

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 ☐ 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 ☐ No ☒

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

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

Large accelerated filer ☐ Accelerated filer ☐ Non-accelerated filer ☒ Smaller reporting company ☐
(Do not check if a smaller reporting company)

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

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, 2014, was \$4,772,901,068. For the purpose of the foregoing calculation only, all directors and executive officers of the registrant are assumed to be affiliates of the registrant.

At January 30, 2015, the registrant had 83,760,143 shares of Common Stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2015 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, 2014, 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, 2014

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

PART I

ITEM 1. BUSINESS

Overview

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

Our research and development strategy is focused primarily on use of our proprietary N-acetylgalactosamine, or GalNAc-conjugate strategy for delivery of small interfering RNAs, or siRNAs—the molecules that mediate RNAi—toward liver-expressed genes involved in the cause or pathway of human diseases. We are also focused on clinical indications where there are high unmet medical needs, early biomarkers for the assessment of clinical activity in Phase 1 clinical studies, and a definable path for drug development, regulatory approval and commercialization.

Specifically, our pipeline of investigational RNAi therapeutics is focused in three Strategic Therapeutic Areas, or STArS: Genetic Medicines, with a broad pipeline of RNAi therapeutics for the treatment of rare diseases; Cardio-Metabolic Disease, with a pipeline of RNAi therapeutics toward genetically validated, liver-expressed disease targets for unmet needs in cardiovascular and metabolic diseases, such as dyslipidemia, hypertension, non-alcoholic steatohepatitis, or NASH, and type 2 diabetes; and Hepatic Infectious Disease, with a pipeline of RNAi therapeutics designed to address the major global health challenges of hepatic infectious diseases. In early 2015, we launched our Alnylam 2020 guidance for the advancement and commercialization of RNAi therapeutics as a whole new class of innovative medicines. Specifically, by the end of 2020, we expect to achieve a company profile with three marketed products and ten RNAi therapeutic clinical programs, including four in late stages of development, across our three STArS.

Based on our expertise in RNAi therapeutics and broad intellectual property estate we have formed alliances with leading pharmaceutical and life sciences companies, including Isis Pharmaceuticals, Inc., or Isis, Medtronic, Inc., or Medtronic, Novartis Pharma AG, or Novartis, F. Hoffmann-La Roche Ltd, or Roche (which assigned its rights and obligations to Arrowhead Research Corporation, or Arrowhead), Takeda Pharmaceutical Company Limited, or Takeda, Kyowa Hakko Kirin Co., Ltd., or Kyowa Hakko Kirin, Cubist Pharmaceuticals, Inc., or Cubist, Ascleptis BioScience Co., Ltd., or Ascleptis, Monsanto Company, or Monsanto, Genzyme Corporation, a Sanofi company, or Genzyme, and The Medicines Company, or MDCO. We also have established collaborations with and, in some instances, received funding from, major medical and disease associations. Finally, to further

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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.

Recent Developments

Public Offering

In January 2015, we sold an aggregate of 5,447,368 shares of our common stock through an underwritten public offering at a price to the public of \$95.00 per share. As a result of the offering, which included the full exercise of the underwriters' option to purchase additional shares, we received aggregate net proceeds of approximately \$496.4 million. We intend to use these proceeds for general corporate purposes, focused on achieving our Alnylam 2020 profile with three marketed products and ten RNAi therapeutic clinical programs, including four in late stages of development, across our three STArS, by the end of 2020.

Genzyme Stock Purchases

In January 2015, in connection with our public offering described above, Genzyme exercised its right under our investor agreement with Genzyme to purchase directly from us, in concurrent private placements, 744,566 shares of common stock, at the public offering price of \$95.00 per share, resulting in proceeds to us of approximately \$70.7 million. The sales of common stock to Genzyme were not registered as part of the public offering, though they were consummated simultaneously with the public offering.

Under the investor agreement, Genzyme also has the right each January to purchase a number of shares of our common stock based on the number of shares we issued during the previous year for compensatory purposes. Genzyme exercised this right to purchase directly from us 196,251 shares of our common stock on January 22, 2015 for approximately \$18.3 million. The sale of these shares to Genzyme was consummated as a private placement.

In each instance, the purchase by Genzyme described above allowed Genzyme to maintain its ownership level of our common stock of approximately 12%.

Isis Agreement

In January 2015, we and Isis entered into a second amended and restated strategic collaboration and license agreement. The 2015 Isis agreement provides for certain new exclusive target cross-licenses of intellectual property on four disease targets, providing each company with exclusive RNA therapeutic license rights for two programs, and extends the parties' existing non-exclusive technology cross-license, which was originally entered into in 2004 and was amended and restated in 2009, through April 2019. The 2015 Isis agreement is described below under the heading Strategic Alliances.

RNA Interference and Opportunity for RNAi Therapeutics

RNAi is a natural biological pathway that occurs within cells 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.

RNAi therapeutics harness the natural RNAi pathway to silence disease-associated genes and knock down production of disease-causing proteins. RNAi therapeutics represent an opportunity to create a whole new class of innovative medicines. This potential new drug class is similar to the opportunity created with other major biological discoveries such as recombinant DNA and monoclonal antibodies. Specifically, RNAi therapeutics achieve their biological effects through a highly potent, catalytic mechanism. Further, RNAi therapeutics have the potential to silence any disease-associated gene, including so-called "undruggable" targets, where conventional therapeutic modalities (e.g., small molecule drugs and biologics) have not been successful.

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RNAi therapeutics also have a distinct mechanism of action, acting upstream of today's medicines. Finally, as a reproducible and modular approach for drug discovery and development, RNAi therapeutics represent a simplified and efficient approach for new medicines.

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

Delivery of RNAi Therapeutics

In the early years of developing RNAi therapeutics, a challenge to the promise of RNAi as a therapeutic modality was delivery, i.e., getting the siRNA into the right body organs and cells so that it could trigger the RNAi mechanism. In recent years, a tremendous amount of progress has been made, and we believe Alnylam has been a leader of this advancement. This delivery success is now enabling execution on our product strategy.

Early efforts focused on delivery of RNAi therapeutics utilizing lipid nanoparticles, or LNPs, where siRNA molecules are encapsulated in specific lipid-based formulations. This technology enables systemic delivery with intravenous drug administration. Results with LNP-based investigational RNAi therapeutics demonstrate potent, rapid and durable target gene silencing in pre-clinical and clinical studies. Further, LNP-based investigational RNAi therapeutics have been found to be generally well tolerated in clinical studies conducted to date.

More recently, we began advancing proprietary technology that conjugates a sugar molecule called GalNAc to the siRNA molecule. This simpler delivery approach enables more convenient, subcutaneous administration of our drug candidates. Recent findings from our Enhanced Stabilization Chemistry (ESC)-GalNAc-conjugate delivery platform demonstrated a substantial increase in potency over our earlier standard template chemistry (STC)-GalNAc-conjugate approach in pre-clinical and clinical studies, and a durability of effect that we believe supports once-monthly or possibly even less frequent subcutaneous dosing regimens. Due to this increased potency and durability, as well as a wide therapeutic index, this conjugate platform has become our primary approach for development of investigational RNAi therapeutics.

In early 2014, we continued and extended our commitment to RNAi therapeutics innovation and delivery through the acquisition of Sirna Therapeutics, Inc., or Sirna, from Merck Sharp & Dohme Corp., or Merck. This acquisition extended and complemented our progress and continued focus on RNAi therapeutics. It also accelerated our overall efforts to develop and commercialize siRNA delivery technologies, including GalNAc-siRNA conjugate technology.

Our Product Platform

We are leading the translation of RNAi as a new class of innovative medicines, with a core focus on investigational RNAi therapeutics toward genetically defined targets for the treatment of serious, life-threatening diseases with limited treatment options for patients and their caregivers. With RNAi therapeutics, we believe that we have created a reproducible and modular approach for the development and commercialization of innovative medicines. The product candidates we are developing with this approach share several key characteristics, including:

the potential to have a major impact in a high unmet need population;

a genetically defined, liver-expressed target gene involved in disease and validated in human genetics;

the ability to leverage our Alnylam RNAi delivery platform;

the opportunity to monitor an early, blood-based biomarker with strong disease correlation in Phase 1 clinical trials for human proof of concept; and

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the existence of clinically relevant endpoints for the filing of a new drug application, or NDA, or foreign regulatory equivalent, with a focused patient database and possible accelerated paths for regulatory approval and commercialization.

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In December 2014, we evolved our strategy with a focus on development and commercialization of investigational RNAi therapeutics in three STArS: Genetic Medicines; Cardio-Metabolic Diseases; and Hepatic Infectious Diseases.

Our Product Pipeline

Our broad pipeline of investigational RNAi therapeutics is focused in three STArS: Genetic Medicines, for the treatment of rare diseases; Cardio-Metabolic Disease, focused on genetically validated, liver-expressed genes for unmet needs in dyslipidemia, hypertension, NASH and type 2 diabetes; and Hepatic Infectious Disease, addressing major global health challenges, including but not limited to the hepatitis B virus, or HBV. The following is a summary of our product development programs in each of our STArS as of January 31, 2015:

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 \$190.2 million in 2014, \$113.0 million in 2013 and \$86.6 million in 2012.

Genetic Medicine STAr

In our Genetic Medicine STAr, we are advancing a broad pipeline of investigational RNAi therapeutics for rare diseases. Across our Genetic Medicine STAr, we plan on commercializing our products through direct marketing and sales in North America and Western Europe, while leveraging our 2014 alliance with Genzyme for commercialization in the rest of the world, subject to certain broader rights. Our Genetic Medicine development programs are described in more detail below.

TTR-Mediated Amyloidosis (ATTR)

Our most advanced Genetic Medicine product development program targets the transthyretin, or TTR, gene for the treatment of TTR-mediated amyloidosis, or ATTR. ATTR is an inherited, progressively debilitating and fatal disease caused by a mutation in the TTR gene, of which over 100 mutations have been identified. TTR protein is produced primarily in the liver and is normally a carrier for retinol binding protein, used to transport vitamin A around the body. We believe TTR is a suitable target for an RNAi therapeutic formulated to maximize

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delivery to liver cells, which are the primary source of TTR synthesis. Mutations in TTR result in the accumulation of damaging toxic deposits of the wild-type and mutant protein in several body organs and tissues, including the peripheral nervous system, heart and/or gastrointestinal tract, which leads to familial amyloidotic polyneuropathy, or FAP, and/or familial amyloidotic cardiomyopathy, or FAC. FAP is associated with severe pain and loss of autonomic nervous system function, whereas FAC is associated with heart failure. ALN-TTR targets wild-type and all known mutant forms of TTR, including the V30M mutation, which is the major mutation of ATTR, particularly in FAP, and therefore is a potential therapeutic for the treatment of all forms of ATTR, including FAP and FAC.

ATTR represents a major unmet medical need with significant morbidity and mortality as an orphan, or rare, disease. Based on our analysis of the available patient and market data, we estimate that FAP affects approximately 10,000 people worldwide and FAC affects at least 40,000 people worldwide. ATTR patients with FAP have a mean life expectancy of five to 15 years from symptom onset, and the only treatment options for early stage disease are liver transplantation and TTR stabilizers such as tafamidis, a small molecule stabilizer of the TTR protein for early-stage FAP patients that has been approved in the European Union, or EU, and diflunisal, a commercially available non-steroidal anti-inflammatory agent. The mean survival for FAC patients is approximately 2.5 to five years following diagnosis, and there are no approved therapies. Senile systemic amyloidosis, or SSA, is a non-hereditary form of TTR cardiac amyloidosis caused by idiopathic deposition of wild-type TTR; its prevalence is generally unknown, but is associated with advanced age. Although limited treatment options are available, there remains a significant need for novel therapeutics to treat patients with TTR amyloid polyneuropathy and/or cardiomyopathy.

We are developing two investigational RNAi therapeutic candidates for ATTR: patisiran and revusiran.

Patisiran (ALN-TTR02). Patisiran is our most advanced product candidate in clinical development. In November 2013, we initiated our ongoing APOLLO Phase 3 clinical trial of patisiran. The APOLLO Phase 3 clinical trial is a randomized, double-blind, placebo-controlled, global study designed to evaluate the efficacy and safety of patisiran in ATTR patients with FAP. The primary endpoint of the study is the difference in the change in the modified composite Neuropathy Impairment Score (NIS), termed mNIS+7, between patisiran and placebo at 18 months. mNIS+7 is an evaluation of muscle weakness, sensory and autonomic function, and nerve conductance across a 304-point scale, where neuropathy progression leads to an increased score over time. Secondary endpoints include: the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) score; Neuropathy Impairment Score, or NIS-weakness; modified body mass index, or mBMI; timed ten-meter walk; and the COMPASS-31 autonomic symptom score. The trial is designed to enroll up to 200 FAP patients with a baseline NIS in the range of five to 130, which represents patients with Stage 1 or Stage 2 disease. Patients are being randomized two-to-one, patisiran-to-placebo, with patisiran administered at 0.30 mg/kg once every three weeks for 18 months. The study was designed with 90% power to conservatively detect as little as a 37.5% difference in change in mNIS+7 between treatment groups, with a two-sided alpha of 0.05. The placebo mNIS+7 progression rate was derived from an Alnylam analysis of natural history data from 283 FAP patients. We presented data from this natural history study during 2014. This cross-sectional analysis demonstrated a rapid progression in NIS and a high correlation of this measurement with disease severity. These results give us confidence that our APOLLO Phase 3 trial of patisiran is robustly powered to show the potential impact of TTR lowering on the mNIS+7 endpoint used in that study. All patients completing the APOLLO Phase 3 clinical trial will be eligible to enroll in a Phase 3 open-label extension, or OLE study.

We have completed a Phase 2 clinical trial of patisiran which showed that multiple doses of patisiran led to robust and statistically significant knockdown of serum TTR protein levels of up to 96%, with mean levels of TTR knockdown exceeding 85%. In addition, patisiran was found to be generally well tolerated in this Phase 2 study. Patients participating in the Phase 2 study were eligible to participate in a Phase 2 OLE study with patisiran; 27 patients rolled into the OLE. Patients in the Phase 2 OLE are receiving patisiran at a dose of 0.30 mg/kg every three weeks for up to two years. The primary objective of this study is to evaluate the long-term safety and tolerability of patisiran administration. In addition, the study is measuring a number of clinical endpoints every six months, including mNIS+7. A number of additional clinical endpoints are being assessed.

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In October 2014, we reported six-month clinical data from this ongoing Phase 2 OLE study. Specifically, results showed a mean 0.95 point decrease in mNIS+7 at six months in 19 patients. This decrease in neuropathy progression compares favorably with the seven to ten point increase in mNIS+7 at six months that can be estimated from published historical data sets in untreated FAP patients with similar baseline characteristics. In addition, patisiran treatment achieved a sustained mean serum TTR knockdown at the 80% target level for over nine months, with an up to 89.6% knockdown achieved between doses. In the ongoing Phase 2 OLE study, patisiran was found to be generally well tolerated in FAP patients (N=27), with minimal adverse events reported for a period of up to one year. Infusion-related reactions were infrequent (14.8%), mild in severity and did not result in any discontinuations. All other reported adverse events were mild to moderate, and there were no clinically significant changes in liver function tests, renal function tests, or other laboratory or hematological parameters.

The Committee for Orphan Medicinal Products, or COMP, of the European Medicines Agency, or EMA, has designated patisiran as an orphan medicinal product for the treatment of FAP. Orphan Drug Designation, or ODD, by the European Commission, or EC, provides regulatory and financial incentives for companies developing orphan drugs to develop and market therapies that treat a life-threatening or chronically debilitating condition affecting no more than five in 10,000 persons in the EU. In addition to a ten-year period of marketing exclusivity in the EU after product approval, ODD provides companies with protocol assistance from the EMA during the product development phase, direct access to centralized marketing authorization and reduced regulatory fees. In addition, the United States Food and Drug Administration, or FDA, provided ODD to patisiran as a therapeutic for the treatment of FAP. The FDA's ODD program provides orphan status to drugs and biologics which are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the United States.

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

Revusiran (ALN-TTRsc). In addition to patisiran, we are also advancing revusiran, which utilizes our proprietary STC-GalNAc-conjugate approach enabling subcutaneous dose administration, with a wide therapeutic index. Revusiran is currently in a Phase 3 clinical trial.

In December 2014, we initiated our ENDEAVOUR Phase 3 clinical trial of revusiran in TTR-mediated FAC. The ENDEAVOUR trial is a randomized, double-blind, placebo-controlled, global study designed to evaluate the efficacy and safety of revusiran in patients with FAC. The co-primary endpoints of the study are the change compared to baseline in 6-minute walk distance, or 6-MWD, and the percent reduction in TTR plasma levels between placebo- and revusiran-treated patients at 18 months. Secondary endpoints include a composite endpoint of cardiovascular mortality and cardiovascular hospitalization, New York Heart Association (NYHA) class, Kansas City Cardiomyopathy Questionnaire (KCCQ), cardiovascular, or CV, mortality, CV hospitalization and all-cause mortality. The trial is designed to enroll up to 200 FAC patients with a documented TTR mutation, including V122I or other mutations, in addition to amyloid deposits as identified by biopsy. Patients will be randomized two-to-one, revusiran-to-placebo, with subcutaneous administration at 500 mg daily for five days then weekly for 18 months. The trial design was informed by results from a natural history study which showed a progressive decrease in 6-MWD in FAC patients over an 18-month period. The ENDEAVOUR study was designed with 90% power to detect as little as 39% difference in the 18-month change from baseline for 6-MWD between treatment groups, with a significance level of $p < 0.05$ (two-sided). An unblinded interim analysis for futility may be conducted when 50% of patients reach 18 months. All patients completing the ENDEAVOUR Phase 3 study will be eligible to enroll in a Phase 3 OLE study.

In November 2014, we announced positive initial results from our Phase 2 open-label, multi-dose clinical trial with revusiran in TTR cardiac amyloidosis patients. Initial results from the pilot Phase 2 study from 26 patients, including 14 with FAC and 12 with SSA, were based on a data cutoff date of October 3, 2014. Study results showed that revusiran was generally well tolerated in patients with significant disease burden. The most common adverse event was injection site reaction (23% of patients). One patient had an approximate four-fold

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elevation in liver transaminases that was deemed a serious adverse event that was graded mild in severity; this event resolved during continued dosing. There were no other clinically significant adverse events, discontinuations or other clinically significant laboratory abnormalities. In addition, data showed an up to 98.2% knockdown of both mutant and wild-type forms of TTR, the disease-causing protein, with a mean maximum knockdown of 87.2% +/- 9.1%. As would be expected with the short treatment duration of five weeks, there were no significant changes observed in exploratory clinical measurements. All patients that completed dosing in our Phase 2 clinical trial are eligible to be enrolled in our open-label, Phase 2 OLE study, which was initiated in November 2014 and is designed to evaluate the tolerability and clinical activity of revusiran with long-term dosing for up to two years. In addition to data on mortality, hospitalization, general tolerability and measurement of serum TTR levels, the Phase 2 OLE study will assess the same clinical measures, every six months, included in the pilot Phase 2 trial noted above as well as additional measures of amyloid burden including technetium imaging of the heart and quantitation of amyloid in abdominal fat pad aspirates.

During 2014, we also initiated our DISCOVERY trial, a screening study examining the prevalence of TTR mutations in patients suspected of having cardiac amyloidosis. With this study, we aim to identify and facilitate the diagnosis of FAC.

The COMP of the EMA has designated revusiran as an orphan medicinal product for the treatment of FAC.

ALN-AT3 Hemophilia and Rare Bleeding Disorders (RBD)

ALN-AT3 is an investigational RNAi therapeutic targeting antithrombin, or AT, a genetically defined target, for the treatment of hemophilia and RBD. Hemophilias are hereditary disorders caused by genetic deficiencies of various blood clotting factors, resulting in recurrent bleeds into joints, muscles and other major internal organs. Hemophilia A, or HA, is defined by loss-of-function mutations in Factor VIII, and there are greater than 40,000 registered people in the United States and EU with HA. Hemophilia B, or HB, defined by loss-of-function mutations in Factor IX, affects greater than 9,500 registered people in the United States and EU. Other RBD are defined by congenital deficiencies of other blood coagulation factors, including Factors II, V, VII, X and XI. Based on our analysis of the available patient and market data, we estimate that there are approximately 1,000 people with RBD worldwide with a severe bleeding phenotype. Standard treatment for people living with hemophilia involves replacement of the missing clotting factor either as prophylaxis or on-demand therapy. However, as many as one-third of people with severe HA will develop an antibody to their replacement factor, a very serious complication. People with inhibitors become refractory to standard replacement therapy. There remains a significant need for novel therapeutics to treat people living with hemophilia and RBD.

There exists a small subset of people living with hemophilia who have co-inherited a prothrombotic mutation, such as Factor V Leiden, antithrombin deficiency, protein C deficiency and prothrombin G20210A. People who have co-inherited these prothrombotic mutations are characterized as having a later onset of disease, lower risk of bleeding, and reduced requirements for Factor VIII or Factor IX treatment as part of their disease management. ALN-AT3 is a novel therapeutic approach aimed at re-balancing the coagulation cascade and normalizing hemostasis in severe HA and HB patients, including patients with inhibitors against their replacement factor. The program aims to reproduce the human genetic findings of a milder clinical disease in people with hemophilia who have co-inherited prothrombotic mutations.

We are evaluating ALN-AT3 in an ongoing Phase 1 study. Part A of the Phase 1 study, which is complete, was a randomized, single-blind, placebo-controlled, single-dose, dose-escalation study (n=4 per cohort; three-to-one randomization of ALN-AT3-to-placebo) in healthy volunteer subjects. This part of the study was completed after the first dose cohort that received a single subcutaneous dose of ALN-AT3 at 30 micrograms/kilogram (mcg/kg). Part B of the study, which is ongoing, is an open-label, multi-dose, dose-escalation study enrolling up to 18 subjects with moderate or severe HA or HB. The primary objective of this part of the study is to evaluate the safety and tolerability of multiple doses of subcutaneously administered ALN-AT3 in hemophilia subjects. Secondary objectives include assessment of clinical activity as determined by knockdown of circulating AT levels and increase in thrombin generation at pharmacologic doses of ALN-AT3.

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In January 2015, we announced updated results from our ongoing Phase 1 study of ALN-AT3. Specifically, new data were presented from the second dose cohort of hemophilia subjects (n=3), where ALN-AT3 was administered subcutaneously once weekly for three weeks at a low dose of 45 mcg/kg; all preliminary results are as of a data cut-off date of January 6, 2015. ALN-AT3 administration resulted in an up to 70% knockdown of AT. Based on the most advanced subject in the cohort, the nadir effect appears to occur at approximately day 28, and AT knockdown effects were found to be highly durable, lasting about 60 days. In addition, initial evidence for the potential correction of the hemophilia phenotype was observed in the severe HA subjects. Specifically, ALN-AT3 administration was found to be associated with statistically significant increase in thrombin generation of up to 334%. This level of thrombin generation increase is consistent with thrombin generation levels observed in mild hemophilia. In addition, ALN-AT3 administration was associated with improvements in whole blood clotting. Finally, as of the current data cut-off date of January 6, 2015, the most advanced subject in the study who has a self-reported Annualized Bleeding Rate (ABR) of 10-12 bleeds per year, was found to be free of bleeding for up to 47 days in association with AT knockdown of over 50%. As of the current data cut-off, ALN-AT3 continues to be generally well tolerated in all subjects receiving study drug in the study (n=9), including subjects enrolled in the second dose cohort (n=3). The most common adverse event observed in hemophilia subjects was the occurrence of mild to moderate bleeds unrelated to study drug and consistent with an underlying hemophilia condition. All bleeds were successfully managed with replacement factor administration.

The ALN-AT3 Phase 1 study continues to enroll hemophilia subjects in additional dose cohorts, including the potential to explore a once-monthly subcutaneous dose regimen following a protocol amendment.

ALN-CC5 Complement-Mediated Diseases

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

ALN-CC5 utilizes Alnylam's ESC-GalNAc conjugate technology, which enables subcutaneous dosing with increased potency and durability and a wide therapeutic index. Our clinical trial application, or CTA, which we filed in November 2014, was approved by the U.K. Medicines and Healthcare products Regulatory Agency, or MHRA and we initiated our Phase 1/2 clinical trial with ALN-CC5 in January 2015. The Phase 1/2 study is designed in three parts: Parts A and B will be single ascending dose and multiple ascending dose studies in normal healthy human volunteers; Part C will be a study in patients with PNH.

Preclinical data presented in December 2014 shows an up to 99.2% knockdown of serum C5 and up to 96.2% inhibition of serum hemolytic activity in non-human primates, or NHPs, with continued bi-weekly or monthly subcutaneous dosing for over seven months. In addition, data showed an up to 96.9% inhibition of complement alternative pathway (CAP) activity (mean $95.1 \pm 0.93\%$), and up to 96.2% inhibition of hemolysis (mean $88.0 \pm 6.1\%$) with twice-monthly dosing. This level of C5 knockdown and inhibition of hemolytic activity exceeds the 80% threshold established by existing therapy and is expected to be associated with clinical benefit.

ALN-AS1 Hepatic Porphyrias

ALN-AS1 is a subcutaneously administered, investigational RNAi therapeutic targeting aminolevulinic acid synthase-1, or ALAS-1, for the treatment of hepatic porphyrias. Porphyrias are a family of rare metabolic disorders caused by a genetic mutation in one of the eight enzymes responsible for heme biosynthesis. Hepatic

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porphyrias constitute a subset where the enzyme deficiency occurs within the liver, and includes acute intermittent porphyria, or AIP, hereditary coproporphyria and variegate porphyria. The initial focus of the ALN-AS1 program is on AIP, the most common acute hepatic porphyria, which is due to a mutation in uroporphobilinogen deaminase, or PBGD. Exposure of AIP patients to certain drugs, dieting or hormonal changes can trigger strong induction of ALAS-1, the first, rate-limiting enzyme in the pathway, which can lead to accumulation of heme intermediates upstream of the deficient PBGD enzyme that precipitate disease symptoms. Patients with AIP can suffer from a range of symptoms that can include acute and/or recurrent life-threatening attacks with severe abdominal pain, peripheral and autonomic neuropathy, neuropsychiatric manifestations, and possibly death if untreated or if there are delays in treatment. It is estimated that approximately 5,000 patients in the United States and Europe suffer AIP attacks annually, and approximately 500 patients are afflicted with recurrent, debilitating attacks. The only available treatment for AIP is the use of hematin, which is a preparation of heme derived from human blood. Hematin requires administration through a central intravenous line and is associated with a number of complications including thrombophlebitis and iron overload. There is a clear unmet need for new therapies for AIP that could be both safer and more effective and convenient than available therapies.

ALN-AS1 utilizes our ESC-GalNac conjugate technology, which enables subcutaneous dosing with increased potency and durability and a wide therapeutic index, and has the potential to be a therapy for the treatment of acute porphyria attacks, as well as a prophylactic approach for the prevention of recurrent attacks. In pre-clinical studies, multi-dose administration of a GalNac-siRNA targeting ALAS-1 led to rapid, dose-dependent knockdown of the ALAS-1 mRNA in NHPs, with an ED₅₀ of approximately 1.25 mg/kg. Further, in a rat model of AIP, ALN-AS1 administration at doses as low as 2.5 mg/kg resulted in a complete inhibition of phenobarbital-induced over-production of ALA and PBG, the toxic heme intermediates in AIP.

In December 2014, we filed a CTA with the Swedish Medical Products Agency, or MPA, to initiate a Phase 1 clinical trial with ALN-AS1. Per the filed CTA, the Phase 1 clinical trial of ALN-AS1 will be performed first in AIP patients who are asymptomatic high excretors, or ASHE, patients with a mutation in the PBGD gene and elevated urinary ALA and PBG levels, but no recent symptoms of a porphyria attack. The Phase 1 clinical trial will then move to AIP patients who experience recurrent porphyria attacks. Following approval of the CTA, we expect to initiate the Phase 1 study in mid-2015.

During 2014, we also initiated the EXPLORE trial with our collaborators from the American Porphyria Consortium and The European Porphyria Network, a prospective observational study of patients with hepatic porphyrias suffering from recurrent attacks. With this study, we and clinical investigators aim to learn more about the clinical course, management and disease burden of patients with hepatic porphyrias who suffer from recurrent attacks.

Additional Genetic Medicine Programs

In addition to the programs described above, we are also advancing other early stage Genetic Medicine programs. These programs include: ALN-AAT, an investigational RNAi therapeutic targeting alpha-1 antitrypsin, or AAT, for the treatment of AAT deficiency liver disease; ALN-GO1, an investigational RNAi therapeutic targeting glycolate oxidase, or GO, for the treatment of primary hyperoxaluria type 1, or PH1; ALN-TMP, an investigational RNAi therapeutic targeting transmembrane protease, serine 6, or TMPRSS6, for the treatment of beta-thalassemia and iron-overload disorders; and other yet to be disclosed programs. We intend to file an Investigational New Drug (IND) application, or IND equivalent, such as a CTA, for AAT in mid-2015 and to advance additional Genetic Medicine programs to support the filing of two or more INDs or IND equivalents in 2016.

Genzyme Alliance

In January 2014, we entered into the 2014 Genzyme collaboration which is an exclusive relationship for the worldwide development and commercialization of RNAi therapeutics in the field of Genetic Medicines, which includes our current and future Genetic Medicine programs that reach human proof-of-principal study

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completion, or Human POP, by the end of 2019, subject to extension to the end of 2021 in various circumstances. We will retain product rights in North America and Western Europe, while Genzyme will obtain exclusive rights to develop and commercialize collaboration products in the rest of the world, referred to as the Genzyme Territory, together with certain broader co-development/co-promote or worldwide rights for certain products. Genzyme's rights are structured as an opt-in that is triggered upon achievement of Human POP. We maintain development control for all programs prior to Genzyme's opt-in and maintain development and commercialization control after Genzyme's opt-in for all programs in our territory.

In addition to its regional rights for our current and future Genetic Medicine STAr programs in the Genzyme Territory, Genzyme has the right to either (i) co-develop and co-promote ALN-AT3 for the treatment of hemophilia and other RBD in our territory, with us maintaining development and commercialization control, or (ii) obtain a global license to ALN-AS1 for the treatment of hepatic porphyrias. Genzyme will exercise this selection right upon the completion of Human POP for both the ALN-AT3 and ALN-AS1 programs. Finally, Genzyme has the right for a global license to a single, future Genetic Medicine program that was not one of our defined Genetic Medicine programs as of the effective date of the 2014 Genzyme collaboration. We will retain global rights to any RNAi therapeutic Genetic Medicine program that does not reach Human POP by the end of 2019, subject to certain limited exceptions.

We are leading development and commercialization of patisiran in North America and Western Europe while Genzyme will develop and commercialize the product in the Genzyme Territory. In addition, we and Genzyme are co-developing and co-commercializing revusiran in North America and Western Europe, with Genzyme developing and commercializing the product in the Genzyme Territory.

The 2014 Genzyme collaboration is described below under the heading Strategic Alliances.

Cardio-Metabolic Disease STAr

In our Cardio-Metabolic Disease STAr, we are advancing our pipeline of investigational RNAi therapeutics toward genetically validated, liver-expressed disease targets for unmet needs in dyslipidemias, hypertension, NASH and type 2 diabetes. We believe that new discoveries in the human genetics of cardio-metabolic disease, together with innovative clinical development strategies in morbid sub-populations, create opportunities for new, potentially transformative medicines. Further, we believe the emerging profile of our ESC-GalNAc conjugates with once-monthly and possibly once-quarterly, low-volume, subcutaneous dose administration and a wide therapeutic index supports advancement of new medicines in this disease area. We intend to seek strategic collaboration opportunities for programs in our Cardio-Metabolic Disease STAr, while retaining significant product commercialization rights in the United States and EU.

Our Cardio-Metabolic Disease development programs are described in more detail below.

ALN-PCS Hypercholesterolemia

ALN-PCSSc is a subcutaneously administered investigational RNAi therapeutic targeting proprotein convertase subtilisin/kexin type 9, or PCSK9, for the treatment of hypercholesterolemia. PCSK9 is a protein involved in the regulation of low-density lipoprotein, or LDL, receptor levels on hepatocytes and the metabolism of LDL cholesterol, or LDL-C, which is commonly referred to as "bad" cholesterol. PCSK9 is produced by the liver and circulates in the bloodstream. Both intracellular and extracellular PCSK9 reduce the liver's capacity to absorb LDL-C by decreasing LDL receptor levels. Published studies indicate that, if PCSK9 activity could be reduced, the liver's uptake of LDL-C should increase and blood cholesterol levels should decrease. In fact, published case reports have shown individuals with loss-of-function genetic mutations in PCSK9 have decreased blood cholesterol levels. In turn, these individuals have been shown to have a dramatically reduced risk of coronary artery disease, or CAD, including myocardial infarction or heart attack. In addition, studies have shown that PCSK9 levels are increased by statin therapy, limiting their effect, suggesting that the introduction of a PCSK9 inhibitor to statin therapy may result in even further reductions in LDL-C levels. Hypercholesterolemia is a condition characterized by very high levels of cholesterol in the blood which is known to increase the risk of coronary artery disease, the leading cause of death in the United States. Some forms of hypercholesterolemia can

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be treated through dietary restrictions, lifestyle modifications (e.g., exercise and smoking cessation) and medicines such as statins. However, a large proportion of patients with hypercholesterolemia, including genetic familial hypercholesterolemia patients, acute coronary syndrome patients, high-risk patient populations (e.g., patients with CAD, diabetes, symptomatic carotid artery disease) and other patients that are statin intolerant, are not achieving target LDL-C goals with statin therapy. Severe forms of hypercholesterolemia are estimated to affect more than 500,000 patients worldwide, and as a result, there is a significant need for novel therapeutics to treat patients with hypercholesterolemia whose disease is inadequately managed by existing therapies.

In December 2014, we initiated a Phase 1 clinical trial with ALN-PCSSc. The Phase 1 trial is being conducted in the U.K. as a randomized, single-blind, placebo-controlled, single ascending- and multi-dose study. The study is designed to enroll up to 76 volunteer subjects with elevated baseline LDL-C (≥ 100 mg/dL), with subjects randomized three-to-one, drug-to-placebo. The study will be performed in two phases: a single ascending dose, or SAD, phase and a multiple dose, or MD, phase. In the MD phase, subjects will receive two subcutaneous doses of either ALN-PCSSc or placebo administered four weeks apart. The MD phase will also include subjects both on and off statin co-medication. The primary objective of the Phase 1 study is to evaluate the safety and tolerability of ALN-PCSSc. Secondary objectives include assessment of clinical activity as determined by knockdown of plasma PCSK9 levels and serum LDL-C levels, as well as pharmacokinetics of ALN-PCSSc.

ALN-PCSSc utilizes our proprietary ESC-GalNAc-siRNA conjugate delivery platform. Pre-clinical data in NHPs demonstrates that monthly subcutaneous administration of ALN-PCSSc resulted in PCSK9 knockdown of up to 92% and LDL-C lowering, in the absence of statin co-administration, of up to 77%; mean maximum knockdown of PCSK9 was 83.2% \pm 7.2%, and mean maximum LDL-C reduction was 59.0% \pm 13.3%. As a PCSK9 synthesis inhibitor, ALN-PCSSc showed rapid, durable and clamped knockdown of PCSK9 and reduction of LDL-C, which contrasts with the cyclical variation in LDL-C observed with monthly dose regimens of anti-PCSK9 monoclonal antibodies. In aggregate, these pre-clinical data are supportive of a once-monthly, and possibly once-quarterly, dosing regimen for ALN-PCSSc, which we believe could represent a highly competitive target product profile.

In February 2013, we and MDCO entered into a license and collaboration agreement pursuant to which we granted to MDCO an exclusive, worldwide license to develop, manufacture and commercialize RNAi therapeutics targeting PCSK9 for the treatment of hypercholesterolemia and other human diseases. Under the terms of the agreement, we will complete certain pre-clinical studies and a Phase 1 clinical study of ALN-PCSSc, and MDCO is responsible for leading and funding development from Phase 2 forward as well as potential commercialization. A description of our agreement with MDCO is included below under the heading Strategic Alliances.

Additional Cardio-Metabolic Disease Programs

In addition to ALN-PCSSc, we are also advancing other early stage Cardio-Metabolic Disease programs. These programs include additional investigational programs for the treatment of dyslipidemias, including ALN-AC3 targeting Apolipoprotein C3, or ApoC3, for the treatment of hypertriglyceridemia and ALN-ANG targeting Angiopoietin-like 3, or ANGPTL3, for the treatment of hypertriglyceridemia and mixed hyperlipidemia. In addition, we are developing ALN-AGT, an investigational RNAi therapeutic targeting angiotensinogen, or AGT, for the treatment of hypertensive disorders of pregnancy including preeclampsia. Finally, we are advancing a number of undisclosed pre-clinical programs for the treatment of NASH and type 2 diabetes. We intend to advance additional Cardio-Metabolic Disease programs to support the filing of at least one IND or IND equivalent in 2016.

Hepatic Infectious Disease STAR

In our Hepatic Infectious Disease STAR, we are advancing a pipeline of investigational RNAi therapeutics that address major global health challenges, including but not limited to HBV. We intend to seek strategic collaboration opportunities for programs in our Hepatic Infectious Disease STAR, while retaining significant product commercialization rights in the United States and EU.

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Our Hepatic Infectious Disease development programs are described in more detail below.

ALN-HBV Hepatitis B Virus (HBV)

HBV is the most common serious liver infection in the world. Worldwide, two billion people (one out of three people) have been infected with HBV and 400 million people have become chronically infected. An estimated one million people die each year from HBV and its complications worldwide; about 5,000 of those are in the United States. The clinical manifestations are severe. Worldwide, chronic infection with hepatitis causes 80% of all hepatocellular carcinoma, or HCC, and more than 500,000 people die each year from this form of cancer. About five percent of the population are chronic carriers of HBV, and nearly 25% of all carriers develop serious liver diseases such as chronic hepatitis, cirrhosis and HCC. Despite the use of nucleoside analog inhibitors of viral DNA synthesis and interferon therapies, the cure rate for chronic HBV infection is less than ten percent. Reduction in HBV surface antigen, or HBsAg, levels of over 0.5 log₁₀ is the single best predictor of immunologic cure. We believe an RNAi therapeutic targeting the HBV genome could have the potential to achieve a functional cure by effectively decreasing expression of HBsAg, in addition to inhibiting all steps of the HBV life cycle.

During 2014, we identified a Development Candidate for our ALN-HBV program. The ALN-HBV Development Candidate is an ESC-GalNAc-siRNA targeting the HBV genome. In a rodent model of HBV, a single subcutaneous dose at 3 mg/kg resulted in an up to 3.9 log₁₀ reduction in HBsAg levels (mean 1.8 log₁₀ reduction). We expect to file an IND or IND equivalent for this program in late 2015.

Our ALN-HBV program derives from our 2014 acquisition of the RNAi assets of Merck, including Sirna.

Additional Hepatic Infectious Disease Programs

In addition to ALN-HBV, we are also advancing other early stage Hepatic Infectious Disease programs. These programs include: ALN-HDV, an investigational RNAi therapeutic targeting the hepatitis delta virus, or HDV, for the treatment of HDV infection; ALN-PDL, an investigational RNAi therapeutic targeting hepatocyte-expressed programmed death ligand 1, or PD-L1, an immune checkpoint inhibitor, for the treatment of chronic liver infections; and other yet to be disclosed programs.

Our Collaboration and Licensing Strategy

Our business strategy is to develop and commercialize a broad pipeline of RNAi therapeutic products directed towards our three STArS: Genetic Medicines; Cardio-Metabolic Diseases; and Hepatic Infectious Diseases. 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 investigational RNAi therapeutic programs.

Our collaboration strategy is to form alliances that create significant value for ourselves and our collaborators in the advancement of RNAi therapeutics as a new class of innovative medicines. Specifically, with respect to our Genetic Medicine pipeline, we formed a broad strategic alliance with Genzyme in 2014 pursuant to which we retain development and commercial rights for our current and future Genetic Medicine products in North America and Western Europe, and Genzyme will develop and commercialize our current and future Genetic Medicine products principally in territories outside of North America and Western Europe, subject to certain broader rights. With respect to our Cardio-Metabolic and Hepatic Infectious Disease pipelines, we intend to seek future strategic alliances for these programs, while retaining significant product commercialization rights in the United States and EU. We currently have a global alliance with MDCO for the development and commercialization of our ALN-PCSSc program.

We also seek to form or advance new ventures and opportunities in areas outside our primary focus on RNAi therapeutics. In 2007, we and Isis formed Regulus to capitalize on our technology and intellectual property in the field of microRNA therapeutics. Currently, we own approximately 12% of Regulus outstanding common stock.

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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 revenues that we can re-invest in the development of our proprietary RNAi therapeutics pipeline. As of January 31, 2015, we had granted such licenses, on both an exclusive and non-exclusive basis, to approximately 20 companies.

Since delivery of RNAi therapeutics has historically been an important objective of our research activities, we have also evaluated potential collaboration and licensing arrangements with other companies and academic institutions to gain access to delivery technologies. For example, we entered into agreements with Tekmira Pharmaceuticals Corporation, or TPC, Protiva Biotherapeutics, Inc., a wholly owned subsidiary of TPC, and together with TPC, referred to as Tekmira, The University of British Columbia, or UBC, and Acuitas Therapeutics Inc. (formerly AlCana Technologies, Inc.), or Acuitas, among others, related to various delivery technologies.

We have also entered into license agreements with Isis, Max Planck Innovation GmbH (formerly known as Garching Innovation GmbH), or Max Planck Innovation, Tekmira, Cancer Research Technology Limited, or CRT, and Whitehead Institute for Biomedical Research, or Whitehead, as well as a number of other entities, to obtain rights to intellectual property in the field of RNAi. Finally, we have sought, and may seek in the future, funding for the development of our proprietary RNAi therapeutics pipeline from the government and foundations.

Strategic Alliances

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

Product Alliances.

Genzyme. In January 2014, we entered into a global, strategic collaboration with Genzyme to discover, develop and commercialize RNAi therapeutics as Genetic Medicines to treat orphan diseases. The 2014 Genzyme collaboration superseded and replaced the previous collaboration between us and Genzyme entered into in October 2012 to develop and commercialize RNAi therapeutics targeting TTR for the treatment of ATTR, including patisiran and revusiran, in Japan and the Asia-Pacific region.

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

Specifically, in addition to its regional rights for our current and future Genetic Medicine programs in the Genzyme Territory, Genzyme has the right to either (i) co-develop and co-promote ALN-AT3 for the treatment of hemophilia and other RBD in the Alnylam Territory, with us maintaining development and commercialization control, or (ii) obtain a global license to ALN-AS1 for the treatment of hepatic porphyrias. Genzyme may

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exercise this selection right upon the completion of Human POP for both the ALN-AT3 and ALN-AS1 programs. Finally, Genzyme has the right for a global license to a single, future Genetic Medicine program that was not one of our defined Genetic Medicine programs as of the effective date of the 2014 Genzyme collaboration. We will retain global rights to any RNAi therapeutic Genetic Medicine program that does not reach Human POP by the end of 2019, subject to certain limited exceptions. We retain full rights to all current and future RNAi therapeutic programs outside of the field of Genetic Medicines, including the right to form new collaborations.

Under the 2014 Genzyme collaboration, Genzyme's specific license rights include the following:

Regional license terms Upon opt-in, we will retain product rights in the Alnylam Territory, while Genzyme will obtain exclusive rights to develop and commercialize the product in the Genzyme Territory. Genzyme can elect this license for any of our current and future Genetic Medicine programs that complete Human POP by the end of 2019, subject to limited extension. Development costs for products, once Genzyme exercises an option, will be shared between Genzyme and us, with Genzyme responsible for twenty percent of the global development costs. Upon the effective date of the 2014 Genzyme collaboration, Genzyme expanded the scope of its regional license and collaboration for patisiran, an investigational RNAi therapeutic currently in a Phase 3 clinical trial for the treatment of ATTR patients with FAP, which was originally established under the 2012 Genzyme agreement. Genzyme will be required to make payments totaling up to \$50.0 million upon the achievement of certain patisiran development milestones. In addition, Genzyme will be required to make payments totaling up to \$75.0 million per product other than patisiran, including up to \$55.0 million in development milestones and \$20.0 million in commercial milestones. Genzyme will also be required to pay tiered double-digit royalties up to twenty percent for each regional product based on annual net sales, if any, of such regional product by Genzyme, its affiliates and sublicensees.

Co-development/co-promote license terms Upon opt-in, we will retain product rights in the Alnylam Territory, while Genzyme will obtain exclusive rights to develop and commercialize the product in the Genzyme Territory, and will co-promote the product in the Alnylam Territory. Upon the effective date of the 2014 Genzyme collaboration, Genzyme expanded its regional rights for revusiran, an investigational RNAi therapeutic currently in a Phase 3 clinical trial for the treatment of ATTR patients with TTR amyloid cardiomyopathy, which were originally granted under the 2012 Genzyme agreement, to include a co-development/co-promote license and collaboration. Genzyme also has the right to elect a co-development/co-promote license and collaboration for ALN-AT3, if it does not elect a global license and collaboration for ALN-AS1. Development costs for co-development/co-promote products, once Genzyme exercises an option, will be shared between Genzyme and us, with Genzyme responsible for fifty percent of the global development costs. Genzyme will be required to make payments totaling up to \$75.0 million in development milestones for each of revusiran and ALN-AT3, if selected. In December 2014, we earned a development milestone payment of \$25.0 million based upon the initiation of the first global Phase 3 clinical trial for revusiran. Genzyme will also be required to pay tiered double-digit royalties up to twenty percent for each co-development/co-promote product based on annual net sales, if any, in the Genzyme Territory for such co-development/co-promote product by Genzyme, its affiliates and sublicensees. The parties will share profits equally and we expect to book product sales in the Alnylam Territory.

Global license terms Upon opt-in, Genzyme will obtain a worldwide license to develop and commercialize the product. Genzyme can elect a global license for ALN-AS1, if it does not elect a co-development/co-promote license for ALN-AT3. Genzyme will also have one right to a global license through 2019, subject to limited extension, for a future Genetic Medicine program that was not one of our defined Genetic Medicine programs as of the effective date of the 2014 Genzyme collaboration. Genzyme shall be responsible for one hundred percent of global development costs. Genzyme will be required to make payments totaling up to \$200.0 million per global product, including up to \$60.0 million in development milestones and \$140.0 million in commercial milestones. Genzyme will also be required to pay tiered double-digit royalties up to twenty percent for each global product based on annual net sales, if any, of each global product by Genzyme, its affiliates and sublicensees.

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Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any additional milestone payments or any royalty payments from Genzyme under the 2014 Genzyme collaboration.

Under the master agreement, the parties will collaborate in the development of option products, with us leading development for all programs prior to Genzyme's opt-in and also leading development and commercialization for all programs in the Alnylam Territory after Genzyme's opt-in. If Genzyme does not exercise its option to license rights to a particular program, we will retain the exclusive right to develop and commercialize such program throughout the world, including the right to sublicense to third parties.

The 2014 Genzyme collaboration is governed by an alliance joint steering committee that is comprised of an equal number of representatives from each party. There will also be additional committees to manage various aspects of each regional, co-developed/co-promoted and global program. We and Genzyme intend to enter into supply agreements to provide for supply of collaboration products to Genzyme for clinical studies, and, at Genzyme's request, commercial sales. Genzyme also has certain rights to manufacture collaboration products. Additionally, Genzyme has certain limited opt-out rights, as specified in the master agreement, upon which products revert fully back to us with no further obligations to Genzyme.

The master agreement (including the license terms appended thereto) contains certain termination provisions, including for material breach by the other party. Unless terminated earlier pursuant to its terms, the master agreement will terminate upon the last to expire of any of the option periods under the master agreement or the license terms appended thereto.

In consideration for the rights granted to Genzyme under the master agreement and pursuant to the terms of a stock purchase agreement dated January 11, 2014, upon the closing of the equity transaction in February 2014, we sold to Genzyme 8,766,338 shares of our common stock and Genzyme paid \$700.0 million in aggregate cash consideration to us. As a condition to the closing of the equity transaction, Genzyme entered into an investor agreement with us. Under the investor agreement, until the earlier of the fifth anniversary of the expiration or earlier termination of the 2014 Genzyme collaboration and the date on which Genzyme and its affiliates cease to beneficially own at least 5% of our outstanding common stock, Genzyme and its affiliates are bound by certain standstill provisions. The standstill provisions include agreements not to acquire more than 30% of our outstanding common stock, call stockholder meetings, nominate directors other than those approved by our board of directors, subject to certain limited exceptions, or propose or support a proposal to acquire us. Further, Genzyme has agreed to vote, and cause its affiliates to vote, all shares of our voting securities they are entitled to vote, up to a maximum of 20% of our outstanding common stock, in a manner either as recommended by our board of directors or proportionally with the votes cast by our other stockholders, except with respect to certain change of control transactions or our liquidation or dissolution. Until Genzyme owns less than 7.5% of our outstanding common stock, subject to Genzyme's limited right to maintain its ownership percentage as described below, if we issue common stock or securities convertible into or exercisable for common stock to a third party that holds at least 30% of our outstanding common stock or, in connection with a collaboration or license transaction, to a third party that will initially hold at least the percentage of our outstanding common stock represented by the shares purchased by Genzyme at the closing of the equity transaction, we will offer Genzyme an opportunity to amend the standstill and voting provisions in the investor agreement to be consistent with the terms provided to such third party.

Under the investor agreement, Genzyme has also agreed not to dispose of any shares of common stock beneficially owned by it immediately after the closing of the stock purchase until the earlier of (i) December 31, 2019 (subject to extension by up to two years if Genzyme's option to select additional compounds under the master agreement is extended beyond December 31, 2019) and (ii) six months after the expiration or earlier valid termination of the collaboration, in each case subject to earlier termination in the event certain clinical activities under the collaboration fail to occur. Following the expiration of this lock-up period, Genzyme will be permitted to sell such shares of common stock subject to certain limitations, including volume and manner of sale restrictions. Notwithstanding the foregoing, following the two-year anniversary of the closing of the stock purchase, in the event that the market price per share of our common stock is at least 100% higher than the

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market price per share of our common stock at closing of the stock purchase (in each case based upon a ten-day trailing average), Genzyme may sell up to 25% of its initial shares, subject to certain restrictions on post-lock-up period dispositions as described above.

Under the investor agreement, following the lock-up period, Genzyme will have three demand rights to require us to conduct a registered underwritten public offering with respect to the shares of common stock beneficially owned by Genzyme immediately after the closing of the stock purchase. In addition, following the lock-up period, subject to certain conditions, Genzyme will be entitled to participate in registered underwritten public offerings by us if other selling stockholders are included in the registration.

The investor agreement provides that, until Genzyme owns less than 7.5% of our outstanding common stock, subject to Genzyme's limited right to maintain its ownership percentage as described herein, in connection with new issuances of common stock, subject to certain exceptions, Genzyme will be entitled to a right of first offer to participate proportionally to maintain its then-current ownership percentage of our common stock. If Genzyme is not entitled to a right of first offer with respect to a new issuance, Genzyme will have the opportunity, on a post-transaction basis, to purchase additional shares sufficient to maintain its pre-transaction ownership percentage of our common stock (subject to the same 7.5% ownership threshold).

In accordance with our investor agreement with Genzyme, as a result of our issuance of shares in connection with our acquisition of Sirna in March 2014, Genzyme exercised its right to purchase an additional 344,448 shares of our common stock for approximately \$23.0 million. In addition, in January 2015, in connection with our public offering, Genzyme exercised its right to purchase directly from us, in concurrent private placements, 744,566 shares of common stock at the public offering price resulting in approximately \$70.7 million in proceeds to us. The sales of common stock to Genzyme were not registered as part of the public offering, though they were consummated simultaneously with the public offering.

In addition, as part of these rights under the investor agreement, Genzyme has the right each January to purchase a number of shares of our common stock based on the number of shares we issued during the previous year for compensatory purposes. Genzyme exercised this right to purchase directly from us 196,251 shares of our common stock on January 22, 2015 for approximately \$18.3 million. The sale of these shares to Genzyme was consummated as a private placement.

In each instance, the purchase by Genzyme described above allowed Genzyme to maintain its ownership level of our common stock of approximately 12%.

Finally, in the event Genzyme and its affiliates acquire at least 20% or more of our outstanding common stock, Genzyme will be entitled to appoint one individual to our board of directors. Genzyme will also be entitled to certain information rights, including with respect to financial information in the event Genzyme or its affiliates require such information for its own financial reporting purposes. The rights and restrictions under the investor agreement are subject to termination upon the occurrence of certain events.

The Medicines Company. In February 2013, we and MDCO entered into a license and collaboration agreement pursuant to which we granted to MDCO an exclusive, worldwide license to develop, manufacture and commercialize RNAi therapeutics targeting PCSK9 for the treatment of hypercholesterolemia and other human diseases. MDCO paid us an upfront cash payment of \$25.0 million. Upon the achievement of certain events, we will be entitled to receive milestone payments, up to an aggregate of \$180.0 million, including up to \$30.0 million in specified development milestones, \$50.0 million in specified regulatory milestones and \$100.0 million in specified commercialization milestones. In addition, we will be entitled to royalties ranging from the low- to high-teens, based on annual worldwide net sales, if any, of licensed products by MDCO, its affiliates and sublicensees, subject to reduction under specified circumstances. In December 2014, we earned a development milestone payment of \$10.0 million based upon the initiation of our Phase 1 clinical trial for ALN-PCSSc. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any additional milestone payments or any royalty payments from MDCO.

Under the MDCO agreement, we and MDCO will collaborate in the further development of ALN-PCSSc. We retain responsibility for the development of ALN-PCSSc until Phase 1 Completion, as defined in the MDCO

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agreement, at our cost, up to an agreed upon initial development cost cap. MDCO will assume all other responsibility for the development and commercialization of ALN-PCSsc, at its sole cost. The collaboration between us and MDCO is governed by a joint steering committee comprised of an equal number of representatives from each party.

We are solely responsible for obtaining supply of finished product reasonably required for the conduct of our obligations under the initial development plan through Phase 1 Completion, and supplying MDCO with finished product reasonably required for the first Phase 2 clinical trial of ALN-PCSsc conducted by MDCO, at our expense, provided such costs do not exceed the development costs cap, subject to certain exceptions. After such time, MDCO will have the sole right and responsibility to manufacture and supply ALN-PCSsc for development and commercialization under the MDCO development plan, subject to the terms of the MDCO agreement. We and MDCO intend to enter into a supply and technical transfer agreement to provide for supply of ALN-PCSsc to MDCO within a specified time following the effective date of the MDCO agreement.

Unless terminated earlier in accordance with the terms of the agreement, the MDCO agreement expires on a licensed product-by-licensed product and country-by-country basis upon expiration of the last royalty term for any licensed product in any country, where a royalty term is defined as the latest to occur of (1) the expiration of the last valid claim of patent rights covering a licensed product, (2) the expiration of the Regulatory Exclusivity, as defined in the MDCO agreement, and (3) the twelfth anniversary of the first commercial sale of the licensed product in such country. We estimate that our fundamental RNAi patents covering licensed products under the MDCO agreement will expire both in and outside of the United States generally between 2015 and 2028. We also estimate that our ALN-PCS product-specific patents covering licensed products under the MDCO agreement in the United States and elsewhere will expire at the end of 2033. These patent rights are subject to potential patent term extensions and/or supplemental protection certificates extending such terms in countries where such extensions may become available. In addition, more patent filings relating to the collaboration may be made in the future.

Either party may terminate the MDCO agreement in the event the other party fails to cure a material breach or upon patent-related challenges by the other party. In addition, MDCO has the right to terminate the agreement without cause at any time upon four months' prior written notice.

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

Platform Alliances.

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

Monsanto paid us \$29.2 million in upfront cash payments, and was also required to make near-term milestone payments to us upon the achievement of specified technology transfer and patent-related milestones. We were also entitled to receive additional funding for collaborative research efforts. In the aggregate, we had the ability to earn up to \$5.0 million in milestone payments and research funding under the Monsanto alliance. We received a total of \$4.0 million in milestone payments from Monsanto based upon the achievement of a specified patent-related event and the completion of technology transfer activities. In September 2014, we and Monsanto mutually determined not to pursue the discovery collaboration originally contemplated under the terms of the Monsanto agreement. Accordingly, Monsanto will not be required to pay us the final milestone of \$1.0 million. There are no remaining milestones under the Monsanto agreement. Monsanto is required to pay to

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us a percentage of specified fees from certain sublicense agreements Monsanto may enter into that include access to our intellectual property, as well as low single-digit royalty payments on worldwide, net sales by Monsanto, its affiliates and sublicensees of certain licensed products, as defined in the Monsanto agreement, if any. Due to the uncertainty of the application of RNAi technology in the field of agriculture, we may not receive any license fees or royalty payments from Monsanto.

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

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

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.

Takeda paid us an upfront payment of \$100.0 million and an additional \$50.0 million upon achievement of specified technology transfer milestones. In addition, for each RNAi therapeutic product developed by Takeda, its affiliates and sublicensees, we are entitled to receive specified development, regulatory and commercialization milestone payments, totaling up to \$171.0 million per product, together with a double-digit percentage royalty payment based on worldwide annual net sales, if any. The potential future milestone payments per product include up to \$26.0 million for the achievement of specified development milestones, up to \$40.0 million for the achievement of specified regulatory milestones and up to \$105.0 million for the achievement of specified commercialization milestones. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any additional milestone payments or any royalty payments from Takeda.

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.

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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 October 2011, Arrowhead acquired certain RNA therapeutics assets from Roche, including our license and collaboration agreement, and now owns all of the rights and obligations of Roche under the license and collaboration agreement. The license is initially limited to four therapeutic areas.

Roche paid us \$273.5 million in upfront cash payments. In addition, for each RNAi therapeutic product developed by Arrowhead, its affiliates or sublicensees under the collaboration agreement, we are entitled to receive milestone payments upon achievement of specified development, regulatory and commercialization events, totaling up to an aggregate of \$100.0 million per therapeutic target, together with a single-digit percentage royalty payment based on worldwide annual net sales, if any. The potential future milestone payments for each therapeutic target include up to \$17.5 million for the achievement of specified development milestones, up to \$62.5 million for the achievement of specified regulatory milestones and up to \$20.0 million for the achievement of specified commercialization milestones. During 2014, we received a \$1.0 million milestone payment from Arrowhead upon the achievement of a specified pre-clinical event for a licensed product. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any additional milestone payments or any royalty payments from Arrowhead.

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

Other Strategic License Agreements.

Isis. In January 2015, we and Isis entered into a second amended and restated strategic collaboration and license agreement. The 2015 Isis agreement provides for certain new exclusive target cross-licenses of intellectual property on four disease targets, providing each company with exclusive RNA therapeutic license rights for two programs, and extends the parties' existing non-exclusive technology cross-license, which was originally entered into in 2004 and was amended and restated in 2009, through April 2019.

Pursuant to the 2015 Isis agreement, Isis granted to us an exclusive, low single-digit royalty-bearing license to its chemistry, motif, mechanism and target-specific intellectual property for oligonucleotide therapeutics against two targets: antithrombin and aminolevulinic acid synthase-1. In exchange, we granted to Isis an exclusive, low single-digit royalty-bearing license to our chemistry, motif, mechanism and target-specific intellectual property for oligonucleotide therapeutics against two targets: Factor XI and apolipoprotein (a).

In addition, under the 2015 Isis agreement, the parties agreed to extend the existing non-exclusive technology cross-license through April 2019. Specifically, Isis granted us a low single-digit royalty-bearing, non-exclusive license to new platform technology arising from May 2014 through April 2019 for double-stranded RNAi therapeutics. In turn, we granted Isis a low single-digit royalty-bearing, non-exclusive license to new platform technology arising from May 2014 through April 2019 for single-stranded antisense therapeutics. This broad, non-exclusive cross-license includes chemistry, motif and mechanism patents, but excludes patent claims on formulations, manufacturing and specific targets.

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Under the original 2004 agreement, Isis licensed to us its patent estate related to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi products in exchange for a previously disclosed technology access fee, participation in fees for our partnering programs and future milestone and royalty payments from us for programs that incorporate Isis' intellectual property. We have the right to use Isis' intellectual property 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 double-stranded RNA products designed to work through an RNAi mechanism, except in the context of a collaboration in which Isis plays an active role.

In turn, under the original 2004 agreement, we non-exclusively licensed to Isis our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded antisense therapeutics, single stranded RNAi therapeutics and to research double-stranded RNAi compounds. Isis also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on a non-exclusive basis. We granted these licenses for RNAi therapeutics in exchange for option fees, and future milestone and royalty payments from Isis for RNAi programs that incorporate certain of our intellectual property.

In August 2012, we and Isis amended the agreement to provide certain terms for the discovery, development and commercialization of double-stranded RNA products by us or our sublicensees in the field of agriculture.

As set forth in the 2015 Isis agreement, under the original 2004 agreement, we agreed to pay Isis milestone payments, totaling up to approximately \$3.4 million, upon the occurrence of specified development and regulatory events, and low single-digit royalties on sales, if any, for each product that we or a collaborator develop 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 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. Isis agreed to pay us, per therapeutic target, a license fee of \$0.5 million, milestone payments for double-stranded RNAi products totaling approximately \$3.4 million, payable upon the occurrence of specified development and regulatory events, and low single-digit royalties on sales, if any, for each double-stranded RNAi or single-stranded RNAi product developed by Isis or a collaborator that utilizes our intellectual property. 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 Isis.

The term of 2015 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. Either party may terminate the 2015 Isis agreement on 90 days' prior written notice if the other party materially breaches the agreement and fails to cure the breach within the 90-day notice period and no substantial steps have otherwise been taken to cure the breach, provided, however, that neither party may terminate licenses granted to the other party to the extent necessary to develop or sell products that have at least reached investigational new drug-enabling studies (except for a party's uncured failure of its payment obligations). Either party may also terminate the agreement in the event the other party undergoes specified bankruptcy events.

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. 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

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property and related technology. Novartis' right of first offer with respect to an exclusive license for additional targets has terminated. Under the terms of the collaboration and license agreement, for any RNAi therapeutic products Novartis develops against its selected 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 additional milestone payments or any royalty payments from Novartis.

During 2014, Novartis publically indicated that they no longer intend to invest in the development of certain RNAi therapeutics and intend to divest certain of their RNAi assets. Novartis has the right to assign our collaboration and license agreement to a third-party that acquires substantially all of its assets relating to RNAi.

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 License Agreements

Tekmira. In November 2012, we, TPC and Protiva agreed to restructure our existing contractual relationship. In connection with this restructuring, the parties entered into a cross-license agreement, and agreed to terminate certain prior agreements, including: the May 2008 amended and restated license and collaboration between us and TPC, the May 2008 amended and restated cross-license agreement between us and Protiva, and the January 2009 manufacturing agreement between us and TPC.

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

In addition, we elected to buy out our manufacturing obligations to TPC with respect to our LNP-based pipeline programs. Pursuant to the terms of the 2012 cross-license agreement, we made a one-time payment of

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\$30.0 million to TPC for the termination of, and our release from, all of our obligations under the manufacturing agreement, including without limitation the obligations to obtain materials and/or services from TPC. We also have the right to manufacture and have manufactured our LNP-based RNAi therapeutics, which right may be sublicensed to our collaborators.

Further, as part of this restructuring, we elected to buy-down certain future potential milestone and royalty payments due to Tekmira for certain of our RNAi therapeutics, formulated using LNP technology. Specifically, pursuant to the cross-license agreement, we made a one-time payment of \$35.0 million to TPC, which amount constituted payment for the termination of the 2008 license agreements with TPC and Protiva and the parties' rights and obligations thereunder, as well as the buy-down of certain milestone payments and the significant reduction of royalty rates for ALN-VSP, ALN-PCS02 and patisiran. As a result of this buy-down, future royalty rates for these LNP-based products are now further reduced from the low single-digit royalties due on other products, as described below. In addition, we agreed to pay TPC an aggregate of \$10.0 million in contingent milestone payments related to advancement of ALN-VSP and patisiran, which represent the only potential milestones due to Tekmira for ALN-VSP, ALN-PCS02 and patisiran. In December 2013, we paid to TPC \$5.0 million in connection with the initiation of our Phase 3 clinical trial for patisiran, fulfilling one of these milestone obligations. With respect to the second \$5.0 million milestone, in August 2013, we initiated binding arbitration proceedings to resolve a disagreement with TPC regarding the achievement by TPC of this milestone under our cross-license agreement relating to the manufacture of ALN-VSP clinical trial material for use in China. We currently expect that the Tekmira arbitration hearing will be held in the second quarter of 2015.

Consistent with the prior license agreements, under the 2012 cross-license agreement, we are obligated to pay TPC up to an aggregate of \$16.0 million in milestone payments for any future RNAi therapeutic formulated using Tekmira LNP technology, excluding ALN-VSP, ALN-PCS02 and patisiran, together with low single-digit royalty payments on annual product sales, if any.

Under the 2012 cross-license Agreement, Tekmira maintains the three exclusive and five non-exclusive licenses previously granted by us under the prior license agreements to research, develop and commercialize RNAi therapeutics directed to up to eight gene targets. In addition, we granted Tekmira a non-exclusive license for two additional gene targets, on the same terms and conditions as the prior non-exclusive licenses. Tekmira also acquired from Acuitas its existing options for three additional non-exclusive licenses, which were included under the 2012 cross-license agreement. Tekmira may sublicense these rights on a product-by-product basis. We waived our right under the prior license agreements to opt-in to the Tekmira research program directed to polo-like kinase 1, or PLK1. Under the 2012 cross-license agreement, we are eligible to receive from Tekmira up to an aggregate of \$8.5 million in milestone payments for RNAi therapeutics directed to nine of the targets for which we have granted licenses to Tekmira, together with single-digit royalties on annual product sales, if any, of RNAi therapeutic products directed to all thirteen of the targets for which we have granted licenses to Tekmira. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any milestone or royalty payments from Tekmira.

The term of the 2012 cross-license agreement generally ends upon the expiration of the last-to-expire royalty term. Royalties are payable on a product-by-product and country-by-country basis commencing on the first commercial sale of a product in a country and continuing during any period in which (a) in the case of us, a valid claim within the Tekmira Royalty-Bearing Patents (as defined in the 2012 cross-license agreement) covers our applicable product in such country of sale, or (b) in the case of Tekmira products, a valid claim within our patents covers the applicable Tekmira product in such country of sale. We estimate that our fundamental RNAi patents covered under the 2012 cross-license agreement will expire both in and outside the United States generally between 2019 and 2021, and that the Tekmira LNP patents covered under the 2012 cross-license agreement will expire both in and outside the United States generally between 2020 and 2030, subject in each case to any potential patent term extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available. Either party may terminate a license it granted to the other in the event that the other party fails to cure a material breach of its obligations relating to that license. Furthermore, either party may terminate the 2012 cross-license agreement in the event the other

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party fails to cure a material breach of an obligation under the agreement. In addition, either party may terminate the 2012 cross-license agreement upon patent-related challenges by the other party.

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

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

microRNA Therapeutics

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

Regulus, which initially was established as a limited liability company, converted to a C corporation as of January 2, 2009 and changed its name to Regulus Therapeutics Inc. In consideration for our and Isis initial interests in Regulus, we and Isis each granted Regulus exclusive licenses to our intellectual property for certain microRNA therapeutics as well as certain patents in the microRNA field. Regulus operates as an independent company with a separate board of directors, scientific advisory board and management team. In October 2012, Regulus completed an underwritten initial public offering. Currently, we own approximately 12% of Regulus outstanding common stock.

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

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

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;

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siRNAs directed to specific targets as treatments for particular diseases;

delivery technologies, such as in the fields of carbohydrate conjugates and 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 2,000 active cases and over 1,100 granted or issued patents, of which over 400 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 double-stranded RNAs of particular lengths and particular structural features, such as blunt and/or overhanging ends, as well as various types and patterns of chemical modifications. 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.

Patent		First					
Licensor/Owner	Subject Matter	Priority Date	Inventors	Status		Expiration Date*	Alnylam Rights
Isis	Inactivation of target mRNA	6/6/1996 (EP) and 6/6/1997 (U.S.)	S. Crooke	U.S. 5,898,031, U.S. 6,107,094,		6/6/2016	Exclusive rights for therapeutic purposes related to siRNAs**
				U.S. 7,432,250 & U.S. 7,695,902			
				EP 0928290		6/6/2017	
				Additional applications pending in the U.S. and several foreign jurisdictions			
Carnegie Institution of Washington	Double-stranded RNAs to induce RNAi	12/23/1997	A. Fire,	U.S. 6,506,559, U.S. 7,560,438 &		12/18/2018	Non-exclusive rights for therapeutic purposes
			C. Mello	U.S. 7,538,095			
				Additional applications pending in the U.S. and several foreign jurisdictions			
Medical College of Georgia Research	Methods for inhibiting gene expression using double-stranded	1/28/1999	Y. Li,	AU 776150 (Australia)		1/28/2020	Exclusive rights
			M. Farrell, M. Kirby				

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Institute, Inc.	RNA			Additional applications pending in the U.S., Europe and Canada		
Alnylam	Small double-stranded RNAs as therapeutic products	1/30/1999	R. Kreutzer, S. Limmer	EP 1214945 (revoked/under appeal), EP 1550719 (revoked/under appeal), CA 2359180 (Canada), AU 778474 (Australia), ZA 2001/5909 (South Africa), DE 20023125 U1, DE 10066235 & DE 10080167 (Germany)	1/29/2020	Owned
				Additional applications pending in the U.S. and several foreign jurisdictions		
Alnylam	Medicament for inhibiting the expression of a target gene and medicament for treating a tumor disease	1/9/2001	R. Kreutzer, S. Limmer, H-P.Vornlocher, P. Hadwiger, A. Geick, M. Ocker, C. Herold, D. Schuppan	EP 1349927 (opposed and maintained in amended form)	1/9/2022	Owned

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Patent		First				
Licensors/Owner	Subject Matter	Priority Date	Inventors	Status	Expiration Date*	Alnylam Rights
Alnylam	Method for inhibiting the expression of a wide variety of oncology target genes with double-stranded RNA between 15-49 nucleotides	1/9/2001	R. Kreutzer, S. Limmer, P. Hadwiger	EP 1352061 (opposed, maintained with no further right to appeal)	1/9/2022	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 cells	11/19/1999	M. Zernicka-Goetz, F. Wianny, M.J. Evans, D.M. Glover	EP 1230375 (revoked/under appeal), SG 89569 (Singapore), AU 774285 (Australia) Additional applications pending in the U.S. and several foreign jurisdictions	11/17/2020	Exclusive rights for therapeutic purposes
Massachusetts Institute of Technology, Whitehead Institute for Biomedical Research, Max Planck Gesellschaft, University of Massachusetts ***	Mediation of RNAi by small RNAs 21-23 base pairs long with claims directed to compositions, methods of use and manufacture	3/30/2000	D.P. Bartel, P.A. Sharp, T. Tuschl, P.D. Zamore	U.S. 8,790,922, U.S. 8,742,092, U.S. 8,632,997, U.S. 8,552,171, U.S. 8,420,391 & U.S. 8,394,628 EP 1309726 (opposed and maintained in amended form/under appeal), EP 2028278 (opposed), EP 2345742, EP 2360253 (opposed) & EP 2361981 (opposed), AU 2001249622 (Australia), NZ 522045 (New Zealand), KR 08724437 & KR 10-0909681 (Korea) Additional applications pending in the U.S. and several foreign jurisdictions	3/30/2021	Exclusive rights for therapeutic purposes***
Massachusetts Institute of Technology, Whitehead Institute, University of Massachusetts, Max Planck Gesellschaft (U.S.)****	Synthetic and chemically modified siRNAs as therapeutic products including patents with claims including those directed to double-stranded RNA of between 19 to 23 or 19 to 25 nucleotides, with and without a 3 overhang; claims directed to	12/1/2000 (EP), 4/24/2004 and 4/27/2004	T. Tuschl, S. Elbashir, W. Lendeckel, M. Wilm#, R. Lührmann# #EMBL inventors	U.S. 7,056,704, U.S. 7,078,196, U.S. 8,329,463, U.S. 8,372,968, U.S. 8,362,231 & U.S. 8,445,237, U.S. 8,765,930, U.S. 8,778,902, U.S. 8,796,016, U.S. 8,853,384, U.S. 8,895,721 & U.S. 8,933,044 EP 1407044 (opposed and maintained in amended form/under appeal), EP 1873259, EP 2348133, EP 2348134 & EP 2351852 (opposed), AU	11/29/2021	Exclusive rights for therapeutic purposes****

Max Planck Gesellschaft (ex-U.S.), European Molecular Biology Laboratory (ex-U.S.)*****	double-stranded RNA of between 19 to 52 nucleotides with a 3' overhang; claims directed to double-stranded RNA of 14 to 24 base pairs or up to 25 base pairs with at least one nucleotide analogue, along with methods of using and making such double-stranded RNA	2002235744 (Australia), ZA 2003/3929 (South Africa), SG 96891 (Singapore), NZ 52588 (New Zealand), JP 4 095 895 (opposed and maintained), JP 4 494 392 (Japan), RU 2322500 (Russia), CN 1568373 (China) Additional applications pending in the U.S. and several foreign jurisdictions
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Patent		First				
Licensors/Owner	Subject Matter	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
Stanford University	RNAi uses <i>in vivo</i> 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
Alnylam	Claims directed to carbohydrate conjugates linked to siRNA	4/17/2003	M. Manoharan	U.S. 7,723,509, U.S. 7,745,608, U.S. 7,851,615, U.S. 8,017,762, U.S. 8,507,661, U.S. 8,344,125, U.S. 8,796,436, U.S. 8,865,677 & U.S. 8,426,377	9/21/2024	Owned
Alnylam	Claims directed to GalNAc-conjugated siRNA	12/13/2007	M. Manoharan	U.S. 8,106,022, U.S. 8,450,467 & U.S. 8,828,956	2029	Owned
Sirna*****	Claims directed to highly chemically modified oligonucleotides with granted claims directed to double-stranded RNA of between 18 and 24 nucleotides with various combinations of chemical modifications	2/20/2002	J. McSwiggen	U.S. 7,923,547, U.S. 7,956,176, U.S. 7,989,612, U.S. 8, 232,383, U.S. 8,268,986, U.S. 8,236,944, U.S. 8,272,979, U.S. 8,273,866, U.S. 8,242,257 & U.S. 8,648,185 EP 1423406 (opposed and maintained), EP 2287306 (opposed), EP2278004 (opposed, opposition withdrawn), EP1627061, EP1458741 (opposed, opposition withdrawn) AU 2003216324, AU 2006203725, CA 2526831 (Canada), JP 49481631 Additional cases pending in US and EP	2/20/2023-2028	Owned

* 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, licensed its interest separately to Sirna. In March 2014, we acquired Sirna from Merck, thus we now hold exclusive rights.

**** We hold exclusive rights to the interest owned by all co-owners in the U.S. UMass had a right to sublicense the U.S. Tuschl II patent family to Merck but such right has been disclaimed by UMass.

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

***** Sirna is our wholly-owned subsidiary.

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 double-stranded RNA products, through a license agreement with Isis. Under the terms of our agreement, Isis agreed not to grant licenses under these patents to any other organization for double-stranded RNA products designed to work through an RNAi mechanism, except in the context of a collaboration in which Isis plays an active role. Our agreement with Isis was amended and restated in January 2015 to, among other things, extend the license for an additional five years, through April 2019.

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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 Glover patent series has resulted in several patent grants, including in Europe (EP 1230375). We have an exclusive license to the Glover patent for therapeutic uses from CRT.

The Tuschl patent applications filed by Whitehead, the Massachusetts Institute of Technology, or MIT, UMass and Max Planck Gesellschaft zur Foerderung der Wissenschaften e.V. on the invention by Dr. Tuschl and his colleagues, which we call the Tuschl I patent series, cover compositions and methods important for RNAi discovery. We are the exclusive licensee of the ownership interests of the Max Planck Gesellschaft zur Foerderung der Wissenschaften e.V., MIT and Whitehead in the Tuschl I patent series for RNAi therapeutics. The Tuschl patent applications filed by Max Planck Gesellschaft zur Foerderung der Wissenschaften e.V. on the invention by Dr. Tuschl and his colleagues, which we call the Tuschl II patent series, cover what we believe are key structural features of siRNAs. Specifically, the Tuschl II patents and patent applications include claims directed to synthetic siRNAs and the use of chemical modifications to stabilize siRNAs. We have obtained an exclusive license to claims in the Tuschl II patent series uniquely covering the use of RNAi for therapeutic purposes. Collectively, the Tuschl I and II patent families cover a wide range of double-stranded RNA molecules including those unmodified and those comprising chemical modifications. Examples of those chemical modifications encompassed by the Tuschl claims include those modifications made in the ribose ring, e.g., at the 2' position such as 2'-OMe, 2'-F or modifications such as those found in locked and unlocked (acyclic) nucleotides.

The Fire and Mello patent owned by the Carnegie Institution covers the use of double-stranded RNAs 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 double-stranded RNAs that are important for the biological activity of siRNAs in mammalian cells. We believe that these specific features are the subjects of the Crooke, Kreutzer-Limmer, Glover and Tuschl II patents and patent applications for which we have secured exclusive rights.

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

Intellectual Property Related to Chemical Modifications

Our amended and restated collaboration and license agreement with Isis provides us with rights to practice the inventions covered by over 200 issued patents worldwide, as well as rights based on future chemistry patent applications through April 2014 for use with double-stranded RNA products. In January 2015, we entered into a second amended and restated agreement with Isis to extend our rights to future chemistry applications through April 2019. These patents will expire both in and outside the United States generally between 2015 and 2035, 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 double-stranded RNA therapeutic products designed to work through an RNAi mechanism. Under the terms of our agreement, Isis agreed not to grant licenses under these patents to any other organization for double-stranded RNA products designed to work through an RNAi mechanism, except in the context of a collaboration in which Isis plays an active role.

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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, various patents 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 and modifications such as those found in locked and unlocked (acyclic) nucleotides. 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.

In addition to the above, in March 2014, we acquired the RNAi assets from Merck, which included intellectual property developed at Sirna and Merck. The acquired patent portfolio includes the McSwiggen patent families with issued and pending claims covering highly chemically modified oligonucleotide compositions, both single- and double-stranded and independent of 5' and 3' architecture. A total of ten patents have been granted in the United States with claims directed to various combinations of chemical modifications to double-stranded RNA of between 18 and 24 nucleotides. Notably, U.S. 8,273,866 was granted in September 2012 with significant patent term adjustment extending the expiration of this patent to mid-2028. EP423406 was granted in September 2010 with claims directed to double-stranded RNA of between 18 and 24 nucleotides with ten or more chemical modifications on the pyrimidine residues of the sense and/or antisense strand. As indicated in the chart above, four additional EP patents have been granted with claims to various combinations of chemically modified compositions comprising double-stranded RNA of between 18 and 24 nucleotides and methods of making and using such combinations.

Intellectual Property Related to the Delivery of siRNAs to Cells

We also pursue 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 cholesterol and carbohydrate conjugation, cationic lipids, peptide and antibody-based targeting, and polymer conjugations. Our collaborative efforts have included 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 and/or acquiring the most promising technology.

In September 2014, the United States Patent and Trademark Office, or USPTO, granted U.S. Patent No. 8,828,956 with claims directed to compositions including those comprising a modified RNA agent linked to a biantennary or triantennary ligand. Specifically, the granted patent includes claims that broadly cover single-stranded or double-stranded, chemically modified RNA therapeutics conjugated with a GalNAc ligand independent of length, sequence or disease target.

As part of the Sirna acquisition, we obtained several patent families directed to various conjugate technologies including tetra-GalNAc compositions and methods. The tetra-GalNAc cases are pending worldwide and will expire May 1, 2033. Also included were patent families directed to novel lipid compositions and formulations that are pending worldwide and set to expire May 31, 2031.

In addition to the Sirna delivery technology, we have a 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 No. 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 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.

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

Intellectual Property Related to siRNAs Directed to Specific Targets

We have filed a number of patent applications claiming specific siRNAs directed to various gene targets that correlate to specific diseases. While there may be a significant number of competing applications filed by other organizations claiming siRNAs to treat the same gene target, we were among the first companies to focus and file on RNAi therapeutics, and thus, we believe that a number of our patent applications may predate competing applications that others may have filed. Reflecting this, in August 2005, the EPO granted a broad patent, which we call the Kreutzer-Limmer II patent, with 103 allowed claims on therapeutic compositions, methods and uses comprising siRNAs that are complementary to mRNA sequences in over 125 disease target genes. In July 2009, the EPO ruled in our favor in an opposition proceeding related to the Kreutzer-Limmer II patent. The decision had been appealed by Sirna and was subsequently withdrawn upon our acquisition of Sirna. No further appeal before the EPO is available. 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. Granted U.S. patent 8,618,277 obtained in the Sirna acquisition and set to expire February 20, 2023, contains claims directed to a highly chemically modified double-stranded siRNA of between 18-24 nucleotides specifically targeting the hepatitis B virus in a sequence independent manner. 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.

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, *inter partes* review, post grant review and opposition proceedings, in various patent offices relating to patent rights in the RNAi field. On September 16, 2012, the America Invents Act went into effect and provided for expanded patent challenge, i.e., *inter partes* review and post-grant review. These provide additional opportunities for third parties to challenge our patents. For example, as noted in the table 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,

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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, to smaller biotechnology companies with fewer resources and expertise than we have. We believe that for most or all of our drug development programs, there will be one or more competing programs under development at other companies. In many cases, the companies with competing programs will have access to greater resources and expertise than we do and may be more advanced in those programs.

Competition for Our Business in General

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 Takeda, Kyowa Hakko Kirin, Marina Biotech, Inc., Arrowhead and its subsidiary, Calando Pharmaceuticals, Inc., or Calando, Quark Pharmaceuticals, Inc., or Quark, Silence Therapeutics plc, Tekmira, Sylentis, S.A.U., or Sylentis, Dicerna Pharmaceuticals, Inc. and Arcturus Therapeutics. Many of these companies have licensed our intellectual property. Benitec Ltd., or Benitec, is working on gene therapy approaches to RNAi therapeutics. Companies working on microRNA therapeutics include Regulus, Rosetta Genomics, Roche, through its acquisition in 2014 of Santaris Pharma A/S, 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 the ASO drugs, fomivirsen, which was approved by the FDA in 1998 for the treatment of cytomegalovirus retinitis, but is no longer available in the United States, and mipomersen, which was approved by the FDA for the treatment of patients with homozygous familial hypercholesterolemia, or HoFH. In addition, a number of other companies have ASO-based product candidates in various stages of pre-clinical and clinical development, including Roche, Celgene, Antisense Therapeutics, Ltd. and Sarepta Therapeutics, 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

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well as potentially new approaches that may result in the more rapid development of RNAi therapeutics or more effective technologies for RNAi drug development or delivery.

Competing Drugs for Our RNAi Therapeutics in Clinical Development

TTR-Mediated Amyloidosis (ATTR). Until recently, organ transplantation was the only treatment option for patients with ATTR. Liver or combined heart/liver transplantations were the only available treatment options for FAP. Only a subset of FAP patients with early stage disease qualify for this costly and invasive procedure and, even following liver transplantation, the disease continues to progress for many patients, presumably due to normal TTR being deposited into preexisting fibrils. Moreover, there is a shortage of donors to provide healthy livers for transplantation. In November 2011, Pfizer received marketing approval from the EC for tafamidis for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. Tafamidis is intended to stabilize wild-type and variant TTR, to prevent dissociation of the TTR protein and thereby inhibit the formation of TTR oligomers and amyloid fibrils.

The only currently available treatments for FAC are aimed at relief of symptoms, such as diuretics, or water pills, to treat the swelling of the ankles, one of the symptoms of FAC. For patients with advanced cardiomyopathy (FAC and SSA) heart transplant is a therapeutic option. Again, the scarcity of organs for transplantation, and the mortality, morbidity and cost associated with this procedure render it a realistic option for only a very small number of patients. In December 2013, Pfizer initiated a Phase 3 clinical trial of tafamidis in patients with TTR amyloidosis cardiomyopathy. The study is expected to enroll up to 400 patients and study two dose levels, with a 30-month treatment duration for each patient.

Several drugs are in clinical development for the treatment of ATTR. Researchers at Boston University, in collaboration with the National Institute of Neurological Disorders and Stroke, conducted a Phase 2/3 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*. This clinical trial concluded that the use of diflunisal compared with placebo for two years reduced the rate of progression of neurological impairment and preserved quality of life. As published, the discontinuation rate was high in this clinical trial in both treatment arms (approximately 50% overall) and the majority of patients continued to deteriorate, including patients on diflunisal. Furthermore, the safety profile of this drug and its known adverse effects, particularly on the kidney and heart, could likely limit the potential use of it in this disease.

In addition, Isis, together with its partner GlaxoSmithKline, is developing ISIS-TTR_{rx}, an ASO designed to treat patients with FAP. Isis has completed a Phase 1 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. This study reported that ISIS-TTR_{rx} was generally well tolerated with no significant adverse events. The occurrence of injection site reactions and flu-like symptoms were reported in patients taking ISIS-TTR_{rx}. Isis announced that ISIS-TTR_{rx} was granted fast track designation by the FDA for the treatment of patients with FAP. Isis initiated a Phase 2/3 clinical trial in early 2013 that is expected to enroll up to 195 patients, with a treatment duration of 15 months for each patient.

Hemophilia. The global market for treatments of hemophilia and bleeding disorders is valued at more than \$9.0 billion. Products on the market include: Factor VIII replacement products marketed by Baxter Healthcare Corporation, Bayer Healthcare Pharmaceuticals, Pfizer and CSL Behring; Factor IX replacement products marketed by Pfizer (Wyeth), Baxter and CSL Behring; a Factor VIIa replacement product marketed by Novo Nordisk; and concentrated products for fibrinogen, FII, FX and FXI deficiencies. In 2014, long-acting factor VIII replacement and factor IX replacement products from Biogen Idec were approved by the FDA. Also in 2014, recombinant porcine Factor VIII was approved by the FDA for the treatment of acquired HA.

A number of products are currently in development for the treatment of hemophilia. Additional long-acting factor therapies will be on the market in the near future, and may extend the time between intravenous doses. For example, Novo Nordisk is developing two long-acting recombinant derivatives for the treatment of HB, both of which are in Phase 3 clinical trials. Baxter is also developing long-acting recombinant factor replacement

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products for the treatment of HB. Bayer is also developing a long-acting recombinant product and Pfizer is developing a recombinant Factor VIIa variant that is in a Phase 1 clinical trial in adults with HA or HB.

A particular segment of people with hemophilia develop neutralizing antibodies to the factors; these are called people with inhibitors. They cannot be given replacement factors VIII or IX since the inhibitor, an antibody, will lead to immediate clearance of any Factor VIII or Factor IX that is administered. Generally speaking, these individuals are monitored for signs of a bleed and then are given recombinant Factor VIIa or FEIBA. FEIBA is an anti-inhibitor coagulant complex from Baxter. It is approved in both the United States and the EU for the treatment of acute bleeds and for prophylactic treatment.

Molecules currently in development may offer new treatments for HA and HB subjects with and without inhibitors. Chugai and Roche are developing a bi-specific antibody (ACE-910) which binds to factors IXa and X and mimics the Factor VIII cofactor function in HA subjects. This product has completed a Phase 1 clinical trial and has been shown to reduce the incidence of bleeding events in people with hemophilia with and without inhibitors. Novo Nordisk is developing Anti-TFPI (NN7415), a monoclonal antibody against a tissue factor pathway inhibitor, for the treatment of HA and HB, currently in Phase 1 clinical trials. Baxter is developing a peptide which also targets a tissue factor pathway inhibitor for the treatment of HA and HB.

A number of companies are actively developing gene therapy products which use a virus to deliver a functional segment of a particular gene into the cells of the subject with hemophilia. In 2013, Biomarin licensed technology from University College London and St. Jude Children's Research Hospital to develop gene therapy products for the treatment of HA. In 2014, Baxter acquired Chatham Therapeutics, which was developing a gene therapy product for the treatment of HB. In 2014, Bayer partnered with Dimension Therapeutics, or Dimension, to develop a gene therapy product for the treatment of HA. Dimension is also developing a gene therapy product for the treatment of HB.

Complement-Mediated Diseases. The global market for drugs that specifically target complement-mediated diseases is significant. The only product in this market is eculizumab, a monoclonal antibody developed by Alexion Pharmaceuticals that inhibits the cleavage of the protein complement component 5 (C5) into its components C5a and C5b. In 2007, eculizumab was approved by the FDA and the EC to treat PNH, a hemolytic anemia caused by a deficiency of proteins on the red blood cell membrane that protect the cells from destruction by the complement system. In 2011, eculizumab was approved by the FDA and EC to treat aHUS, a systemic disease caused by chronic uncontrolled activation of the complement system. Eculizumab is also currently being studied in a number of other diseases that are believed to be complement-mediated including: neuromyelitis optica, myasthenia gravis, antibody-mediated rejection and delayed graft function.

A number of products are in development for the treatment of complement-mediated diseases. Swedish Orphan Biovitrum (SOBI) is developing SOBI002, an antibody to inhibit C5. In 2014, the Phase 1 trial for SOBI002 was placed on hold when adverse effects were observed in the study. Shire is conducting Phase 1 trials of a plasma-derived C1 esterase inhibitor for the treatment of PNH and acute neuromyelitis optica that is currently approved for the prevention of hereditary angioedema attacks. Apellis Pharmaceuticals is developing APL-2, a subcutaneously administered analogue of compstatin which inhibits Complement Component C3 (C3). A Phase 1 trial for APL-2 began in October 2014.

Hepatic Porphyrrias. The global market for hepatic porphyrias is less than \$150.0 million. This market is made up of intravenous hemin in the United States and intravenous heme arginate in the EC. Both products are currently manufactured by Recordati S.p.A. Both molecules are human-derived blood products which have been shown to reduce the duration of porphyria attacks.

Several other products are in development for the treatment of AIP. The AIPGENE consortium, a European collaboration which included industry sponsors UniQure and Digna Biotech, is developing AMT-021, a gene therapy product for the treatment of AIP. In 2014, the consortium released one-year follow-up data on the AMT-021 which confirmed the safety and the successful transduction of the virus. No data on the observations related to protein expression have been publically disclosed.

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Hypercholesterolemia. The current standard of care for patients with hypercholesterolemia includes the use of several agents. Front line therapy consists of HMG CoA reductase inhibitors, commonly known as statins, which block production of cholesterol by the liver and increase clearance of LDL-C from the bloodstream. These include atorvastatin, simvastatin, rosuvastatin and pravastatin. A different class of compounds, which includes ezetimibe and ezetimibe/simvastatin, function by blocking cholesterol uptake from the diet and are utilized on their own or in combination with statins. Aegerion Pharmaceuticals, Inc. is developing lomitapide, an microsomal triglyceride protein, or MTP, inhibitor for the treatment of dyslipidemia. In December 2012, the FDA approved lomitapide for use in patients with HoFH and in July 2013 lomitapide was approved for HoFH in the EU.

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

With regard to future therapies in clinical development, several anti-PCSK9 antibodies have advanced into clinical development, including alirocumab, which is being developed by Regeneron Pharmaceuticals, Inc., in collaboration with Sanofi. Data reported from a Phase 3 clinical trial evaluating alirocumab in 2,341 patients with heterozygous familial hypercholesterolemia or coronary heart disease demonstrated mean reductions in LDL-C from baseline of 61% and showed a statistically significant reduction in a post-hoc analysis of adjudicated major CV events. Numerous other Phase 3 clinical studies demonstrated similar results. In 2012, Regeneron announced the launch of ODYSSEY OUTCOMES, an 18,000 patient Phase 3 clinical trial designed to test the efficacy and safety of REGN727 added to maximal doses of statins in reducing cardiovascular morbidity and mortality in patients with recent acute coronary syndrome, a population at high risk of cardiovascular events despite best contemporary therapy. Regeneron filed an NDA for alirocumab with the FDA in 2014.

Amgen Inc. has also advanced evolocumab, an anti-PCSK9 antibody, through late-stage clinical development. Data reported from the 52-week Phase 3 DESCARTES trial in 905 patients showed that evolocumab reduced LDL-C by 57%. Numerous other phase 3 studies demonstrated similar results. In August 2014, Amgen filed an NDA with the FDA for evolocumab. In September 2014, Amgen filed a marketing application with the EC.

We are also aware of ongoing programs at Pfizer and other companies to develop anti-PCSK9 molecules, and we are aware of several additional similar compounds in advanced pre-clinical development.

In addition, Esperion Therapeutics is developing bempedoic acid (ETC-1002), a small molecule drug which is both an ATP citrate lyase inhibitor and an activator of AMP kinase. In a Phase 2 trial in patients with hypercholesterolemia with or without statin intolerance, patients taking ETC-1002 had a 30% reduction in LDL-C compared with baseline. ETC-1002 is in Phase 2b clinical trials.

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. For example, with respect to ALN-HBV, oral nucleoside/nucleotide analogues have demonstrated the ability to potently inhibit HBV replication and suppress levels of HBV DNA in patients with HBV and are approved for the treatment of these patients in the United States, Europe and other countries. In addition, a large number of novel agents, including agents using chemically synthesized siRNA, are currently in development for the treatment of patients with HBV. However, notwithstanding the availability of existing 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

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rigorous regulation by the FDA. The Federal Food, Drug, and Cosmetic Act, or FDCA, 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 nonclinical 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 institutional 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 practice, 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 patisiran, revusiran, ALN-AT3 and ALN-PCSsc, 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.

Nonclinical 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 nonclinical tests and formulation of compounds for testing must comply with federal regulations and requirements. The results of nonclinical testing are submitted to the FDA as part of an IND, together with chemistry, manufacturing and controls, or CMC, information, analytical and stability data, a proposed clinical trial protocol and other information.

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

Clinical trials involve the administration of an investigational new drug to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted in compliance with federal regulations and requirements, including GCP, which are ethical and scientific quality standards and FDA requirements for conducting, recording and reporting clinical trials to assure data integrity and protect the rights, safety and well-being of trial participants and include the requirement that all research subjects provide their informed consent for their participation in any clinical study. Clinical studies are conducted 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

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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 1, 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 2 usually involves trials in a limited patient population, to assess the optimum dosage and dose regimen, identify possible adverse effects and safety risks, and provide preliminary support for the efficacy of the drug in the indication being studied.

If Phase 2 clinical trials demonstrate that a drug may be effective and the risks are considered acceptable given the observed efficacy of the drug and the severity of the illness, Phase 3 clinical trials may be undertaken to further evaluate the drug's clinical efficacy, side effects, and 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 1, Phase 2 or Phase 3 testing of any drug candidates may not be completed successfully within any specified time period, if at all. The FDA closely monitors the progress of each of the three phases of clinical trials that are conducted in the United States. The FDA may, at its discretion, reevaluate, alter, suspend or terminate the testing based upon the data accumulated to that point and the FDA's assessment of the risk/benefit ratio to the subject. The FDA, an IRB, or a clinical trial sponsor may suspend or terminate clinical trials at any time for various reasons, including a finding that the subjects or patients are being exposed to an unacceptable health risk. The FDA can also request that additional clinical trials be conducted as a condition to product approval. Finally, sponsors are required to publicly disseminate information about ongoing and completed clinical trials on a government website administered by the National Institutes of Health, or NIH, and are subject to civil monetary penalties and other civil and criminal sanctions for failing to meet these obligations. After successful completion of the required clinical testing, as well as nonclinical testing and manufacturing requirements, generally an NDA is prepared and submitted to the FDA.

We believe that any RNAi product candidate we develop, whether for the treatment of ATTR, hemophilia and RBD, complement mediated diseases, hypercholesterolemia or the various indications targeted in our development or 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 effectiveness 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. Under the Prescription Drug User Fee Act, or PDUFA, as amended, each NDA must be accompanied by a user fee. The FDA adjusts the PDUFA user fees on an annual basis. According to the FDA's fee schedule, effective through September 30, 2015, the user fee for each NDA application requiring clinical data, is approximately \$2.3 million. PDUFA also imposes an annual product fee for drugs and an annual establishment fee on facilities used to manufacture prescription drugs. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. Additionally, no user fees are assessed on NDAs for products designated as orphan drugs, unless the product also includes a non-orphan indication.

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. If the submission is accepted for filing, the FDA begins an in-depth review of the NDA. The FDA has agreed to specified performance goals

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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 independent 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 conducts a pre-approval inspection to gain assurance that 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 bioequivalence monitoring inspection of select clinical trial sites involved in conducting pivotal studies to assure data integrity and compliance with applicable GCP requirements.

If the FDA evaluation of the NDA and the inspections of manufacturing facilities and clinical trial sites are favorable, the FDA may issue an approval letter, which authorizes commercial marketing of the drug with specific prescribing information for a specific indication. As a condition of NDA approval, the FDA may require post-approval testing, sometimes referred to as Phase 4 trials, and surveillance to monitor the drug's safety or effectiveness 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.

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

If the FDA's evaluation of the NDA submission or manufacturing facilities is not favorable, the FDA may refuse to approve the NDA 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 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/devices. 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. The FDA may regulate the product as a combination product or

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require additional approvals or clearances for the modified device. In addition, to the extent the delivery device is owned by another company, we would need that company's cooperation to implement the necessary changes to the device and to obtain any additional approvals or clearances. Obtaining such additional approvals or clearances, and cooperation of other companies, when necessary, could significantly delay, and increase the cost of obtaining marketing approval, which could reduce the commercial viability of a product candidate. To the extent that we rely on previously unapproved drug delivery systems, we may be subject to additional testing and approval requirements from the FDA above and beyond those described above.

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

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

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

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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.

The Patient Protection and Affordable Care Act, also referred to as the PPACA or the Affordable Care Act, signed into law on March 23, 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCI Act, which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. This amendment to the Public Health Service Act attempts to minimize duplicative testing. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical study or studies. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. However, complexities associated with the larger, and often more complex, structure of biological products, as well as the process by which such products are manufactured, pose significant hurdles to implementation that are still being worked out by the FDA.

A reference biologic is granted twelve years of exclusivity from the time of first licensure of the reference product. The first biologic product submitted under the abbreviated approval pathway that is determined to be interchangeable with the reference product has exclusivity against other biologics submitting under the abbreviated approval pathway for the lesser of (i) one year after the first commercial marketing, (ii) 18 months after approval if there is no legal challenge, (iii) 18 months after the resolution in the applicant's favor of a lawsuit challenging the biologics' patents if an application has been submitted, or (iv) 42 months after the application has been approved if a lawsuit is ongoing within the 42-month period.

Under the Orphan Drug Act, the FDA may grant ODD 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. ODD must be requested before submitting an NDA. After the FDA grants ODD, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. We intend to request ODD designation for our product candidates, if applicable. For example, the FDA has granted ODD for patisiran as a therapeutic for the treatment of FAP and for ALN-AT3 as a therapeutic for hemophilia.

If a product that has ODD 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, to market the same drug for the same indication, except in very limited circumstances, for seven years. For purposes of small molecule drugs, the FDA defines "same drug" as a drug that contains the same active moiety and is intended for the same use as the previously approved orphan drug. For purposes of large molecule drugs, the FDA defines "same drug" as a drug that contains the same principal molecular structural features, but not necessarily all of the same structural features, and is intended for the same use as the drug in question. Notwithstanding the above definitions, a drug that is clinically superior to an orphan drug will not be considered the "same drug" and thus will not be blocked by orphan drug exclusivity.

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

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The Orphan Products Grants Program in FDA's Office of Orphan Products Development, or OOPD, with an annual budget of approximately \$14.0 million, supports clinical development of products including drugs, biologics, medical devices and medical foods for use in rare diseases and conditions where no current therapy exists or where the proposed product will be superior to the existing therapy. This program provides grants for clinical studies on safety and/or effectiveness that will either result in, or substantially contribute to, market approval of these products. In addition, OOPD will administer a new grant program, the Pediatric Device Consortia Grant Program, resulting from the 2007 FDAAA legislation to support nonprofit consortia to facilitate pediatric medical device development. The future availability of such grants is subject to uncertainties regarding continued federal funding.

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

Recently, the Food and Drug Administration Safety and Innovation Act, or FDASIA, which was signed into law on July 9, 2012, amended the FDCA. FDASIA requires that a sponsor who is planning to submit a marketing application for a drug or biological product that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration submit an initial Pediatric Study Plan, or PSP, within sixty days of an end-of-phase 2 meeting or as may be agreed between the sponsor and FDA. The initial PSP must include an outline of the pediatric study or studies that the sponsor plans to conduct, including study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. FDA and the sponsor must reach agreement on the PSP. A sponsor can submit amendments to an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from nonclinical studies, early phase clinical trials, and/or other clinical development programs.

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new drugs and biological products that meet certain criteria. Specifically, new drugs and biological products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug or biological product may request the FDA to designate the drug or biologic as a Fast Track product at any time during the clinical development of the product. Unique to a Fast Track product, the FDA may consider for review sections of the marketing application on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the application, the FDA agrees to accept sections of the application and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the application. We intend to request Fast Track designation for our product candidates, if applicable. For example, the FDA granted Fast Track designation to patisiran for the treatment of FAP.

Any product submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. Any product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biological product designated for priority review in an effort to facilitate the review. Additionally, a product may be eligible for accelerated approval. Drug or biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and

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that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical studies establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. As a condition of approval, the FDA may require that a sponsor of a drug or biological product receiving accelerated approval perform adequate and well-controlled post-marketing clinical studies. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product. Fast Track designation, priority review and accelerated approval do not change the standards for approval but may expedite the development or approval process.

The Food and Drug Administration Safety and Innovation Act of 2012 also amended the FDCA to require FDA to expedite the development and review of a breakthrough therapy. A drug or biological product can be designated as a breakthrough therapy if it is intended to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that it may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. A sponsor may request that a drug or biological product be designated as a breakthrough therapy at any time during the clinical development of the product. If so designated, FDA shall act to expedite the development and review of the product's marketing application, including by meeting with the sponsor throughout the product's development, providing timely advice to the sponsor to ensure that the development program to gather nonclinical, manufacturing/controls and clinical data is as efficient as practicable, involving senior managers and experienced review staff in a cross-disciplinary review, assigning a cross-disciplinary project lead for the FDA review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the review team and the sponsor, and taking steps to ensure that the design of the clinical trials is as efficient as practicable. We intend to request breakthrough therapy designation for our product candidates, if applicable.

Foreign Regulation of New Drug Compounds

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

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

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provides for the grant of a single marketing authorization that is valid in all EU member states. The decentralized procedure is a mutual recognition procedure that is available at the request of the applicant for medicinal products that are not subject to the centralized procedure. We intend to 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, the emphasis on managed care in the United States has increased and we expect will continue to exert downward pressure on pharmaceutical pricing. Coverage policies, third-party reimbursement rates and pharmaceutical pricing regulations may change at any time. 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.

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In March 2010, the PPACA, as amended by the Health Care and Education Reconciliation Act of 2010, was enacted, which includes measures that have or will significantly change the way health care is financed by both governmental and private insurers. Among the provisions of PPACA of greatest importance to the pharmaceutical industry are the following:

The Medicaid Drug Rebate Program requires pharmaceutical manufacturers to enter into and have in effect a national rebate agreement with the Secretary of the Department of Health and Human Services a condition for states to receive federal matching funds for the manufacturer's outpatient drugs furnished to Medicaid patients. Effective in 2010, PPACA made several changes to the Medicaid Drug Rebate Program, including increasing pharmaceutical manufacturers' rebate liability by raising the minimum basic Medicaid rebate on most branded prescription drugs and biologic agents from 15.1% of average manufacturer price, or AMP, to 23.1% of AMP and adding a new rebate calculation for line extensions (i.e., new formulations, such as extended release formulations) of solid oral dosage forms of branded products, as well as potentially impacting their rebate liability by modifying the statutory definition of AMP. PPACA also expanded the universe of Medicaid utilization subject to drug rebates by requiring pharmaceutical manufacturers to pay rebates on Medicaid managed care utilization as of 2010 and by expanding the population potentially eligible for Medicaid drug benefits, to be phased-in by 2014. The Centers for Medicare and Medicaid Services, or CMS, have proposed to expand Medicaid rebate liability to the territories of the United States as well. In addition, PPACA provides for the public availability of retail survey prices and certain weighted average AMPs under the Medicaid program. The implementation of this requirement by the CMS may also provide for the public availability of pharmacy acquisition of cost data, which could negatively impact our sales.

In order for a pharmaceutical product to receive federal reimbursement under the Medicare Part B and Medicaid programs or to be sold directly to U.S. government agencies, the manufacturer must extend discounts to entities eligible to participate in the 340B drug pricing program. The required 340B discount on a given product is calculated based on the AMP and Medicaid rebate amounts reported by the manufacturer. Effective in 2010, PPACA expanded the types of entities eligible to receive discounted 340B pricing, although, under the current state of the law, with the exception of children's hospitals, these newly eligible entities will not be eligible to receive discounted 340B pricing on orphan drugs when used for the orphan indication. In addition, as 340B drug pricing is determined based on AMP and Medicaid rebate data, the revisions to the Medicaid rebate formula and AMP definition described above could cause the required 340B discount to increase.

Effective in 2011, PPACA imposed a requirement on manufacturers of branded drugs and biologic agents to provide a 50% discount off the negotiated price of branded drugs dispensed to Medicare Part D patients in the coverage gap (i.e., donut hole).

Effective in 2011, PPACA imposed an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications.

Effective in 2012, PPACA required pharmaceutical manufacturers to track certain financial arrangements with physicians and teaching hospitals, including any transfer of value made or distributed to such entities, as well as any investment interests held by physicians and their immediate family members. Manufacturers were required to begin tracking this information in 2013 and to report this information to CMS beginning in 2014.

As of 2010, a new Patient-Centered Outcomes Research Institute was established pursuant to PPACA to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research. The research conducted by the Patient-Centered Outcomes Research Institute may affect the market for certain pharmaceutical products.

PPACA created the Independent Payment Advisory Board which, beginning in 2014, will have authority to recommend certain changes to the Medicare program to reduce expenditures by the program that could

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result in reduced payments for prescription drugs. Under certain circumstances, these recommendations will become law unless Congress enacts legislation that will achieve the same or greater Medicare cost savings.

PPACA established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending. Funding has been allocated to support the mission of the Center for Medicare and Medicaid Innovation from 2011 to 2019.

Hazardous Materials

Our research, development and manufacturing 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

To date, we have manufactured only limited supplies of drug substance for use in IND-enabling toxicology studies in animals at our own facility and have contracted with several third-party contract manufacturing organizations for the supply of drug substance and finished product to meet our testing needs for pre-clinical toxicology and clinical testing. We expect to continue to rely on third-party contract manufacturing organizations for the supply of drug substance and certain drug product, including siRNAs and siRNA conjugates, for our product candidates for the foreseeable future. During 2012, we established a manufacturing facility and have developed cGMP capabilities and processes for the manufacture of patisiran formulated bulk drug product for late-stage clinical trials and commercial use. During 2013, we manufactured our first cGMP batches of patisiran for use in our Phase 2 OLE and Phase 3 clinical trials. We expect to manufacture late-stage clinical and commercial supply for patisiran formulated bulk drug product in our facility. In the future, we may also develop our own capabilities to manufacture drug substance, including siRNAs and siRNA conjugates for human clinical use. Commercial quantities of any drugs that we may seek to develop will have to be manufactured in facilities, and by processes, that comply with FDA regulations and other federal, state and local regulations, as well as comparable foreign regulations.

We believe we have sufficient manufacturing capacity through our third-party contract manufacturers and our internal cGMP manufacturing facility to meet our current research, clinical and early-stage commercial needs. We believe that the supply capacity we have established externally, together with the internal capacity we developed to support pre-clinical trials, will be sufficient to meet our anticipated needs for the next several years. We monitor the capacity availability for the manufacture of drug substance and drug product and believe that our supply agreements with our contract manufacturers and the lead times for new supply agreements would allow us to access additional capacity to meet our currently anticipated needs. We also believe that our products can be manufactured at a scale and with production and procurement efficiencies that will result in commercially competitive costs.

Scientific Advisors

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

our research and development programs;

the design and implementation of our clinical programs;

our patent and publication strategies;

new technologies relevant to our research and development programs; and

specific scientific and technical issues relevant to our business.

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The current members of our scientific advisory board are:

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

Employees

At January 31, 2015, we had 256 employees, 220 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 seven entities, Alnylam Pharmaceuticals, Inc. and six wholly owned subsidiaries (Alnylam U.S., Inc., Alnylam Europe AG, Alnylam (Bermuda) Ltd., Alnylam UK Limited, Alnylam Securities Corporation and Sirna Therapeutics, 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. 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. Alnylam (Bermuda) Ltd., an entity organized under the laws of Bermuda, was formed in August 2013. Alnylam UK Limited, an entity organized under the laws of the United Kingdom, was formed in January 2014. Sirna Therapeutics, Inc. is a Delaware corporation that was acquired by Alnylam Pharmaceuticals, Inc. from Merck in March 2014. Our principal executive office is located at 300 Third Street, Cambridge, Massachusetts 02142, and our telephone number is (617) 551-8200.

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Investor Information

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

Set forth below is information about our executive officers, as of December 31, 2014.

Name	Age	Position
John M. Maraganore, Ph.D.	52	Chief Executive Officer and Director
Barry E. Greene	51	President and Chief Operating Officer
Akshay K. Vaishnav, M.D., Ph.D.	52	Executive Vice President and Chief Medical Officer
Laurie B. Keating	60	Senior Vice President, General Counsel and Secretary
Michael P. Mason	40	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 (now Millennium: The Takeda Oncology Company). Dr. Maraganore serves as a member of the board of directors of Agios Pharmaceuticals, Inc., a biotechnology company and bluebird bio, Inc., a biotechnology company.

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 (now Millennium: The Takeda Oncology Company). Mr. Greene serves as a member of the board of directors of Acorda Therapeutics, Inc., a biotechnology company and Karyopharm Therapeutics Inc., a clinical-stage pharmaceutical company.

Akshay K. Vaishnav, M.D., Ph.D. has served as our Executive Vice President of Research and Development since December 2014 and has served as our Chief Medical Officer since June 2011. He served as our Executive Vice President from June 2012 to December 2014 and prior to that as our Senior Vice President from June 2011 to June 2012. He served as our Senior Vice President, Clinical Research from December 2008 to June 2011, and prior to that served as our Vice President, Clinical Research from the time he joined us in January 2006. From December 1998 through December 2005, Dr. Vaishnav held various positions at Biogen Idec Inc. (formerly Biogen, Inc.), a biopharmaceutical company. Dr. Vaishnav is a Member of the Royal College of Physicians, United Kingdom.

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Laurie B. Keating has served as our Senior Vice President, General Counsel and Secretary since September 2014. Prior to joining Alnylam, Ms. Keating served as Senior Vice President, General Counsel and Secretary of Millennium: The Takeda Oncology Company, a biopharmaceutical company, from September 2004 to January 2014. Prior to Millennium, Ms. Keating was co-founder and the first chief executive officer of Hydra Biosciences, Inc. Before co-founding Hydra, she served as an executive at several high growth technology companies. Upon graduating from law school, Ms. Keating practiced law at McCutchen, Doyle, Brown and Enersen (which became Bingham McCutchen and is now a part of Morgan, Lewis & Bockius).

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, plan, anticipate, estimate, predict, may, could, shall, will, target, goal and similar 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 a Clinical Stage Company

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

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

execute product development activities using unproven technologies related to both RNAi and to the delivery of siRNAs to the relevant tissues and cells;

build and maintain a strong intellectual property portfolio;

gain regulatory acceptance for the development and commercialization 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 safe RNAi therapeutics based on the so-called off-target effects and activation of the interferon response. In

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addition, decisions by other companies with respect to their RNAi development efforts or their adoption of different or related technologies 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 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, 2014, we had an accumulated deficit of \$956.6 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 product 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, but cannot be certain that we will be able to secure or maintain these alliances, 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 and achieve desired clinical effects;

our ability to develop relatively standard procedures for selecting and modifying siRNA product candidates;

progress in our research and development programs, as well as what may be required by regulatory bodies to advance these programs;

the timing, receipt and amount of milestone and other payments, if any, from present and future collaborators, 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 studies, 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;

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 agreement with Genzyme provides Genzyme with the right, subject to certain exceptions, generally to maintain its ownership position in us until Genzyme owns less than 7.5% of our outstanding common stock, subject to certain additional limited rights of Genzyme to maintain its ownership percentage. In accordance with the investor agreement, as a result of our issuance of shares in connection with our acquisition of Sirna in March 2014, Genzyme exercised its right to purchase an additional 344,448 shares of our common stock. In January 2015, Genzyme also exercised its right to purchase 196,251 shares based on its 2014 compensatory right and its right to

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purchase 744,566 shares in connection with our public offering. These purchases allowed Genzyme to maintain its ownership level of approximately 12% of our outstanding common stock. While the exercise of these rights by Genzyme has provided us with an additional \$112.0 million in cash to date, and while we expect the exercise of these rights by Genzyme in the future will provide us with further additional cash, these exercises caused, and any future exercise of these rights by Genzyme will also cause further, dilution to our stockholders. Debt financing, if available, may involve restrictive covenants that could limit our flexibility in conducting future business activities and, in the event of insolvency, would be paid before holders of equity securities received any distribution of corporate assets.

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

At December 31, 2014, we had \$881.9 million in cash, cash equivalents and fixed income marketable securities. We historically have invested these amounts in corporate bonds, commercial paper, securities issued or sponsored by the U.S. government, 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. 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, for each RNAi therapeutic product developed by Arrowhead, its affiliates, or sublicensees under the collaboration agreement, we are entitled to receive milestone payments upon achievement of specified development and sales events, totaling up to an aggregate of \$100.0 million per therapeutic target, together with royalty payments based on worldwide annual net sales, if any. Our receipt of milestone payments under this agreement is dependent upon Arrowhead's ability to successfully develop and commercialize RNAi therapeutic products.

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

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 any. During 2014, Novartis publicly indicated that they no longer intend to invest in the development of certain RNAi therapeutics and intend to divest certain of their RNAi assets. Novartis has the right to assign our collaboration and license agreement to a third-party that acquires substantially all of its assets relating to RNAi.

If Takeda, Arrowhead or any assignee of Novartis fails to successfully develop products using our technology, we may not receive any milestone or royalty payments under our agreements with them. Finally, Takeda or Arrowhead 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 currently have any capability for sales or distribution and have early capability for marketing and market access, and limited capacity for drug development due to our growing pipeline of RNAi therapeutic opportunities. 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. Our collaboration strategy is to form alliances that create significant value for ourselves and our collaborators in the advancement of RNAi therapeutics as a new class of innovative medicines. Specifically, with respect to our Genetic Medicine pipeline, we formed a broad strategic alliance with Genzyme in 2014 pursuant to which we retain development and commercial rights for our current and future Genetic Medicine products in North America and Western Europe, and Genzyme will develop and commercialize our current and future Genetic Medicine products principally in territories outside of North America and Western Europe, subject to certain broader rights. With respect to our Cardio-Metabolic and Hepatic Infectious Disease pipelines, we intend to seek future strategic alliances for these programs, while retaining significant product commercialization rights in the United States and EU. We currently have a global alliance with MDCO to advance our ALN-PCS program.

In such alliances, we expect our current, and may expect our future, collaborators to provide substantial capabilities in clinical development, regulatory affairs, and/or marketing, sales and distribution. Under certain of our alliances, we also may expect our collaborators to develop, market and/or sell certain of our product candidates. We may have limited or no control over the development, sales, marketing and distribution activities of these third parties. Our future revenues may depend heavily on the success of the efforts of these third parties. For example, we will rely entirely on (i) Genzyme for the development and commercialization of patisiran, revusiran and potentially other of our Genetic Medicine programs in territories outside of North America and Western Europe under the 2014 Genzyme collaboration, and (ii) MDCO for later stage development and commercialization of ALN-PCS worldwide. If Genzyme and/or MDCO are not successful in their commercialization efforts, our future revenues from RNAi therapeutics for these indications may be adversely affected.

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

Furthermore, any delay in entering into collaboration agreements would likely either delay the development and commercialization of 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 collaboration with MDCO. We may not, however, be able to enter into additional collaborations for certain other programs, 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 our product candidates, we may not have sufficient funds to develop that or other product candidates internally, or to bring our 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 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. In addition, our collaborators may have additional termination rights for convenience under certain circumstances. For example, our agreement with MDCO relating to the development and commercialization of ALN-PCS worldwide may be terminated by MDCO at any time upon four months' prior written notice. If we were to lose a commercialization collaborator, we would have to attract a new collaborator or develop internal sales, distribution and marketing capabilities, which would require us to invest significant amounts of financial and management resources.

In addition, if we have a dispute with a collaborator over the ownership of technology or other matters, or if a collaborator terminates its collaboration with us, for breach or otherwise, or determines not to pursue the research and development of RNAi therapeutics, it could delay our development of product candidates, result in the need for additional company resources to develop product candidates, require us to expend time and resources to develop sales and marketing capabilities outside of the United States and EU, 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, among other things, misappropriation of its confidential and proprietary information and trade secrets. As a result of the litigation, which was settled in November 2012, we were required to expend resources and management attention

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that would otherwise have been engaged in other activities. In addition, in August 2013, we initiated binding arbitration proceedings to resolve a disagreement with Tekmira regarding the achievement by Tekmira of a \$5.0 million milestone payment under our cross-license agreement relating to the manufacture of ALN-VSP clinical trial material for use in China. We currently expect that the Tekmira arbitration hearing will be held in the second quarter of 2015.

Moreover, a collaborator, or in the event of a change in control of a collaborator or the assignment of a collaboration agreement to a third party, the successor entity or assignee, could determine that it is in its interests to:

pursue alternative technologies or develop alternative products, either on its own or jointly with others, that may be competitive with the products on which it is collaborating with us or which could affect its commitment to the collaboration with us;

pursue higher-priority programs or change the focus of its development programs, which could affect the collaborator's commitment to us; or

if it has marketing rights, choose to devote fewer resources to the marketing of our product candidates, if any are approved for marketing, than it does for product candidates developed without us.

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

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

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

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

We have very limited manufacturing experience. In order to develop our product candidates, apply for regulatory approvals and commercialize our products, if approved, we will need to develop, contract for, or otherwise arrange for the necessary manufacturing capabilities. Historically, our internal manufacturing capabilities were limited to small-scale production of material for use in in vitro and in vivo experiments that is not required to be produced under current cGMP standards. During 2012, we developed cGMP capabilities and processes for the manufacture of patisiran for late-stage clinical trial use and early commercial supply.

We may manufacture limited quantities of clinical trial materials ourselves, but otherwise we rely on third parties 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 a few 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 potential synthesis and purification failures and contamination during the manufacturing process, which could result in unusable product and cause delays in our manufacturing timelines and ultimately delay our clinical trials, as well as additional expense to us. To fulfill our siRNA requirements, we may need to secure alternative suppliers of synthetic siRNAs and such alternative

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suppliers may not be readily available, or we may be unable to enter into agreements with them on reasonable terms and in a timely manner.

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. In addition, the scale up of our delivery technologies 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. 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 efforts, as well as additional expense to us. Given the limited number of suppliers for our delivery technology and other materials, we have developed cGMP capabilities and processes for the manufacture of patisiran formulated bulk drug product for late-stage clinical use and early commercial supply, and in the future, we may also develop our own capabilities to manufacture drug substance, including siRNAs and siRNA conjugates for human clinical use. In developing these manufacturing capabilities by building our own manufacturing facility, we have incurred substantial expenditures. Also, we have had to, and will likely need to continue to, hire and train qualified employees to staff our new facility. We do not currently have a second source of supply for patisiran formulated bulk drug product. If we are unable to manufacture sufficient quantities of material or if we encounter problems with our facility in the future, we may also need to secure alternative suppliers of patisiran formulated bulk drug product and such alternative suppliers may not be available, or we may be unable to enter into agreements with them on reasonable terms and in a timely manner.

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

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

we or our current or future collaborators may not be able to initiate or continue clinical trials of product candidates 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 facilities and those of our third party manufacturers, and our products could be the subject of inspections by regulatory authorities that could have a negative outcome and result in delays in supply;

we may be required to cease distribution or recall some or all batches of our products or take action to recover clinical trial material from clinical trial sites; and

ultimately, we may not be able to meet commercial demands for our products.

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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 either scenario, our clinical trials or commercial distribution could be delayed significantly as we establish alternative supply sources. 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. We will also need to verify, such as through a manufacturing comparability study, that any new manufacturing process will produce our product according to the specifications previously submitted to or approved by the FDA or another regulatory authority. 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 or distribution experience and only early capabilities for marketing and market access, and expect to invest significant financial and management resources to establish these capabilities.

We have no sales or distribution experience and only early capabilities for marketing and market access. We currently expect to rely heavily on third parties to launch and market certain of our product candidates in certain geographies, if approved. However, we intend to commercialize the majority of our products on our own in the United States and EU, and accordingly, we will need to develop internal sales, distribution and marketing capabilities as part of our core product strategy, which will require significant financial and management resources. For our Genetic Medicine programs where we will perform sales, marketing and distribution functions ourselves in North America and Western Europe, and for future Cardio-Metabolic and Hepatic Infectious Disease products we successfully develop where we intend to retain significant product commercialization rights in the United States and EU, 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 Genetic Medicine pipeline or our future Cardio-Metabolic and Hepatic Infectious Disease pipelines in our sales territories without reliance on third parties.

Credit and financial market conditions may exacerbate certain risks affecting our business from time to time.

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

Risks Related to Managing Our Operations

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

We are highly dependent upon our senior management and our scientific, clinical and medical staff. The loss of the service of any of the members of our senior management, including Dr. John Maraganore, our Chief

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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 person life insurance on any of our employees.

We have grown our workforce significantly over the past year and expect to continue to add a significant number of additional employees during 2015. 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. We may be unable to attract and retain suitably qualified individuals in order to support our growing research, development and commercialization efforts and initiatives, and our failure to do so could have an adverse effect on our ability to implement our future business plan.

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

We expect that as we increase the number of product candidates we are developing we will also need to expand our operations. As noted above, we have grown our workforce significantly over the past year and expect to continue to add a significant number of additional employees during 2015. This expected growth will likely place a strain on our administrative and operational infrastructure, and we will likely need to develop additional infrastructure and capabilities to support our growth and obtain additional space to conduct our operations. If we are unable to develop such additional infrastructure or obtain sufficient space to accommodate our growth in a timely manner and on commercially reasonable terms, our business could be negatively impacted. As 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. In addition, 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 and systems, reporting systems and infrastructure, and policies 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

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product candidates is high. We currently have several programs in clinical development, including patisiran in a Phase 3 clinical trial, revusiran in a Phase 3 clinical trial, ALN-AT3 in a Phase 1 clinical trial, ALN-PCSsc in a Phase 1 clinical trial and ALN-CC5 in a Phase 1/2 clinical trial. Assuming regulatory clearance, we expect to initiate a Phase 1 clinical trial for ALN-AS1 in mid-2015. 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 subjects or in subsequent human clinical trials of that product candidate or any other product candidate. For example, in early 2015, we announced updated results from our Phase 1 clinical trial of ALN-AT3, including initial clinical data on three subjects with hemophilia from the second dose cohort of this study. Although the initial clinical data on these three subjects are encouraging, the data are preliminary in nature, based on a limited number of subjects and the ALN-AT3 Phase 1 study is not complete. These data, or other positive data, may not continue for these subjects or occur for any future subjects in this study, and may not be repeated or observed in any future studies. There can be no assurance that this study will ultimately be successful or support further clinical advancement of this product candidate. There is a high failure rate for drugs proceeding through clinical studies. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in clinical development even after achieving promising results in earlier studies, and any such setbacks in our clinical development could have a material adverse effect on our business and operating results. Moreover, patisiran, revusiran and ALN-AT3 each employ novel delivery technologies that have yet to be extensively evaluated in human clinical trials and proven safe and effective. In May 2014, we reported the first human study results for our Enhanced Stabilization Chemistry, or ESC-GalNAc conjugate technology, which enables subcutaneous dosing with increased potency, durability and a wide therapeutic index. While these initial clinical results of ALN-AT3 demonstrated a greater than 50-fold potency improvement with ESC-GalNAc conjugates relative to standard template chemistry conjugates, we cannot assure you that we will see similar results with other clinical candidates.

In addition, 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 healthy volunteer 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 healthy volunteer 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, and the eligibility criteria for the clinical trial. For example, we may experience difficulty enrolling our clinical trials, including, but not limited to, our clinical trials for patisiran, due to the small population of ATTR patients suffering from FAP and the availability of existing approved treatments, as well as other investigational treatments in development. Delays or difficulties in patient enrollment or difficulties retaining trial participants, including as a result of the availability of existing or other investigational treatments, can result in increased costs, longer development times or termination of a clinical trial.

Although our investigational RNAi therapeutics have been generally well tolerated in our clinical trials to date, in our ALN-VSP clinical trial, one patient with advanced pancreatic neuroendocrine cancer with extensive involvement of the liver developed hepatic failure five days following the second dose of ALN-VSP and subsequently died; this was deemed possibly related to the study drug. In our patisiran Phase 2 open label extension study in FAP patients, infusion reactions occurred in approximately 15% of patients, were mild in severity and did not result in any discontinuations. In our revusiran Phase 1 clinical trial, we observed injection site reactions, or ISRs, in a minority of subjects receiving revusiran or placebo. These were reported as being clinically mild and consisted of transient erythema associated in a minority of cases with edema and/or pain. In

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all cases, these reactions were self-limiting and resolved within approximately two hours of onset. In our revusiran Phase 2 trial in FAC and SSA patients, the most common adverse event was ISRs that occurred in 23% of patients. These were all mild in severity and were similar to the ISRs observed and previously reported in the revusiran Phase 1 study. The next most common adverse event was a low incidence of transient mild liver function test changes (15%) that, in all cases, resolved without discontinuing therapy. In three of four patients, these elevations appeared to be clinically insignificant and were less than one and a half times the upper limit of normal. One patient had an approximate four-fold elevation in liver transaminases that was deemed a serious adverse event and mild in severity; this event resolved during continued dosing. The occurrence of adverse events can result in the suspension or termination of clinical trials of a product candidate by us or the FDA or a foreign regulatory authority, or refusal to approve a particular product candidate for any or all indications of use.

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 or 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 an IRB, or the FDA or comparable foreign authorities regarding the scope or design of our clinical trials;

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

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

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

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

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

greater than anticipated clinical trial costs;

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

poor or disappointing effectiveness of our product candidates during clinical trials;

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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 disease for which it was being tested.

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, packaging, advertising and promotion, pricing, 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 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. 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 a new drug application, or NDA, or after approval, which may impose further requirements or

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restrictions on the distribution or use of an approved drug, 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.

Even if we obtain regulatory approvals, our marketed drugs will be subject to ongoing regulatory oversight. 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 oversight, 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 our product candidates, including our Cambridge facility, will also be subject to periodic review and inspection by the FDA and other regulatory agencies. To date, our manufacturing facility has not been subject to an inspection by any regulatory authority. The discovery of any new or previously unknown problems with us or our third-party manufacturers, or our or their manufacturing processes or facilities, may result in restrictions on the drug or manufacturer or facility, including withdrawal of the drug from the market. We have developed cGMP capabilities and processes for the manufacture of patisiran for Phase 3 clinical and early commercial use. We may not have the ability or capacity to manufacture material at a broader commercial scale in the future. 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 will also be 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 or foreign regulatory authorities 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.

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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;

the safety and efficacy of our product candidates, as demonstrated in clinical trials and as compared with alternative treatments, if any;

relative convenience and ease of administration of our product candidates;

the willingness of patients to accept potentially new routes of administration;

the success of our physician education programs;

the availability of adequate government and third-party payor reimbursement;

the pricing of our products, particularly as compared to alternative treatments; and

availability of alternative effective treatments for the diseases that product candidates we develop are intended to treat and the relative risks, benefits and costs of the treatments.

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

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

As a manufacturer of pharmaceuticals, we are subject to federal, state, and comparable 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;

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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 and Health Information Technology for Economic and Clinical Health Act, which impose requirements relating to the privacy, security, and transmission of individually identifiable health information; and require notification to affected individuals and regulatory authorities of certain breaches of security of individually identifiable health information;

the U.S. federal Open Payments requirements were implemented by CMS pursuant to the PPACA. Under the National Physician Payment Transparency Program, manufacturers of medical devices, biological

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products and drugs covered by Medicare, Medicaid and Children's Health Insurance Programs report all transfers of value, including consulting fees, travel reimbursements, research grants, and other payments or gifts with values over \$10 made to physicians and teaching hospitals; and

state and foreign 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 government reimbursement programs, 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, criminal prosecution, 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, or the imposition of a corporate integrity agreement with the Office of Inspector General of the Department of Health and Human Services, any of which could adversely affect our financial results. Although effective compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, these risks cannot be entirely eliminated. Any action against us for an alleged or suspected violation could cause us to incur significant legal expenses and could divert our management's attention from the operation of our business, even if our defense is successful. In addition, achieving and sustaining compliance with applicable laws and regulations may be costly to us in terms of money, time and resources.

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

adverse regulatory inspection findings;

warning letters;

voluntary or mandatory product recalls or public notification or medical product safety alerts to healthcare professionals;

restrictions on, or prohibitions against, marketing our products;

restrictions on, or prohibitions against, importation or exportation of our products;

suspension of review or refusal to approve pending applications or supplements to approved applications;

exclusion from participation in government-funded healthcare programs;

exclusion from eligibility for the award of government contracts for our products;

suspension or withdrawal of product approvals;

product seizures;

injunctions; and

civil and criminal penalties, up to and including criminal prosecution resulting in fines, exclusion from healthcare reimbursement programs and imprisonment.

Moreover, federal, state or foreign laws or regulations are subject to change, and while we, our collaborators, manufacturers and/or service providers currently may be compliant, that could change due to changes in interpretation, prevailing industry standards or the legal structure.

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

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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. We are monitoring these regulations as several of our programs move into later stages of development, however, many of our programs are currently in the earlier 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 and potentially in other countries due to reference pricing.

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. Increasingly, the third-party payors who reimburse patients or healthcare providers, such as government and private insurance plans, are requiring that drug companies provide them with predetermined discounts from list prices, and are seeking to reduce the prices charged or the amounts reimbursed for pharmaceutical products. If the price we are able to charge for any products we develop, or the reimbursement provided for such products, is inadequate in light of our development and other costs, our return on investment could be adversely affected.

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

they are incident to a physician's services;

they are reasonable and necessary for the diagnosis or treatment of the illness or injury for which they are administered according to accepted standards of medical practice; and

they have been approved by the FDA and meet other requirements of the statute.

There may be significant delays in obtaining coverage for newly-approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA or foreign regulatory authorities. 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 in 2003 and took effect in January 2006, healthcare reform legislation enacted by certain states, and major healthcare reform legislation that was passed by

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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 PPACA was 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 Service 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 reference innovator biologic product was first licensed by the FDA, with a possible six-month extension for pediatric products. After this exclusivity ends, it will be easier for generic manufacturers to enter the market, which is likely to reduce the pricing for such products and could affect our profitability.

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

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

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

Under the Budget Control Act of 2011, the failure of Congress to enact deficit reduction measures of at least \$1.2 trillion for the years 2013 through 2021 triggered automatic cuts to most federal programs. These cuts included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, starting in 2013. Under the American Taxpayer Relief Act of 2012, which was enacted on January 1, 2013, the imposition of these automatic cuts was delayed until March 1, 2013. As required by law, President Obama issued a sequestration order on March 1, 2013. Certain of these automatic cuts have been implemented resulting in reductions in Medicare payments to physicians, hospitals, and other healthcare providers, among other things. The full impact on our business of these automatic cuts is uncertain.

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

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

Our business exposes us to significant potential product liability risks that are inherent in the development, testing, manufacturing and marketing of human therapeutic products. Product liability claims could delay or prevent completion of our clinical development programs. If we succeed in marketing products, such claims could result in an FDA investigation of the safety and effectiveness of our products, our manufacturing processes 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 decreased demand for our products, injury to our reputation, costs to defend the related litigation, a diversion of management's time and our resources, substantial monetary awards to trial participants or patients and a decline in our stock price. 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, development and manufacturing 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, development and manufacturing activities. We are subject to federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. We believe our procedures for storing, handling and disposing these materials in our Cambridge facilities comply with the relevant guidelines of the City of Cambridge, the Commonwealth of Massachusetts and the Occupational Safety and Health Administration of the U.S. Department of Labor. Although we believe that our safety procedures for handling and disposing of these materials comply with the standards mandated by applicable regulations, the risk of accidental contamination or injury from these materials cannot be eliminated. If an accident occurs, we could be held liable for resulting damages, which could be substantial. We are also subject to numerous environmental, health and workplace safety laws and regulations, including those governing laboratory procedures, exposure to blood-borne pathogens and the handling of biohazardous materials.

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

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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. Any challenge to, finding of unenforceability or invalidation or circumvention of, our patents or patent applications, would be costly, would require significant time and attention of our management and could have a material adverse effect on our business.

Our pending patent applications may not result in issued patents. The patent position of pharmaceutical or biotechnology companies, including ours, is generally uncertain and involves complex legal and factual considerations. The standards that the USPTO and its foreign counterparts use to grant patents are not always applied predictably or uniformly and can change. Similarly, the ultimate degree of protection that will be afforded to biotechnology inventions, including ours, in the United States and foreign countries, remains uncertain and is dependent upon the scope of the protection decided upon by patent offices, courts and lawmakers. Moreover, there are periodic discussions in the Congress of the United States and in international jurisdictions about modifying various aspects of patent law. For example, the America Invents Act includes a number of changes to the patent laws of the United States. If any of the enacted changes 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. One major provision of the America Invents Act, which took effect in March 2013, changed United States patent practice from a first-to-invent to a first-to-file system. If we fail to file an invention before a competitor files on the same invention, we no longer have the ability to provide proof that we were in possession of the invention prior to the competitor's filing date, and thus would not be able to obtain patent protection for our invention. There is also no uniform, worldwide policy regarding the subject matter and scope of claims granted or allowable in pharmaceutical or biotechnology patents.

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

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independently developed by a competitor, our business and financial condition could be materially adversely affected.

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

We are a party to a number of licenses that give us rights to third-party intellectual property that is necessary or useful for our business. In particular, we have obtained licenses from, among others, CRT, Isis, MIT, Whitehead, Max Planck Innovation, Tekmira 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 parties to circumvent or invalidate our intellectual property rights could be costly to us, could require significant

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time and attention of our management and could have a material adverse effect on our business and our ability to successfully compete in the field of RNAi.

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

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

Third parties may sue us for infringing their patent rights. Likewise, we may need to resort to litigation to enforce a patent issued or licensed to us or to determine the scope and validity of proprietary rights of others. In addition, a third party may claim that we have improperly obtained or used its confidential or proprietary information. For example, in March 2011, Tekmira filed a civil complaint against us alleging, among other things, misappropriation of the plaintiffs' confidential and proprietary information and trade secrets. In November 2012, we settled this litigation and restructured our contractual relationship with Tekmira. In connection with this restructuring, we incurred a \$65.0 million charge to operating expenses during the quarter ended December 31, 2012. In addition, during the pendency of the litigation, we incurred significant costs, and the defense of this litigation diverted the attention of our management and other resources that would otherwise have been engaged in other activities.

Furthermore, third parties may challenge the inventorship of our patents or licensed patents. For example, in March 2011, University of Utah, or Utah, filed a complaint in the United States District Court for the District of Massachusetts against us, Max Planck Gesellschaft Zur Foerderung Der Wissenschaften e.V. and Max Planck Innovation, together, Max Planck, Whitehead, MIT and UMass, claiming that a professor of Utah is the sole inventor, or in the alternative, a joint inventor of certain of our in-licensed patents. Utah is seeking correction of inventorship of the Tuschl patents, unspecified damages and other relief. In October 2011, we, Max Planck, Whitehead, MIT and UMass filed a motion to dismiss and UMass filed a motion to dismiss on separate grounds, which we, Max Planck, Whitehead and MIT have joined. In December 2011, Utah filed a second amended complaint dropping UMass as a defendant and adding as defendants several UMass officials. In June 2012, the Court denied both motions to dismiss. We, Max Planck, Whitehead, MIT and UMass filed an appeal of the Court's ruling on the motion to dismiss for lack of jurisdiction and a motion requesting that the Court stay the case pending the outcome of the appeal. In July 2012, the Court stayed discovery in the case pending the outcome of the defendants' appeal. In August 2013, the United States Court of Appeals for the Federal Circuit, or CAFC, affirmed the lower Court's ruling, in a split decision. In September 2013, we filed a petition with the CAFC for rehearing or rehearing en banc. In November 2013, the CAFC denied our petition for rehearing or rehearing en banc and remanded the case back to the lower Court. In February 2014, we filed a petition for writ of certiorari from the Supreme Court and a motion to stay the lower Court proceedings pending a decision from the Supreme Court on our petition. The lower Court granted our motion to stay the proceedings, however, in June 2014, the Supreme Court denied our petition for certiorari and remanded the case back to the United States District Court for the District of Massachusetts for trial, which is now scheduled to begin on November 2, 2015.

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.

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

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

Our current licenses impose, and any future licenses we enter into are likely to impose, various development, commercialization, funding, milestone, royalty, diligence, sublicensing, insurance, patent prosecution and enforcement, and other obligations on us. If we breach any of these obligations, or use the intellectual property licensed to us in an unauthorized manner, we may be required to pay damages and the licensor may have the right to terminate the license or render the license non-exclusive, which could result in us being unable to develop, manufacture and sell products that are covered by the licensed technology or enable a competitor to gain access to the licensed technology. For example, Tekmira has notified us that it believes it has achieved a \$5.0 million milestone payment under our cross-license agreement relating to the manufacture of ALN-VSP clinical trial material for use in China. We have notified Tekmira that we do not believe that the milestone has been achieved under the terms of the cross-license agreement. In August 2013, we initiated binding arbitration proceedings seeking a declaratory judgment that Tekmira has not yet met the conditions of the milestone and is not entitled to payment at this time. If it is determined through arbitration that Tekmira has met the requirements of the milestone, we will have to pay Tekmira the milestone. We currently expect that the Tekmira arbitration hearing will be held in the second quarter of 2015.

Moreover, our licensors may own or control intellectual property that has not been licensed to us and, as a result, we may be subject to claims, regardless of their merit, that we are infringing or otherwise violating the licensor's rights. In addition, while we cannot currently determine the amount of the royalty obligations we will be required to pay on sales of future products, if any, the amounts may be significant. The amount of our future royalty obligations will depend on the technology and intellectual property we use in products that we successfully develop and commercialize, if any. Therefore, even if we successfully develop and commercialize products, we may be unable to achieve or maintain profitability.

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

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

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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. These drugs may be more effective, safer, less expensive, or marketed and sold more effectively, than any products we develop. For example, we are developing patisiran for the treatment of ATTR patients suffering from FAP. We are aware of other approved products used to treat this disease, as well as product candidates in various stages of clinical development. Patisiran may not compete favorably with these products and product candidates, and even if approved, it may not achieve commercial success.

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 relative to alternative therapies, if any;

the ease with which our products can be administered and the extent to which patients accept relatively new routes of administration;

the timing and scope of regulatory approvals for these products;

the availability and cost of manufacturing, marketing and sales capabilities;

price;

reimbursement coverage; and

patent position.

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

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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, 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.

In addition, as a result of agreements that we have entered into, Arrowhead, as the assignee of Roche, and Takeda have obtained non-exclusive licenses, and Novartis has obtained specific exclusive licenses for 31 gene targets, to certain aspects of our technology that give them the right to compete with us in certain circumstances. We also compete with companies working to develop antisense-based drugs. Like RNAi therapeutics, antisense drugs target mRNAs, in order to suppress the activity of specific genes. Isis is currently marketing an antisense drug and has several antisense product candidates in clinical trials, including one for the treatment of ATTR. 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 competitors are able to negotiate exclusive access to those delivery solutions developed by third parties, we may be unable to successfully commercialize our product candidates.

Risks Related to Our Common Stock

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

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

We may incur significant costs from class action litigation due to 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.

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

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

Genzyme's ownership of our common stock could delay or prevent a change in corporate control.

Genzyme currently holds approximately 12% of our outstanding common stock and has the right to increase its ownership up to 30%, as well as the right to maintain its ownership percentage through the term of our collaboration, subject to certain limitations. 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.

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, 2015, 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 18,000 square feet is under sublease to a third party through September 2016. The term of our lease ends in September 2021, and we have the option to extend the lease for one additional five-year period. We also lease approximately 15,000 square feet of additional office and laboratory space in Cambridge, Massachusetts for our cGMP manufacturing facility. The lease for this property expires in August 2017, and we have the option to extend this lease for two successive five-year periods.

We have grown our workforce significantly over the past year and expect to continue to add a significant number of additional employees during 2015. We expect to obtain additional space to accommodate our growth and we believe that additional space will be available to us on commercially reasonable terms as required.

ITEM 3. LEGAL PROCEEDINGS

University of Utah Litigation

On March 22, 2011, Utah filed a civil complaint in the United States District Court for the District of Massachusetts against us, Max Planck, Whitehead, MIT and UMass, claiming a professor at Utah is the sole inventor or, in the alternative, a joint inventor, of the Tuschl patents. Utah did not serve the original complaint on us or the other defendants. On July 6, 2011, Utah filed an amended complaint alleging substantially the same claims against us, Max Planck, Whitehead, MIT and UMass. The amended complaint was served on us on July 14, 2011. Utah is seeking changes to the inventorship of the Tuschl patents, unspecified damages and other relief. On October 31, 2011, we, Max Planck, Whitehead, MIT and UMass filed a motion to dismiss. Also on October 31, 2011, UMass filed a motion to dismiss on separate grounds, which we, Max Planck, Whitehead and MIT joined. On December 31, 2011, Utah filed a second amended complaint dropping UMass as a defendant and adding as defendants several UMass officials. In June 2012, the Court denied both motions to dismiss. We, Max Planck, Whitehead, MIT and UMass filed an appeal of the Court's ruling on the motion to dismiss for lack of jurisdiction and a motion requesting that the Court stay the case pending the outcome of the appeal. In July 2012, the Court stayed discovery in the case pending the outcome of the defendants' appeal. Oral arguments in the appeal were heard in early March 2013 in the CAFC. In August 2013, the CAFC affirmed the lower Court's ruling, in a split decision. We believe the majority made an error in law when affirming the lower Court's decision, and in September 2013, we filed a petition with the CAFC for rehearing or rehearing en banc. In October 2013, the CAFC invited Utah to file an answer to the petition. In November 2013, the CAFC denied our petition for rehearing or rehearing en banc and remanded the case back to the lower Court. In February 2014, we filed a petition for writ of certiorari from the Supreme Court and a motion to stay the lower Court proceedings pending a decision from the Supreme Court on our petition. The lower Court granted our motion to stay the proceedings, however, in June 2014 the Supreme Court denied our petition for certiorari and remanded the case back to the United States District Court for the District of Massachusetts for trial, which is now scheduled to begin on November 2, 2015.

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. We have not recorded an estimate of the possible loss associated with this legal proceeding due to the uncertainties related to both the likelihood and the amount of any possible loss or range of loss.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

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

Year Ended December 31, 2013:	High	Low
First Quarter	\$ 25.80	\$ 18.61
Second Quarter	\$ 31.79	\$ 21.60
Third Quarter	\$ 65.83	\$ 31.75
Fourth Quarter	\$ 67.97	\$ 48.16
 Year Ended December 31, 2014:	 High	 Low
First Quarter	\$ 112.57	\$ 60.24
Second Quarter	\$ 71.40	\$ 47.03
Third Quarter	\$ 79.88	\$ 51.93
Fourth Quarter	\$ 111.49	\$ 72.80

Holders of record

At January 30, 2015, there were 37 holders of record of our common stock. Because many of our shares are held by brokers and other institutions on behalf of stockholders, we are unable to estimate the total number of beneficial holders represented by these record holders.

Dividends

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

Securities Authorized for Issuance Under Equity Compensation Plans

We intend to file with the SEC a definitive Proxy Statement, which we refer to herein as the Proxy Statement, not later than 120 days after the close of the fiscal year ended December 31, 2014. 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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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, 2009, to the close of the last trading day of 2014, in each of (i) our common stock, (ii) the NASDAQ US Benchmark TR Index and (iii) the NQ US Benchmark Pharma TR 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 US Benchmark TR Index and NQ US Benchmark Pharma TR Index**

	12/31/2009	12/31/2010	12/30/2011	12/31/2012	12/31/2013	12/31/2014
Alnylam Pharmaceuticals, Inc.	\$ 100.00	\$ 55.96	\$ 46.25	\$ 103.58	\$ 364.93	\$ 550.51
NASDAQ US Benchmark TR Index	\$ 100.00	\$ 117.55	\$ 117.91	\$ 137.29	\$ 183.26	\$ 206.09
NQ US Benchmark Pharma TR Index	\$ 100.00	\$ 102.60	\$ 120.54	\$ 137.81	\$ 186.98	\$ 227.77

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The following selected consolidated financial data for each of the five years in the period ended December 31, 2014 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,				
	2014	2013	2012	2011	2010
Statements of Comprehensive Loss Data:					
Net revenues from collaborators	\$ 50,561	\$ 47,167	\$ 66,725	\$ 82,757	\$ 100,041
Operating expenses(1)	455,541	140,109	196,181	137,575	144,111
Loss from operations	(404,980)	(92,942)	(129,456)	(54,818)	(44,070)
Net loss	(360,395)	(89,225)	(106,014)	(57,649)	(43,515)
Net loss per common share basic and diluted	\$ (4.85)	\$ (1.45)	\$ (2.11)	\$ (1.36)	\$ (1.04)
Weighted-average common shares outstanding basic and diluted	74,278	61,551	50,286	42,410	42,040

(1) Non-cash stock-based compensation expenses

included in operating expenses \$ 33,061 \$ 20,703 \$ 12,360 \$ 16,676 \$ 19,118

The increase in operating expenses for the year ended December 31, 2014 resulted primarily from a \$220.8 million charge to operating expenses in connection with our acquisition of the Sirna RNAi assets from Merck, which is described below in Management's Discussion and Analysis of Financial Condition and Results of Operations Discussion of Results of Operations for 2014 and 2013 under the heading In-process research and development. Operating expenses for the year ended December 31, 2012 included a \$65.0 million charge to operating expenses in connection with the restructuring of our license agreement with Tekmira in November 2012.

	2014	2013	December 31, 2012	2011	2010
Balance Sheet Data:					
Cash, cash equivalents and fixed income marketable securities	\$ 881,929	\$ 350,472	\$ 226,228	\$ 260,809	\$ 349,904
Working capital	651,033	200,164	77,212	71,038	152,093
Total assets	1,079,595	420,530	287,520	281,917	393,265
Total stockholders' equity	936,267	270,347	134,053	117,997	158,233

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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 expertise, we are developing what we believe to be a reproducible and modular approach to develop RNAi therapeutics for a variety of human diseases.

Our research and development strategy is focused primarily on use of our proprietary GalNAc-conjugate strategy for delivery of siRNAs—the molecules that mediate RNAi—toward liver-expressed genes involved in the cause or pathway of human diseases. We are also focused on clinical indications where there are high unmet medical needs, early biomarkers for the assessment of clinical activity in Phase 1 clinical studies, and a definable path for drug development, regulatory approval and commercialization.

Specifically, our pipeline of investigational RNAi therapeutics is focused in three STArS: Genetic Medicines, with a broad pipeline of RNAi therapeutics for the treatment of rare diseases; Cardio-Metabolic Disease, with a pipeline of RNAi therapeutics toward genetically validated, liver-expressed disease targets for unmet needs in cardiovascular and metabolic diseases such as dyslipidemia, hypertension, NASH and type 2 diabetes; and Hepatic Infectious Disease, with a pipeline of RNAi therapeutics designed to address the major global health challenges of hepatic infectious diseases, including but not limited to HBV. In early 2015, we launched our guidance for 2020 for the advancement and commercialization of RNAi therapeutics as a whole new class of innovative medicines. Specifically, by the end of 2020, we expect to achieve a company profile with three marketed products and ten RNAi therapeutic clinical programs, including four in late stages of development, across our three STArS.

We have incurred significant losses since we commenced operations in 2002 and expect such losses to continue for the foreseeable future. At December 31, 2014, we had an accumulated deficit of \$956.6 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 optimization of drug delivery technologies, clinical trial and manufacturing costs, the establishment of late-stage clinical and commercial capabilities, 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 also anticipate that our operating results will fluctuate for the foreseeable future. Therefore, period-to-period comparisons should not be relied upon as predictive of the results in future periods.

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

In January 2015, we sold an aggregate of 5,447,368 shares of our common stock through an underwritten public offering at a price to the public of \$95.00 per share. As a result of the offering, which included the full exercise of the underwriters' option to purchase additional shares, we received aggregate net proceeds of approximately \$496.4 million, after deducting underwriting discounts and commissions and other estimated offering expenses of approximately \$21.1 million. We intend to use these proceeds for general corporate

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purposes, focused on achieving our Alnylam 2020 profile with three marketed products and ten RNAi therapeutic clinical programs, including four in late stages of development, across our three STArS, by the end of 2020.

Significant 2014 Events

Acquisition of Sirna Therapeutics. In March 2014, we purchased from Merck all of Merck's right, title and interest in and to all of the outstanding shares of common stock of Sirna. Sirna possesses intellectual property and RNAi assets including pre-clinical therapeutic candidates, chemistry, and siRNA-conjugate and other delivery technologies that we are integrating into our platform for delivery of RNAi therapeutics. We did not acquire any employees, manufacturing or other facilities, developed processes or clinical-stage assets as part of the acquisition of Sirna. In consideration for the Sirna common stock, we (i) paid Merck \$25.0 million in cash and (ii) issued to Merck an aggregate of 2,520,044 shares of our common stock, having a value of \$150.0 million as calculated under the terms of the stock purchase agreement on the date of execution.

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

Genzyme Collaboration. In January 2014, we entered into a global, strategic collaboration with Genzyme to discover, develop and commercialize RNAi therapeutics as Genetic Medicines to treat orphan diseases. The 2014 Genzyme collaboration superseded and replaced our 2012 agreement with Genzyme. The 2014 Genzyme collaboration is structured as an exclusive relationship for the worldwide development and commercialization of RNAi therapeutics in the field of Genetic Medicines, which includes our current and future Genetic Medicine programs that reach Human POP by the end of 2019, subject to extension to the end of 2021 in various circumstances. We will retain product rights in North America and Western Europe, which we refer to as the Alnylam Territory, while Genzyme will obtain exclusive rights to develop and commercialize collaboration products in the rest of the world, which we refer to as the Genzyme Territory, together with certain broader co-development/co-promote or worldwide rights for certain products. Genzyme's regional, co-development/co-promote and worldwide rights are structured as an opt-in that is triggered upon achievement of Human POP. We will maintain development control for all programs prior to Genzyme's opt-in and maintain development and commercialization control after Genzyme's opt-in for all programs in our territory.

Upon the effective date of the 2014 Genzyme collaboration, Genzyme expanded the scope of its regional license and collaboration for patisiran for the Genzyme Territory. We retain full product rights in the Alnylam Territory. We and Genzyme have also expanded our current collaboration on revusiran, so that we and Genzyme are co-developing and will co-promote revusiran in the Alnylam Territory. We maintain development and commercialization control with revusiran in the Alnylam Territory. Genzyme will develop and commercialize the product in the Genzyme Territory. In addition to its regional rights for our current and future Genetic Medicine programs in the Genzyme Territory, Genzyme has the right to either (i) co-develop and co-promote ALN-AT3 for the treatment of hemophilia and other RBD in our territory, with us maintaining development and commercialization control, or (ii) obtain a global license to ALN-AS1 for the treatment of hepatic porphyrias. Genzyme may exercise this selection right upon completion of Human POP for both the ALN-AT3 and ALN-AS1 programs. Finally, Genzyme has the right for a global license to a single, future Genetic Medicine program that was not one of our defined Genetic Medicine programs as of the effective date of the 2014 Genzyme collaboration. We will retain global rights to any RNAi therapeutic Genetic Medicine program that does not reach Human POP by the end of 2019, subject to certain limited exceptions. We retain full rights to all current and future RNAi therapeutic programs outside of the field of Genetic Medicines, including the right to form new collaborations.

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Pursuant to the terms of a stock purchase agreement, we sold Genzyme 8,766,338 shares of our common stock and Genzyme paid us \$700.0 million in aggregate cash consideration. Our investor agreement with Genzyme provides Genzyme with the right, subject to certain exceptions, generally to maintain its ownership position in us until Genzyme owns less than 7.5% of our outstanding common stock, subject to certain additional limited rights of Genzyme to maintain its ownership percentage. In accordance with our investor agreement with Genzyme, as a result of our issuance of shares in connection with our acquisition of Sirna in March 2014, on March 25, 2014, Genzyme exercised its right to purchase an additional 344,448 shares of our common stock, at a purchase price of \$66.88, the closing price of our common stock that day, and paid us approximately \$23.0 million. Genzyme also has the right each January to purchase a number of shares of our common stock based on the number of shares we issued during the previous year for compensatory purposes. Genzyme exercised this right to purchase directly from us 196,251 shares of our common stock on January 22, 2015 for approximately \$18.3 million. The sale of these shares to Genzyme was consummated as a private placement. In January 2015, in connection with our public offering described above, Genzyme exercised its right to purchase directly from us, in concurrent private placements, 744,566 shares of common stock, at the public offering price of \$95.00 per share, resulting in proceeds to us of approximately \$70.7 million. The sales of common stock to Genzyme were not registered as part of the public offering, though they were consummated simultaneously with the public offering. Each of these purchases allowed Genzyme to maintain its ownership level of our outstanding common stock of approximately 12%.

A description of our 2014 Genzyme collaboration and the related stock purchase and investor agreements is included in Part I, Item 1, Strategic Alliances Product Alliances Genzyme.

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. In early 2015, we launched our guidance for the advancement and commercialization of RNAi therapeutics as a whole new class of innovative medicines. Specifically, by the end of 2020, we expect to achieve a company profile with three marketed products and ten RNAi therapeutic clinical programs, including four in late stages of development, across our three STArS.

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 effectiveness of the product candidate. Moreover, there are uncertainties specific to any new field of drug discovery, including RNAi. The successful development of any product candidate we develop is highly uncertain. Due to the numerous risks associated with developing drugs, we cannot reasonably estimate or know the nature, timing and estimated costs of the efforts necessary to complete the development of, or the period, if any, in which material net cash inflows will commence from, any potential product candidate. These risks include the uncertainty of:

our ability to discover new product candidates;

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

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

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

clinical trial results;

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

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

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

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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 and ultimately commercialize;

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

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

the effect of competing technological and market developments.

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

Strategic Alliances

A significant component of our business plan is to enter into strategic alliances and collaborations with leading pharmaceutical and life sciences companies, academic institutions, research foundations and others, as appropriate, to gain access to funding, capabilities, technical resources and intellectual property to further our development efforts and to generate revenues. We may 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 revenues that we can re-invest in the development of our proprietary RNAi therapeutics pipeline. At January 31, 2015, we had granted such licenses, on both an exclusive and non-exclusive basis, to approximately 20 companies.

Since delivery of RNAi therapeutics has historically been an important objective of our research activities, we have also evaluated potential collaboration and licensing arrangements with other companies and academic institutions to gain access to delivery technologies. For example, we have entered into agreements with Tekmira and Acuitas, among others, to focus on various delivery strategies. We have also entered into license agreements with Isis, Max Planck Innovation, Tekmira, CRT and Whitehead, as well as a number of other entities, to obtain rights to intellectual property in the field of RNAi. Finally, we have sought, and may seek in the future, funding for the development of our proprietary RNAi therapeutics pipeline from the government and foundations.

Critical Accounting Policies and Estimates

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

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

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

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 standalone value and the fair value of the undelivered performance obligations, typically including research and/or steering committee services, can be determined. If the fair value of the undelivered performance obligations can be determined, such obligations would then be accounted for separately as performed. If the license is considered to either not have standalone value or have standalone value but the fair value of any of the undelivered performance obligations cannot be determined, the arrangement would then be accounted for as a single unit of accounting and the license payments and payments for performance obligations are recognized as revenue over the estimated period of when the performance obligations are performed or deferred indefinitely until the undelivered performance obligation can be determined.

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

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

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

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

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

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

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

The estimate of deferred revenue also reflects management's estimate of the periods of our involvement in certain of our collaborations. Our performance obligations under these collaborations consist of participation on steering committees and the performance of other research and development services. In certain instances, the timing of satisfying these obligations can be difficult to estimate. Accordingly, our estimates may change in the future. Such changes to estimates would result in a change in revenue recognition amounts. If these estimates and judgments change over the course of these agreements, it may affect the timing and amount of revenue that we recognize and record in future periods. At December 31, 2014, we had short-term and long-term deferred revenue of \$23.9 million and \$43.0 million, respectively, related to our collaborations.

Genzyme. In January 2014, we entered into a global, strategic collaboration with Genzyme to discover, develop and commercialize RNAi therapeutics as Genetic Medicines to treat orphan diseases. The 2014 Genzyme collaboration superseded and replaced the previous collaboration between us and Genzyme entered into in October 2012 to develop and commercialize RNAi therapeutics targeting TTR for the treatment of ATTR, including patisiran and revusiran, in Japan and the Asia-Pacific region.

Genzyme paid us an upfront cash payment of \$22.5 million under the 2012 Genzyme agreement. We were also entitled to receive certain milestone payments under the 2012 Genzyme agreement. In the fourth quarter of 2013, we earned a milestone of \$7.0 million based upon the completion of a successful patisiran Phase 2 clinical trial and a milestone of \$4.0 million based upon the initiation of the Phase 3 clinical trial for patisiran. The parties agreed to collaborate in the development and commercialization of licensed products, with Genzyme assuming primary responsibility in the Genzyme territory, which included Japan and the Asia-Pacific region, and us retaining primary responsibility in the rest of the world.

We determined that the deliverables under the 2012 Genzyme agreement included the license, a joint steering committee and any additional TTR-specific RNAi therapeutic compounds that comprised the ALN-TTR program. We also determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the license and undelivered joint steering committee and any additional TTR-specific RNAi therapeutic compounds did not have standalone value due to the specialized nature of the services to be provided by us. In addition, while Genzyme had the ability to grant sublicenses, it could not sublicense all or substantially all of its rights under the 2012 Genzyme agreement. The uniqueness of our services and the limited sublicense right were indicators that standalone value was not present in the arrangement. Therefore the deliverables were not separable and, accordingly, the license and undelivered services were treated as a single unit of accounting. We were unable to reasonably estimate the period of performance under the 2012 Genzyme agreement, as we were unable to estimate the timeline of our deliverables related to the deliverable for any additional TTR-specific RNAi therapeutic compounds. Through December 31, 2013, we had deferred all revenue, or \$33.5 million, under the 2012 Genzyme agreement.

In January 2014, we entered into the 2014 Genzyme collaboration. As noted above, the 2014 Genzyme collaboration superseded and replaced the 2012 Genzyme agreement. Upon the effective date of the 2014

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Genzyme collaboration, Genzyme expanded the scope of its regional license and collaboration for patisiran for the Genzyme Territory. We retain full product rights in the Alnylam Territory. We and Genzyme also expanded our current collaboration on revusiran, so that we and Genzyme are co-developing and will co-promote revusiran in the Alnylam Territory. We maintain development and commercialization control with revusiran in the Alnylam Territory and Genzyme will develop and commercialize the product in the Genzyme Territory.

In connection with the 2014 Genzyme collaboration, we sold to Genzyme 8,766,338 shares of our common stock and Genzyme paid us \$700.0 million in aggregate cash consideration. Based on the common stock price of \$85.72, the fair value of the shares issued was \$751.5 million, which was \$51.5 million in excess of the proceeds received from Genzyme for the issuance of our common stock. This \$51.5 million is being amortized on a straight-line basis over the performance period, which is currently approximately six years as described below.

In addition, Genzyme will be required to make payments totaling up to \$50.0 million upon the achievement of certain patisiran development milestones. We could potentially earn the next patisiran milestone payment, ranging between \$5.0 million and \$20.0 million based on the geographic region, upon the achievement of specified events in connection with a regulatory filing or approval. In addition, Genzyme will be required to make payments totaling up to \$75.0 million per regional product other than patisiran, including up to \$55.0 million in development milestones and \$20.0 million in commercial milestones. Genzyme will also be required to pay tiered double-digit royalties up to twenty percent for each regional product based on annual net sales, if any, of such regional product by Genzyme, its affiliates and sublicensees. In consideration for the rights granted to Genzyme under the co-development/co-promote license terms, Genzyme will be required to make payments totaling up to \$75.0 million in development milestones for each of revusiran and ALN-AT3, if selected. In December 2014, we earned a development milestone payment of \$25.0 million based upon the initiation of the first global Phase 3 clinical trial for revusiran. We could potentially earn the next revusiran milestone payment, ranging between \$5.0 million and \$25.0 million based on the geographic region, upon the achievement of specified events in connection with regulatory approval. Genzyme will also be required to pay tiered double-digit royalties up to twenty percent for each co-development/co-promote product based on annual net sales, if any, in the Genzyme Territory for such co-development/co-promote product by Genzyme, its affiliates and sublicensees. The parties will share profits equally and we expect to book product sales in the Alnylam Territory. Finally, with respect to global products, Genzyme will be required to make payments totaling up to \$200.0 million per product, including up to \$60.0 million in development milestones and \$140.0 million in commercial milestones. Genzyme will also be required to pay tiered double-digit royalties up to twenty percent for each global product based on annual net sales, if any, of each global product by Genzyme, its affiliates and sublicensees.

Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any additional milestone payments or any royalty payments from Genzyme under the 2014 Genzyme collaboration.

We determined that the deliverables for the programs Genzyme is currently collaborating with us on include the licenses to our patisiran and revusiran clinical programs, which licenses were delivered to Genzyme upon the closing date of the transaction, and the associated development activities, joint steering committee participation and information exchange for these clinical programs. We also determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the license and associated undelivered development activities, joint steering committee participation and information exchange activities did not have standalone value due to the specialized nature of the services to be provided by us. In addition, while Genzyme has the ability to grant sublicenses, it cannot sublicense all or substantially all of its rights under the 2014 Genzyme collaboration. The uniqueness of our services and the limited sublicense rights are indicators that standalone value is not present in the arrangement. Therefore the deliverables are not separable and, accordingly, the license and undelivered services were treated as a single unit of accounting. When multiple deliverables are accounted for as a single unit of accounting, we base our revenue recognition model on the final deliverable. Under the 2014 Genzyme collaboration, the last deliverables for patisiran and revusiran are expected to be completed within approximately six years.

We determined that the total cash received from Genzyme under the now superseded 2012 Genzyme agreement reflects consideration for certain of the performance obligations for ALN-TTR programs included in

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the 2014 Genzyme collaboration. Therefore we are recognizing the \$33.5 million of deferred revenue under the 2012 Genzyme agreement on a straight-line basis over the period of performance of the ALN-TTR programs, which, as noted above, is currently approximately six years. In addition, during the fourth quarter of 2014, we recognized as revenue a portion of the \$25.0 million milestone payment earned in December 2014 equal to the percentage of the performance period completed when the milestone was earned. As future consideration, including any milestones or reimbursement for development activities, are achieved, we will recognize as revenue a portion of these payments equal to the percentage of the performance period completed when the milestone or activities have been satisfied, multiplied by the amount of the payment. We will recognize the remaining portion of consideration received over the remaining performance period on a straight-line basis. At December 31, 2014, deferred revenue under the 2014 Genzyme collaboration was \$6.7 million.

The Medicines Company. In February 2013, we and MDCO entered into a license and collaboration agreement pursuant to which we granted to MDCO an exclusive, worldwide license to develop, manufacture and commercialize RNAi therapeutics targeting PCSK9 for the treatment of hypercholesterolemia and other human diseases, including ALN-PCSsc. MDCO paid us an upfront cash payment of \$25.0 million. In addition, MDCO is required to make payments to us upon achievement of certain milestones, up to an aggregate of \$180.0 million, including up to \$30.0 million in specified development milestones, \$50.0 million in specified regulatory milestones and \$100.0 million in specified commercialization milestones. In December 2014, we earned a development milestone payment of \$10.0 million under the MDCO agreement based upon the initiation of our Phase 1 clinical trial for ALN-PCSsc. In addition, in December 2014, we also earned \$4.8 million of development costs reimbursable from MDCO. We could potentially earn the next development milestone payment of \$20.0 million under the MDCO agreement based upon the initiation of an ALN-PCSsc pivotal study. In addition, we will be entitled to royalties ranging from the low- to high- teens based on annual worldwide net sales, if any, of ALN-PCSsc by MDCO, its affiliates and sublicensees, subject to reduction under specified circumstances. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any additional milestone payments or any royalty payments from MDCO.

Under the MDCO agreement, we retain responsibility for the development of ALN-PCSsc until Phase 1 Completion (as defined in the MDCO agreement) at our cost, up to an agreed upon initial development cost cap. MDCO will assume all other responsibility for the development and commercialization of ALN-PCSsc, at its sole cost. The collaboration between us and MDCO is governed by a joint steering committee that is comprised of an equal number of representatives from each party. We are solely responsible for obtaining supply of finished product reasonably required for the conduct of our obligations through Phase 1 Completion, and supplying MDCO with finished product reasonably required for the first Phase 2 clinical trial of an ALN-PCSsc conducted by MDCO, at our expense, provided such costs do not exceed the development costs cap, subject to certain exceptions. After such time, MDCO will have the sole right and responsibility to manufacture and supply ALN-PCSsc for development and commercialization under the MDCO development plan, subject to the terms of the MDCO agreement.

We have determined that the significant deliverables under the MDCO agreement include the license, the joint steering committee, technology transfer obligations, development activities through Phase 1 Completion and supply of product for a Phase 2 clinical trial. We also determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the license and collective undelivered activities and services do not have standalone value due to the specialized nature of the activities and services to be provided by us. In addition, while MDCO has the ability to grant sublicenses, it must receive our prior written consent to sublicense all or substantially all of its rights. The uniqueness of our services and the limited sublicense right are indicators that standalone value is not present in the arrangement. Therefore the deliverables are not separable and, accordingly, the license and undelivered services are being treated as a single unit of accounting. When multiple deliverables are accounted for as a single unit of accounting, we base our revenue recognition pattern on the final deliverable. Under the MDCO agreement, all deliverables are expected to be completed within five years. We are recognizing revenue under the MDCO agreement on a straight-line basis over five years. We are not utilizing a proportional performance model since we are unable to reasonably estimate the level of effort to fulfill these obligations, primarily because the effort required under the development activities is largely unknown.

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The initial upfront payment of \$25.0 million from MDCO was initially recorded as deferred revenue. We recognized as revenue a portion of the \$10.0 million milestone and \$4.8 million in expense reimbursement earned in December 2014 equal to the percentage of the performance period completed when the milestone was earned. As future milestones are earned, if any, we will recognize as revenue a portion of the milestone payment equal to the percentage of the performance period completed when the milestone is achieved, multiplied by the amount of the milestone payment. At December 31, 2014, deferred revenue under the MDCO agreement was \$24.7 million.

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

Monsanto paid us \$29.2 million in upfront cash payments, and was also required to make near-term milestone payments to us upon the achievement of specified technology transfer and patent-related milestones. We were also entitled to receive additional funding for collaborative research efforts. In the aggregate, we had the ability to earn up to \$5.0 million in milestone payments and research funding under the Monsanto alliance. We received a total of \$4.0 million in milestone payments from Monsanto based upon the achievement of a specified patent-related event and the completion of technology transfer activities. In September 2014, we and Monsanto mutually determined not to pursue the discovery collaboration originally contemplated under the terms of the Monsanto agreement. Accordingly, Monsanto will not be required to pay us the final milestone of \$1.0 million. There are no remaining milestones under the Monsanto agreement. Monsanto is required to pay to us a percentage of specified fees from certain sublicense agreements Monsanto may enter into that include access to our intellectual property, as well as low single-digit royalty payments on worldwide, net sales by Monsanto, its affiliates and sublicensees of certain licensed products, as defined in the Monsanto agreement, if any. Due to the uncertainty of the application of RNAi technology in the field of agriculture, we may not receive any license fees or royalty payments from Monsanto.

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

We have determined that the significant deliverables under the Monsanto agreement include the license, the technology transfer activities and the services that we will be obligated to perform under the Monsanto discovery collaboration. We have also determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the license and undelivered technical transfer activities and Monsanto discovery collaboration services do not have standalone value due to the specialized nature of the services to be provided by us. In addition, while Monsanto has the ability to grant sublicenses, it cannot grant access to certain of our proprietary technology. The uniqueness of our services and the limited sublicense right are indicators that standalone value is not present in the arrangement. Therefore the deliverables are not separable and, accordingly, the license and undelivered technical transfer activities and Monsanto discovery collaboration services are being treated as a single unit of accounting. When multiple deliverables are accounted for as a single unit of accounting, we base our revenue recognition model on the final deliverable. Under the Monsanto agreement, the last deliverable expected to be completed was the discovery collaboration, which was originally to be completed within five years. Therefore, prior to the September 2014 amendment, we were recognizing revenue under the Monsanto agreement on a straight-line basis over five years. However, as a result of the September 2014

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amendment, we have determined that the final deliverable in the collaboration is the technology transfer activities, know-how exchange and access to intellectual property controlled by us as of the date of the Monsanto agreement or during the 30 months thereafter, in the field of agriculture. Consequently, we are now recognizing the remaining deferred revenue of \$16.8 million at the date of the amendment on a prospective basis from September 2014 through February 2015, the date which is the end of the 30-month obligation, which excludes \$5.0 million related to a potential refund due to Monsanto under certain circumstances pursuant to the original terms of the Monsanto agreement. We will continue to recognize this revenue on a straight-line basis over the remaining obligation period. We cannot use a proportional performance model since we are unable to reasonably estimate the level of effort to fulfill these obligations, primarily because the potential effort required is unknown. At December 31, 2014, deferred revenue under the Monsanto agreement was \$10.6 million, of which \$5.6 million will be recognized through February 2015 and \$5.0 million will be recognized when the potential refund obligation ceases and can be considered fixed or determinable.

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.

Takeda paid us an upfront payment of \$100.0 million and an additional \$50.0 million upon achievement of specified technology transfer milestones. In addition, for each RNAi therapeutic product developed by Takeda, its affiliates and sublicensees, we are entitled to receive specified development, regulatory and commercialization milestone payments, totaling up to \$171.0 million per product, together with a double-digit percentage royalty payment based on worldwide annual net sales, if any. The potential future milestone payments per product include up to \$26.0 million for the achievement of specified development milestones, up to \$40.0 million for the achievement of specified regulatory milestones and up to \$105.0 million for the achievement of specified commercialization milestones. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any additional milestone payments or any royalty payments from Takeda.

Pursuant to the Takeda agreement, we and Takeda also agreed to collaborate on the research of RNAi therapeutics directed to one or two disease targets agreed to by the parties, subject to our existing contractual obligations with third parties. The collaboration is governed by a 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.

We have determined that the deliverables under the Takeda agreement include the license, the joint committees, the technology transfer activities and the services that we were obligated to perform under the research collaboration with Takeda. We also have determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the license and undelivered services (i.e., the joint committees and the research collaboration) are not separable and, accordingly, the license and services are being treated as a single unit of accounting. Under the Takeda agreement, the last elements to be delivered are the joint technology transfer committee and joint delivery collaboration committee services, each of which has a life of no more than seven years. We are recognizing the upfront payment of \$100.0 million and the technology transfer milestones of \$50.0 million, the receipt of which we believed was probable at the commencement of the collaboration, on a straight-line basis over seven years because we are unable to reasonably estimate the level of effort to fulfill these obligations, primarily because the effort required under the research collaboration is largely unknown, and therefore, cannot utilize a proportional performance model. As future milestones are achieved, we will recognize as revenue a portion of the milestone payment equal to the percentage of the performance period completed when the milestone is achieved, multiplied by the amount of the milestone payment. At December 31, 2014, deferred revenue under the Takeda agreement was \$8.9 million. This remaining deferred revenue will be recognized in full through May 30, 2015.

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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, 2014, we have not recorded significant interest and penalty expense related to uncertain tax positions.

We operate in the United States, as well as in several countries outside of the United States, 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, 2014, we had no unrecognized tax benefits that, if recognized, would favorably impact our effective income tax rate in future periods.

We recognize income taxes when transactions are recorded in our consolidated statements of comprehensive loss, with deferred taxes provided for items that are recognized in different periods for financial statement and tax reporting purposes. We record a valuation allowance to reduce the deferred tax assets to the amount that is more likely than not to be realized.

For the years ended December 31, 2014, 2013 and 2012, we recorded a benefit from income taxes of \$40.2 million, \$2.7 million and \$10.6 million, respectively. A benefit of \$19.5 million, \$2.7 million and \$10.6 million for the years ended December 31, 2014, 2013, and 2012, respectively, is due primarily to our recognition of the corresponding income tax benefit associated with the increase in the value of our investment in Regulus that we carried at fair market value during the same respective period. In addition, for the year ended December 31, 2014, we recorded a benefit of \$20.7 million due to the recognition of corresponding income tax expense associated with the excess of the proceeds received from Genzyme for the issuance of our common stock. The corresponding income tax expense has been recorded in other comprehensive income and additional paid-in capital, respectively.

At December 31, 2014, 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, 2014, we had federal and state net operating loss carryforwards of \$639.3 million and \$701.8 million, respectively, to reduce future taxable income that will expire at various dates through 2034. At December 31, 2014, we had federal and state research and development credit carryforwards of \$32.3 million and \$10.1 million, respectively, available to reduce future tax liabilities that expire at various dates through 2034. At December 31, 2014, we had foreign tax credit carryforwards of \$3.2 million available to reduce future tax liabilities that expire in 2017. At December 31, 2014, we had alternative minimum tax credits of \$0.8 million available to reduce future regular tax liabilities to the extent such regular tax less other non-refundable credits exceeds the tentative minimum tax. We have a valuation allowance against the net operating loss and credit deferred tax assets as it is unlikely that we will realize these assets. Ownership changes, as defined in the Internal Revenue Code, including those resulting from the issuance of common stock in connection with our public offerings, may limit the amount of net operating loss and tax credit carryforwards that can be utilized to offset future taxable income or tax liability. The amount of the limitation is determined in accordance with Section 382 of the Internal Revenue Code. We have determined that based on our value, in the event there was an annual limitation under Section 382, all net operating loss and tax credit carryforwards would still be available to offset taxable income.

Accounting for Stock-Based Compensation

We have stock incentive plans and an employee stock purchase plan under which we grant equity instruments. We account for all stock-based awards granted to employees at their fair value and generally recognize compensation expense over the vesting period of the award. Determining the amount of stock-based

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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 the historical volatility of our publicly traded stock.

For stock option awards granted during the year ended December 31, 2014, we used a weighted-average expected stock-price volatility assumption of 55%. Our expected life assumption is based on our historical data. Our weighted-average expected term was 5.8 years for the year ended December 31, 2014. 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. Expense is recognized over the vesting period, commencing when we determine that it is probable that the awards will vest.

For performance-based 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, 2014, the estimated fair value of time-based unvested employee stock options and restricted stock awards was \$61.4 million, net of estimated forfeitures. We will recognize this amount over the weighted-average remaining vesting period of approximately three years for these awards. Stock-based employee compensation expense was \$33.1 million for the year ended December 31, 2014. 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 have applied an annual forfeiture rate to all unvested employee stock options and restricted stock awards at December 31, 2014 based on an analysis of our historical forfeitures. Ultimately, the actual expense recognized over the vesting period will only be for those shares that vest.

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

Results of Operations

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

	Year Ended December 31,		
	2014	2013	2012
Net revenues from collaborators	\$ 50,561	\$ 47,167	\$ 66,725
Operating expenses	455,541	140,109	196,181
Loss from operations	(404,980)	(92,942)	(129,456)
Net loss	\$ (360,395)	\$ (89,225)	\$ (106,014)

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The increase in operating expenses for the year ended December 31, 2014 resulted primarily from a \$220.8 million charge to operating expenses in connection with our acquisition of the Sirna RNAi assets from Merck, which is described below under the heading In-process research and development. Operating expenses for the year ended December 31, 2012 included a \$65.0 million charge to operating expenses in connection with the restructuring of our license agreement with Tekmira in November 2012.

Discussion of Results of Operations for 2014 and 2013***Net revenues from collaborators***

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

	Year Ended December 31,	
	2014	2013
Takeda	\$ 21,973	\$ 21,973
Monsanto	14,985	5,640
MDCO	10,753	4,604
Roche/Arrowhead	1,000	
Cubist		9,721
Other	1,850	5,229
Total net revenues from collaborators	\$ 50,561	\$ 47,167

Net revenues from collaborators increased for the year ended December 31, 2014 as compared to the year ended December 31, 2013 due primarily to revenue recognized in connection with the September 2014 amendment of our remaining performance obligations under the Monsanto agreement. In addition, net revenues from collaborators increased for the year ended December 31, 2014 as a result of the achievement of a milestone as well as expense reimbursement under our MDCO agreement. This increase was partially offset by recognition of the remaining deferred revenue under the Cubist agreement of \$9.7 million due to the termination of the Cubist agreement in February 2013 and the end of our performance obligations thereunder.

We expect net revenues from collaborators to decrease during 2015 on a comparative basis due primarily to the planned completion of our performance obligations under each of the Monsanto agreement in February 2015 and the Takeda agreement in May 2015.

We had \$66.9 million of deferred revenue at December 31, 2014, which consists primarily of payments we have received from collaborators, primarily MDCO, Kyowa Hakko Kirin, Monsanto, Takeda and Genzyme, but have not yet recognized pursuant to our revenue recognition policies.

For the foreseeable future, we expect our revenues to be derived primarily from our alliances with Genzyme, MDCO and other strategic alliances, as well as new collaborations and licensing activities.

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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:

	2014	% of Total Operating Expenses	2013	% of Total Operating Expenses	Increase (Decrease)	
					\$	%
Research and development	\$ 190,249	42%	\$ 112,957	81%	\$ 77,292	68%
In-process research and development	220,766	48%		0%	220,766	N/A
General and administrative	44,526	10%	27,152	19%	17,374	64%
Total operating expenses	\$ 455,541	100%	\$ 140,109	100%	\$ 315,432	225%

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:

	2014	% of Expense Category	2013	% of Expense Category	Increase (Decrease)	
					\$	%
Research and development						
Clinical trial and manufacturing	\$ 64,195	34%	\$ 27,415	24%	\$ 36,780	134%
Compensation and related	39,993	21%	25,518	23%	14,475	57%
External services	27,432	14%	15,320	14%	12,112	79%
Non-cash stock-based compensation	18,233	10%	14,369	13%	3,864	27%
Facilities-related	18,068	10%	14,299	13%	3,769	26%
License fees	12,064	6%	7,968	7%	4,096	51%
Lab supplies and materials	5,908	3%	4,983	4%	925	19%
Other	4,356	2%	3,085	2%	1,271	41%
Total research and development expenses	\$ 190,249	100%	\$ 112,957	100%	\$ 77,292	68%

Research and development expenses increased during year end December 31, 2014 as compared to the year ended December 31, 2013 due to additional expenses for clinical trial and manufacturing and external services resulting primarily from the significant advancement of certain of our clinical and pre-clinical programs. In addition, compensation and related expense increased during the year ended December 31, 2014 as compared to the year ended December 31, 2013 due primarily to a significant increase in headcount during the period as we expand and advance our development pipeline. Non-cash stock-based compensation increased during the year ended December 31, 2014 as compared to the year ended December 31, 2013 due primarily to the vesting of certain performance-based stock option awards during the fourth quarter. License fees increased during the year ended December 31, 2014 as compared to the year ended December 31, 2013 due to payments to certain entities, primarily fees paid to Isis as a result of the 2014 Genzyme collaboration.

We expect to continue to devote a substantial portion of our resources to research and development expenses, including for the advancement of our Genetic Medicine, Cardio-Metabolic Disease and Hepatic Infectious Disease STArS, to support the goal of three marketed products and ten programs in clinical development, including four late stage programs, by 2020. We expect that research and development expenses will increase significantly in 2015 as we continue to develop our pipeline and advance our product candidates into clinical trials.

A significant portion of our research and development costs are not tracked by project as they benefit multiple projects or our technology platform. However, certain of our collaboration agreements contain cost-

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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.

In-process research and development. For the year ended December 31, 2014, we recorded \$220.8 million to in-process research and development expense in connection with the purchase of the Sirna RNAi assets from Merck. Specifically, at the closing of the transaction, we paid Merck \$25.0 million in cash and issued 2,142,037 shares of our common stock, resulting in a charge to in-process research and development expense of \$199.3 million. We issued an additional 378,007 shares of common stock to Merck in May 2014 upon the completion of certain technology transfer activities during the second quarter of 2014. In the first quarter of 2014, we recorded a liability of \$25.4 million associated with the then future obligation to issue these shares, which was also charged to in-process research and development expense. Upon completion of these technology transfer activities in the second quarter of 2014, we re-measured the expense recorded in connection with these shares using the then current price of our common stock, resulting in a credit of \$3.9 million. In future periods, there will be no additional charges recorded to in-process research and development related to the purchase of the Sirna RNAi assets from Merck.

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:

	2014	% of Expense Category	2013	% of Expense Category	Increase (Decrease) \$	%
General and administrative						
Consulting and professional services	\$ 15,068	34%	\$ 9,706	36%	\$ 5,362	55%
Non-cash stock-based compensation	14,828	33%	6,334	23%	8,494	134%
Compensation and related	9,539	21%	7,102	26%	2,437	34%
Facilities-related	2,157	5%	1,450	5%	707	49%
Other	2,934	7%	2,560	10%	374	15%
Total general and administrative expenses	\$ 44,526	100%	\$ 27,152	100%	\$ 17,374	64%

General and administrative expenses increased during the year ended December 31, 2014 as compared to the year ended December 31, 2013 due primarily to an increase in non-cash stock-based compensation expenses. This increase was due primarily to the vesting of certain performance-based stock option awards and a one-time charge recorded for certain stock options that were modified in the second quarter of 2014. Consulting and professional services increased during the year ended December 31, 2014 as compared to the year ended December 31, 2013 related to business development activities.

We expect that general and administrative expenses will increase slightly in 2015 as we continue to grow our operations.

Benefit from income taxes

Our benefit from income taxes was \$40.2 million for the year ended December 31, 2014 as compared to \$2.7 million for the year ended December 31, 2013. The increase during the quarter and year ended December 31, 2014 as compared to the prior year periods was due primarily to our recognition of the corresponding income tax benefit associated with the increase in the value of our investment in Regulus that we carried at fair market value during the same respective period, as well as the difference between the value of

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stock and the cash proceeds received from Genzyme for the issuance of our common stock. The corresponding income tax expense has been recorded in other comprehensive income and additional paid-in capital, respectively.

Discussion of Results of Operations for 2013 and 2012*Net revenues from collaborators*

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

	Year Ended December 31,	
	2013	2012
Takeda	\$ 21,973	\$ 21,973
Cubist	9,721	2,777
Monsanto	5,640	1,954
MDCO	4,604	
Roche/Arrowhead		37,318
Other	5,229	2,703
Total net revenues from collaborators	\$ 47,167	\$ 66,725

Net revenues from collaborators decreased for the year ended December 31, 2013 as compared to the year ended December 31, 2012 due primarily to the completion of our remaining performance obligations under the Roche/Arrowhead alliance in August 2012. This decrease was partially offset by recognition of the remaining deferred revenue under the Cubist agreement of \$9.7 million due to the termination of the Cubist agreement in February 2013 and the end of our performance obligations thereunder. In addition, the decrease was partially offset by revenues recorded under our agreements with Monsanto and MDCO.

We had \$126.1 million of deferred revenue at December 31, 2013, which consisted of payments we had received from collaborators, primarily Takeda, Kyowa Hakko Kirin, Monsanto, MDCO and Genzyme, but have not yet recognized pursuant to our revenue recognition policies.

Operating expenses

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

	2013	% of Total Operating Expenses	2012	% of Total Operating Expenses	Increase (Decrease)	
					\$	%
Research and development	\$ 112,957	81%	\$ 86,569	44%	\$ 26,388	30%
General and administrative	27,152	19%	44,612	23%	(17,460)	(39)%
Restructuring of Tekmira license agreement		0%	65,000	33%	(65,000)	(100)%
Total operating expenses	\$ 140,109	100%	\$ 196,181	100%	\$ (56,072)	(29)%

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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:

	2013	% of Expense Category	2012	% of Expense Category	Increase (Decrease) \$	%
Research and development						
Clinical trial and manufacturing	\$ 27,415	24%	\$ 15,930	18%	\$ 11,485	72%
Compensation and related	25,518	23%	20,438	24%	5,080	25%
External services	15,320	14%	13,743	16%	1,577	11%
Non-cash stock-based compensation	14,369	13%	8,041	9%	6,328	79%
Facilities-related	14,299	13%	12,647	15%	1,652	13%
License fees	7,968	7%	5,693	7%	2,275	40%
Lab supplies and materials	4,983	4%	4,422	5%	561	13%
Restructuring		0%	2,817	3%	(2,817)	(100)%
Other	3,085	2%	2,838	3%	247	9%
Total research and development expenses	\$ 112,957	100%	\$ 86,569	100%	\$ 26,388	30%

Research and development expenses increased during the year ended December 31, 2013 as compared to the year ended December 31, 2012 due primarily to higher clinical trial and manufacturing costs related to our patisiran, revusiran and ALN-AT3 programs. In addition, stock-based compensation increased during the year ended December 31, 2013 as compared to the year ended December 31, 2012 due primarily to an increase in the Black-Scholes value and vesting of stock options granted in 2013. Compensation and related expenses also increased due primarily to the increase in workforce during the year. License fees increased for the year ended December 31, 2013 as compared to the year ended December 31, 2012 due primarily to payments to certain entities for the advancement of our patisiran program into a Phase 3 clinical trial during the fourth quarter, including a \$5.0 million milestone paid to Tekmira. Partially offsetting these increases was a one-time charge related to our 2012 restructuring, including employee severance, benefits and other related cost.

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:

	2013	% of Expense Category	2012	% of Expense Category	Increase (Decrease) \$	%
General and administrative						
Consulting and professional services	\$ 9,706	36%	\$ 28,949	65%	\$ (19,243)	(66)%
Compensation and related	7,102	26%	6,384	14%	718	11%
Non-cash stock-based compensation	6,334	23%	4,319	10%	2,015	47%
Facilities-related	1,450	5%	1,648	4%	(198)	(12)%
Restructuring		0%	890	2%	(890)	(100)%
Other	2,560	10%	2,422	5%	138	6%
Total general and administrative expenses	\$ 27,152	100%	\$ 44,612	100%	\$ (17,460)	(39)%

The decrease in general and administrative expenses during the year ended December 31, 2013 as compared to the year ended December 31, 2012 was due primarily to a decrease in consulting and professional services expenses related to business activities, primarily legal activities related to litigation with Tekmira that was

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resolved in November 2012. Also included in the year ended December 31, 2012 was a one-time charge related to our January 2012 strategic corporate restructuring, including employee severance, benefits and other related costs.

Other income (expense)

We incurred zero in equity in loss of joint venture (Regulus Therapeutics Inc.) for the year ended December 31, 2013 as compared to \$4.5 million for the year ended December 31, 2012 related to our share of the net losses incurred by Regulus. In October 2012, Regulus completed an initial public offering, resulting in our ownership percentage decreasing from approximately 44% to 17% of Regulus' outstanding common stock. As of December 31, 2013, our ownership percentage had decreased to approximately 15%.

Our benefit from income taxes was \$2.7 million in 2013 as compared to \$10.6 million for 2012. The change was due to our recognition of the corresponding income tax benefit associated with the increase in the value of our investment in Regulus that we carried at fair market value during the same respective period.

Liquidity and Capital Resources

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

	Year Ended December 31,		
	2014	2013	2012
Net loss	\$ (360,395)	\$ (89,225)	\$ (106,014)
Adjustments to reconcile net loss to net cash used in operating activities	224,155	28,686	(630)
Changes in operating assets and liabilities	(29,401)	(8,118)	(8,965)
Net cash used in operating activities	(165,641)	(68,657)	(115,609)
Net cash (used in) provided by investing activities	(548,814)	(130,505)	3,374
Net cash provided by financing activities	736,465	200,926	93,412
Net increase (decrease) in cash and cash equivalents	22,010	1,764	(18,823)
Cash and cash equivalents, beginning of period	53,169	51,405	70,228
Cash and cash equivalents, end of period	\$ 75,179	\$ 53,169	\$ 51,405

Since we commenced operations in 2002, we have generated significant losses. At December 31, 2014, we had an accumulated deficit of \$956.6 million. At December 31, 2014, we had cash, cash equivalents and fixed income marketable securities of \$881.9 million, excluding our investment in equity securities of Regulus, compared to cash, cash equivalents and fixed income marketable securities of \$350.5 million at December 31, 2013.

In January 2015, we sold an aggregate of 5,447,368 shares of our common stock through an underwritten public offering at a price to the public of \$95.00 per share. As a result of the offering, which included the full exercise of the underwriters' option to purchase additional shares, we received aggregate net proceeds of approximately \$496.4 million, after deducting underwriting discounts and commissions and other estimated offering expenses of approximately \$21.1 million. We intend to use these proceeds for general corporate purposes, focused on achieving our Alnylam 2020 profile with three marketed products and ten RNAi therapeutic clinical programs, including four in late stages of development, across our three STAr, by the end of 2020. In January 2013, we sold an aggregate of 9,200,000 shares of our common stock through an underwritten public offering for aggregate net proceeds of approximately \$173.6 million, after deducting underwriting discounts and commissions and other estimated offering expenses of approximately \$11.6 million. In February 2012, we sold

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an aggregate of 8,625,000 shares of our common stock through an underwritten public offering for aggregate net proceeds of approximately \$86.8 million, after deducting underwriting discounts and commissions and other estimated offering expenses of approximately \$5.9 million.

In February 2014, in connection with our 2014 Genzyme collaboration, we sold to Genzyme 8,766,338 shares of our common stock and Genzyme paid \$700.0 million in aggregate cash consideration to us. In March 2014, as a result of our issuance of shares in connection with our acquisition of Sirna, Genzyme exercised its right under our investor agreement to purchase an additional 344,448 shares of our common stock and paid us approximately \$23.0 million. Genzyme also has the right each January to purchase a number of shares of our common stock based on the number of shares we issued during the previous year for compensatory purposes. Genzyme exercised this right to purchase directly from us 196,251 shares of our common stock on January 22, 2015 for approximately \$18.3 million. In January 2015, in connection with our public offering described above, Genzyme also exercised its right to purchase directly from us, in concurrent private placements, 744,566 shares of common stock, resulting in proceeds to us of approximately \$70.7 million. Each of these purchases allowed Genzyme to maintain its ownership level of our outstanding common stock of approximately 12%.

We invest primarily in cash equivalents, U.S. government-sponsored enterprise securities, U.S. treasury securities, 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, 2014.

Operating activities

We have required significant amounts of cash to fund our operating activities as a result of net losses since our inception. 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 have historically included stock-based compensation, in-process research and development, intraperiod tax allocation 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.

The increase in net cash used in operating activities for the year ended December 31, 2014 compared to the year ended December 31, 2013 was due primarily to our net loss adjusted for noncash activities, such as in-process research and development expense of \$220.8 million and partially offset by a benefit from intraperiod tax allocation of \$40.2 million. The decrease in net cash used in operating activities for the year ended December 31, 2013 compared to the year ended December 31, 2012 was due primarily to our net loss and other changes in our working capital and a decrease in deferred revenue of \$6.2 million.

Investing activities

For the year ended December 31, 2014, net cash used in investing activities of \$548.8 million was due primarily to \$514.9 million of net purchases of fixed income marketable securities. For the year ended December 31, 2013, net cash used in investing activities of \$130.5 million resulted primarily from net purchases of fixed income marketable securities of \$126.5 million. For the year ended December 31, 2012, net cash provided by investing activities of \$3.4 million resulted primarily from sales and maturities of fixed income marketable securities of \$11.9 million offset by purchases of property and equipment of \$8.3 million primarily in connection with the build-out of our cGMP manufacturing facility.

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Financing activities

For the year ended December 31, 2014, net cash of \$736.5 million provided by financing activities was due primarily to proceeds of \$723.0 million received from our issuances of common stock to Genzyme, as well as proceeds of \$29.4 million from the issuance of common stock in connection with stock option exercises and other types of equity, partially offset by \$16.0 million of payments for the repurchase of common stock for employee tax withholding. For the year ended December 31, 2013, net cash provided by financing activities of \$200.9 million was due primarily to proceeds of \$173.6 million received from our January 2013 underwritten public offering, as well as proceeds of \$28.7 million from the issuance of common stock in connection with stock option exercises and other types of equity. For the year ended December 31, 2012, net cash of \$93.4 million provided by financing activities was due primarily to proceeds of \$86.8 million received from our February 2012 underwritten public offering, as well as proceeds of \$7.0 million from the issuance of common stock in connection with stock option exercises and other types of equity.

Operating Capital Requirements

We do not know when, if ever, we will successfully develop or be able to commence sales of any product. Therefore, we anticipate that we will continue to generate significant losses for the foreseeable future as a result of planned expenditures for research and development activities relating to our drug development programs, including the optimization of drug delivery technologies, clinical trial and manufacturing costs, the establishment of late-stage clinical and commercial capabilities, 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, including the proceeds from our public offering and Genzyme's purchases of additional shares of our common stock in January 2015, together with the cash we expect to generate under our current alliances, will be sufficient to enable us to achieve our Alnylam 2020 guidance. For reasons discussed below, we may require significant additional funds earlier than we currently expect in order to develop, conduct clinical trials for and commercialize any product candidates.

In the future, we may seek additional funding through additional collaborative arrangements and public or private financings. In December 2012, we filed an automatically effective shelf registration statement with the SEC for an indeterminate number of shares. Additional funding may not be available to us on acceptable terms or at all. In addition, the terms of any additional financing may further adversely affect the holdings or the rights of our stockholders. For example, if we raise additional funds by issuing equity securities, further dilution to our existing stockholders may result. In addition, as a condition to providing additional funds to us, future investors may demand, and may be granted, rights superior to those of existing stockholders. If we are unable to obtain funding on a timely basis, we may be required to significantly delay or curtail one or more of our research or development programs. We also could be required to seek funds through arrangements with collaborators or others that may require us to relinquish rights to some of our technologies or product candidates that we would otherwise pursue.

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

our progress in demonstrating that siRNAs can be active as drugs and achieve desired clinical effects;

our ability to develop relatively standard procedures for selecting and modifying siRNA product candidates;

progress in our research and development programs, as well as what may be required by regulatory bodies to advance these programs;

the timing, receipt and amount of milestone and other payments, if any, from present and future collaborators, if any;

our ability to maintain and establish additional collaborative arrangements and/or new business initiatives;

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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;

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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;

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 Acuitas, we have agreed to indemnify Acuitas for certain legal costs, subject to certain exceptions and limitations. Amounts paid under the Acuitas indemnification agreement in connection with our previous litigation with Tekmira were 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 certain previously settled litigation related to the Tuschl patents and our disputes with Tekmira, and certain ongoing costs related to the University of Utah litigation, we have not encountered material costs as a result of such obligations and have not accrued any liabilities related to such obligations in our consolidated financial statements. See Note 7 to our consolidated financial statements included in Part II, Item 8, Financial Statements and Supplementary Data, of 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, 2014, as well as obligations related to contracts that we are likely to continue, regardless of the fact that they were cancelable at December 31, 2014. 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.

Contractual Obligations	2015	Payments Due by Period			Total
		2016 and 2017	2018 and 2019	After 2019	
Operating lease obligations(1)	\$ 6,810	\$ 14,529	\$ 14,995	\$ 13,845	\$ 50,179
Purchase commitments(2)	59,279	45,222			104,501
Technology license commitments(3)	7,379	1,468	1,516	8,592	18,955
Total contractual cash obligations	\$ 73,468	\$ 61,219	\$ 16,511	\$ 22,437	\$ 173,635

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

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- (2) Includes commitments related to purchase orders, clinical, manufacturing 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.

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

Recent Accounting Pronouncements

See Note 2 to our consolidated financial statements included in Part II, Item 8, Financial Statements and Supplementary Data, of this annual report on Form 10-K for a description of recent accounting pronouncements applicable to our business.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

As part of our investment portfolio, we own financial instruments that are sensitive to market risks. The investment portfolio is used to preserve our capital until it is required to fund operations, including our research and development activities. Our fixed income marketable securities consist of U.S. government-sponsored enterprise securities, U.S. treasury securities, 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, 2014, the net fair value of our interest-sensitive financial instruments would have resulted in a hypothetical decline of \$3.2 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. Historically, foreign currency fluctuations have not been material. We did not record any impairment charges to our fixed income marketable securities during the year ended December 31, 2014.

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ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA
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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, 2014. 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 (2013).

Based on its assessment, management concluded that, as of December 31, 2014, 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, 2014 has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in their report. This report appears on page 102.

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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, the accompanying consolidated balance sheets and the related consolidated statements of 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, 2014 and 2013, and the results of their operations and their cash flows for each of the three years in the period ended December 31, 2014 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, 2014, based on criteria established in *Internal Control – Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). The Company's management is responsible for these financial statements, for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Management's Annual Report on Internal Control over Financial Reporting. Our responsibility is to express opinions on these financial statements and on the Company's internal control over financial reporting based on our integrated audits. We 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 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 13, 2015

Table of Contents**ALNYLAM PHARMACEUTICALS, INC.****CONSOLIDATED BALANCE SHEETS**

(In thousands, except share and per share amounts)

	December 31,	
	2014	2013
ASSETS		
Current assets:		
Cash and cash equivalents	\$ 75,179	\$ 53,169
Marketable securities	526,929	192,701
Investment in equity securities of Regulus Therapeutics Inc	94,583	
Billed and unbilled collaboration receivables	39,937	4,248
Prepaid expenses and other current assets	9,739	3,910
Total current assets	746,367	254,028
Marketable securities	279,821	104,602
Deferred tax assets	31,667	
Investment in equity securities of Regulus Therapeutics Inc.		45,452
Property and equipment, net	21,740	16,448
Total assets	\$ 1,079,595	\$ 420,530
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	\$ 15,111	\$ 5,896
Accrued expenses	23,680	14,160
Deferred tax liabilities	31,667	
Deferred rent	1,005	1,112
Deferred revenue	23,871	32,696
Total current liabilities	95,334	53,864
Deferred rent, net of current portion	5,011	2,925
Deferred revenue, net of current portion	42,983	93,394
Total liabilities	143,328	150,183
Commitments and contingencies (Note 7)		
Stockholders' equity:		
Preferred stock, \$0.01 par value per share, 5,000,000 shares authorized and no shares issued and outstanding at December 31, 2014 and 2013		
Common stock, \$0.01 par value per share, 125,000,000 shares authorized; 77,202,753 shares issued and outstanding at December 31, 2014; 63,741,573 shares issued and outstanding at December 31, 2013	772	637
Additional paid-in capital	1,843,362	846,228
Accumulated other comprehensive income	48,763	19,717
Accumulated deficit	(956,630)	(596,235)
Total stockholders' equity	936,267	270,347
Total liabilities and stockholders' equity	\$ 1,079,595	\$ 420,530

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

Table of Contents**ALNYLAM PHARMACEUTICALS, INC.****CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS****(In thousands, except per share amounts)**

	Year Ended December 31,		
	2014	2013	2012
Net revenues from collaborators	\$ 50,561	\$ 47,167	\$ 66,725
Operating expenses:			
Research and development(1)	190,249	112,957	86,569
In-process research and development	220,766		
General and administrative(1)	44,526	27,152	44,612
Restructuring of Tekmira license agreement			65,000
Total operating expenses	455,541	140,109	196,181
Loss from operations	(404,980)	(92,942)	(129,456)
Other income (expense):			
Equity in loss of joint venture (Regulus Therapeutics Inc.)			(4,522)
Gain on issuance of stock by Regulus Therapeutics Inc.			16,084
Interest income	2,559	1,069	977
Other income (expense)	1,817	(47)	331
Total other income	4,376	1,022	12,870
Loss before income taxes	(400,604)	(91,920)	(116,586)
Benefit from income taxes	40,209	2,695	10,572
Net loss	\$ (360,395)	\$ (89,225)	\$ (106,014)
Net loss per common share basic and diluted	\$ (4.85)	\$ (1.45)	\$ (2.11)
Weighted-average common shares used to compute basic and diluted net loss per common share	74,278	61,551	50,286
Comprehensive loss:			
Net loss	\$ (360,395)	\$ (89,225)	\$ (106,014)
Unrealized gain on marketable securities, net of tax	31,127	4,055	15,827
Reclassification adjustment for realized gain on marketable securities included in net loss	(2,081)		
Comprehensive loss	\$ (331,349)	\$ (85,170)	\$ (90,187)

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

Research and development	\$ 18,233	\$ 14,369	\$ 8,041
General and administrative	14,828	6,334	4,319

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

Table of Contents**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, 2011	42,721,942	\$ 427	\$ 518,731	\$ (165)	\$ (400,996)	\$ 117,997
Exercise of common stock options	661,909	7	6,395			6,402
Issuance of common stock under other types of equity plans	97,459	1	878			879
Issuance of restricted stock, net of cancellations and tax withholdings	383,626	4	(523)			(519)
Issuance of common stock, net of offering costs	8,625,000	86	86,714			86,800
Stock-based compensation expense			12,360			12,360
Joint venture stock-based compensation expense (Regulus Therapeutics Inc.)			321			321
Other comprehensive income				15,827		15,827
Net loss					(106,014)	(106,014)
Balance at December 31, 2012	52,489,936	525	624,876	15,662	(507,010)	134,053
Exercise of common stock options	2,031,916	20	27,974			27,994
Issuance of common stock under other types of equity plans	60,180	1	1,183			1,184
Tax withholdings and cancellations of restricted stock, net of issuances of new awards	(40,459)	(1)	(1,988)			(1,989)
Issuance of common stock, net of offering costs	9,200,000	92	173,480			173,572
Stock-based compensation expense			20,703			20,703
Other comprehensive income				4,055		4,055
Net loss					(89,225)	(89,225)
Balance at December 31, 2013	63,741,573	637	846,228	19,717	(596,235)	270,347
Exercise of common stock options	1,972,204	20	28,429			28,449
Issuance of common stock under other types of equity plans	31,122	1	1,580			1,581
Tax withholdings and cancellations of restricted stock, net of issuances of new awards	(172,976)	(2)	(15,390)			(15,392)
Issuance of common stock to Genzyme	9,110,786	91	774,396			774,487
Issuance of common stock in connection with an asset acquisition	2,520,044	25	195,741			195,766
Stock-based compensation expense			33,061			33,061
Tax provision associated with intraperiod tax allocation			(20,683)			(20,683)
Other comprehensive income before reclassifications, net of tax				31,127		31,127
Reclassification adjustment for realized gain on marketable securities included in net loss				(2,081)		(2,081)

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Net loss					(360,395)	(360,395)
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Balance at December 31, 2014	77,202,753	\$ 772	\$ 1,843,362	\$ 48,763	\$ (956,630)	\$ 936,267
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The accompanying notes are an integral part of these consolidated financial statements.

Table of Contents**ALNYLAM PHARMACEUTICALS, INC.****CONSOLIDATED STATEMENTS OF CASH FLOWS****(In thousands)**

	Year Ended December 31,		
	2014	2013	2012
Cash flows from operating activities:			
Net loss	\$ (360,395)	\$ (89,225)	\$ (106,014)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	11,926	10,229	9,035
Non-cash stock-based compensation	33,061	20,703	12,360
Charge for 401(k) company stock match	692	449	364
Equity in loss of joint venture (Regulus Therapeutics Inc.)			4,522
Realized gain on sale of marketable securities	(2,081)		(255)
Gain on issuance of stock by joint venture			(16,084)
Benefit from intraperiod tax allocation	(40,209)	(2,695)	(10,572)
In-process research and development	220,766		
Changes in operating assets and liabilities:			
Proceeds from landlord tenant improvements	1,941	204	1,780
Billed and unbilled collaboration receivables	(35,689)	(4,144)	1,364
Prepaid expenses and other assets	(5,829)	(1,356)	1,780
Accounts payable	8,840	1,832	(1,736)
Accrued expenses and other	9,122	1,547	(3,591)
Deferred revenue	(7,786)	(6,201)	(8,562)
Net cash used in operating activities	(165,641)	(68,657)	(115,609)
Cash flows from investing activities:			
Purchases of property and equipment	(8,961)	(4,006)	(8,348)
Increase in restricted cash			(162)
Purchases of marketable securities	(977,775)	(364,305)	(277,129)
Sales and maturities of marketable securities	462,922	237,806	289,013
Payment for asset acquisition	(25,000)		
Net cash (used in) provided by investing activities	(548,814)	(130,505)	3,374
Cash flows from financing activities:			
Proceeds from exercise of stock options and other types of equity	29,420	28,743	6,971
Proceeds from issuance of common stock, net of offering costs		173,572	86,800
Proceeds from issuance of common stock to Genzyme	723,037		
Payments for repurchase of common stock for employee tax withholding	(15,992)	(1,389)	(359)
Net cash provided by financing activities	736,465	200,926	93,412
Net increase (decrease) in cash and cash equivalents	22,010	1,764	(18,823)
Cash and cash equivalents, beginning of period	53,169	51,405	70,228
Cash and cash equivalents, end of period	\$ 75,179	\$ 53,169	\$ 51,405
Supplemental disclosure of cash flows:			
Net cash proceeds from income tax refunds (cash paid for income taxes)	\$ 517	\$ (11)	\$ (17)
Supplemental disclosure of noncash investing and financing activities:			
Fixed asset expenditures included in accounts payable and accrued expenses	\$ 1,526	\$ 161	\$ 1,441
Fair value of common stock issued for asset acquisition	\$ 195,766	\$	\$
Receipt of common stock for exercises of stock options	\$ 1,219	\$	\$
Difference in fair value of common stock issued to Genzyme less cash proceeds received	\$ 51,450	\$	\$

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Repurchase of common stock for employee tax withholding in accrued expenses	\$	\$	600	\$
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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

We commenced operations on June 14, 2002 as a biopharmaceutical company seeking to develop and commercialize novel therapeutics based on RNA interference, or RNAi. We are focused on discovering, developing and commercializing RNAi therapeutics by establishing strategic alliances with leading pharmaceutical and life sciences companies, establishing and maintaining a strong intellectual property position in the RNAi field, generating revenues through licensing agreements, and ultimately developing and commercializing RNAi therapeutics for our own account. We have devoted substantially all of our 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 accompanying consolidated financial statements reflect the operations of Alnylam and our wholly-owned subsidiaries. All intercompany accounts and transactions have been eliminated.

Use of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the United States of America, or 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 us to concentrations of credit risk consist primarily of cash, cash equivalents and fixed income marketable securities. At December 31, 2014 and 2013, substantially all of our cash, cash equivalents and fixed income marketable securities were invested in money market mutual funds, certificates of deposit, commercial paper, corporate notes, municipal debt securities, U.S. government-sponsored enterprise securities and U.S. treasury securities through highly rated financial institutions. Investments are restricted, in accordance with our investment policy, to a concentration limit per issuer.

In recent periods, our 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, or Arrowhead, in 2011, Takeda Pharmaceutical Company Limited, or Takeda, Cubist Pharmaceuticals, Inc., or Cubist, Monsanto Company, or Monsanto, and The Medicines Company, or MDCO. For the year ended December 31, 2014, our billed and unbilled collaboration receivables were composed primarily of amounts due from Genzyme Corporation, a Sanofi company, or Genzyme, and MDCO based upon the achievement of certain milestones and, also with respect to MDCO, expense reimbursement. For the year ended December 31, 2013, our billed and unbilled collaboration receivables were composed primarily of an amount due from Genzyme based upon the initiation of a Phase 3 clinical trial.

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

	Year Ended December 31,		
	2014	2013	2012
Takeda	43%	47%	33%
Monsanto	30%	12%	*
MDCO	21%	*	*
Cubist	*	21%	*
Roche/Arrowhead	*	*	56%

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

	At December 31,	
	2014	2013
Genzyme	63%	94%
MDCO	37%	*

* 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. 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.

Investments in Marketable Securities

We invest our excess cash balances in short-term and long-term marketable debt and equity securities. We classify our investments in marketable debt securities as either held-to-maturity or available-for-sale based on facts and circumstances present at the time we purchased the securities. At each balance sheet date presented, we classified all of our investments in debt and equity securities as available-for-sale. We report available-for-sale investments at fair value at each balance sheet date and include any unrealized holding gains and losses (the adjustment to fair value) in accumulated other comprehensive income (loss), a component of stockholders' equity. At December 31, 2014, the balance in our accumulated other comprehensive income was composed solely of activity related to our available-for-sale marketable securities, including our investment in equity securities of Regulus Therapeutics Inc., or Regulus. Realized gains and losses are determined using the specific identification method and are included in other income. We recognized \$2.1 million of realized gains from sales of our Regulus available-for-sale securities as other income on our consolidated statements of comprehensive loss during the year ended December 31, 2014. If any adjustment to fair value reflects a decline in the value of the investment, we consider all available evidence to evaluate the extent to which the decline is other than temporary, including our intention to sell and, if so, mark the investment to market through a charge to our consolidated statements of comprehensive loss. We did not record any impairment charges related to our fixed income marketable securities during the years ended December 31, 2014, 2013 or 2012. Our marketable securities are classified as cash equivalents if the original maturity, from the date of purchase, is 90 days or less, and as marketable securities if the original maturity, from the date of purchase, is in excess of 90 days. Our cash equivalents are composed of money market funds.

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In the fourth quarter of 2012, we began accounting for our investment in Regulus as an available-for-sale marketable security. Intraproduct tax allocation rules require us to allocate our provision for income taxes between continuing operations and other categories of earnings, such as other comprehensive income. In periods in which we have a year-to-date pre-tax loss from continuing operations and pre-tax income in other categories of earnings, such as other comprehensive income, we must allocate the tax provision to the other categories of earnings. We then record a related tax benefit in continuing operations. Upon sales of our available-for-sale marketable securities, we apply the aggregate portfolio approach. As a result, the disproportionate tax effect remains in accumulated other comprehensive income as long as we maintain an investment portfolio.

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 we have received or services that we have incurred, 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 the estimate for this accrual on at least a quarterly basis. The assessment of these costs is a subjective process that requires judgment. Upon settlement, these costs may differ materially from the amounts accrued in our consolidated financial statements. Our historical accrual estimates have not been materially different from our actual costs.

Revenue Recognition

We have entered into collaboration agreements with leading pharmaceutical and life sciences companies, including Novartis Pharma AG and one of its affiliates, together, Novartis, Roche, Takeda, Kyowa Hakko Kirin Co., Ltd., or Kyowa Hakko Kirin, Cubist, Monsanto, Genzyme and MDCO. The terms of our collaboration agreements typically include non-refundable license fees, funding of research and development, payments based upon achievement of clinical and pre-clinical development milestones, regulatory milestones, manufacturing services, sales milestones and royalties on product sales.

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

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

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has standalone value and the fair value of the undelivered performance obligations, typically including research and/or steering committee services, can be determined. If the fair value of the undelivered performance obligations can be determined, such obligations are accounted for separately as such obligations are fulfilled. If the license is considered to either not have standalone value or have standalone value but the fair value of any of the undelivered performance obligations cannot be determined, the arrangement would then be accounted for as a single unit of accounting and the license payments and payments for performance obligations are recognized as revenue over the estimated period of when the performance obligations are performed and or deferred indefinitely until the undelivered performance obligation can be determined.

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

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

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

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

We perform an assessment to determine whether a substantive milestone exists at the inception of our collaborative arrangements. In evaluating if a milestone is substantive, we consider whether uncertainty exists as to the achievement of the milestone event at the inception of the arrangement, the achievement of the milestone involves substantive effort and can only be achieved based in whole or part on the performance or the occurrence of a specific outcome resulting from our performance, the amount of the milestone payment appears reasonable either in relation to the effort expected to be expended or to the projected enhancement of the value of the

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delivered items, there is any future performance required to earn the milestone, and the consideration is reasonable relative to all deliverables and payment terms in the arrangement. When a substantive milestone is achieved, the accounting rules permit us to recognize revenue related to the milestone payment in its entirety.

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

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

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

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 within the next 12 months are classified as long-term deferred revenue. However, this estimate is based on our current operating plan and, if our operating plan should change in the future, we may recognize a different amount of deferred revenue over the next 12-month period.

The estimate of deferred revenue also reflects management's estimate of the periods of our involvement in certain of our collaborations. Our performance obligations under these collaborations consist of participation on steering committees and the performance of other research and development services. In certain instances, the timing of satisfying these obligations can be difficult to estimate. Accordingly, our estimates may change in the future. Such changes to estimates would result in a change in revenue recognition amounts. If these estimates and judgments change over the course of these agreements, it may affect the timing and amount of revenue that we recognize and record in future periods. At December 31, 2014, we had short-term and long-term deferred revenue of \$23.9 million and \$43.0 million, respectively, related to our collaborations.

Income Taxes

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

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We account for uncertain tax positions using a more-likely-than-not threshold for recognizing and resolving uncertain tax positions. The evaluation of uncertain tax positions is based on factors that include, but are not limited to, changes in tax law, the measurement of tax positions taken or expected to be taken in tax returns, the effective settlement of matters subject to audit, new audit activity and changes in facts or circumstances related to a tax position. Our policy is to accrue interest and penalties related to unrecognized tax positions in income tax expense. As of December 31, 2014, we have not recorded significant interest and penalty expense related to uncertain tax positions.

Research and Development Costs

We expense research and development costs as incurred. Included in research and development costs are wages, benefits and other operating costs, facilities, supplies, external services, clinical trial and manufacturing costs, and overhead directly related to our research and development operations, as well as costs to acquire technology licenses.

We have entered into several license agreements for rights to utilize certain technologies. The terms of the licenses may provide for upfront payments, annual maintenance payments, milestone payments based upon certain specified events being achieved and royalties on product sales. We charge costs to acquire and maintain licensed technology that has not reached technological feasibility and does not have alternative future use to research and development expense as incurred. During the years ended December 31, 2014, 2013 and 2012, we charged to research and development expense costs associated with license fees of \$12.1 million, \$8.0 million and \$5.7 million, respectively.

Accounting for Stock-Based Compensation

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

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

The fair value of restricted stock awards granted to employees is based upon the quoted closing market price per share on the date of grant, adjusted for assumed forfeitures. Expense is recognized over the vesting period, commencing when we determine that it is probable that the awards will vest.

For performance-based stock awards, expense is first recorded when we determine that the achievement of such performance conditions is deemed probable. This determination requires significant judgment by management. At the probable date, we record a cumulative expense catch-up, with remaining expense amortized over the remaining service period.

Comprehensive Loss

Comprehensive loss is comprised of net loss and certain changes in stockholders' equity that are excluded from net loss. We include foreign currency translation adjustments in other comprehensive loss for Alnylam Europe AG, or Alnylam Europe, as the functional currency is not the United States dollar. We include unrealized gains and losses on certain marketable securities in other comprehensive loss.

Table of Contents***Net Loss Per Common Share***

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

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

	At December 31,		
	2014	2013	2012
Options to purchase common stock	8,169	8,713	8,932
Unvested restricted common stock	30	500	604
	8,199	9,213	9,536

Segment Information

We operate in a single reporting segment, the discovery, development and commercialization of RNAi therapeutics.

Subsequent Events

We did not have any material recognized subsequent events. However, we did have the following nonrecognized subsequent events, which are more fully described in Notes 3 and 8:

In January 2015, we sold an aggregate of 5,447,368 shares of our common stock through an underwritten public offering at a price to the public of \$95.00 per share. See Note 8.

In January 2015, in connection with our public offering, we sold an aggregate of 744,566 shares of our common stock to Genzyme through concurrent private placements at the public offering price of \$95.00 per share. See Note 3.

Recent Accounting Pronouncements

In May 2014, the Financial Accounting Standards Board, or FASB, issued a new revenue recognition standard which amends revenue recognition principles and provides a single, comprehensive set of criteria for revenue recognition within and across all industries. The new standard provides a five step framework whereby revenue is recognized when promised goods or services are transferred to a customer at an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. The standard also requires enhanced disclosures pertaining to revenue recognition in both interim and annual periods. For public companies, the standard is effective for interim and annual reporting periods beginning after December 15, 2016. Early adoption is not permitted. The standard allows for adoption using a full retrospective method or a modified retrospective method. We are currently evaluating the method of adoption and the expected impact that the standard could have on our consolidated financial statements and related disclosures.

In June 2014, the FASB issued guidance that share-based payment awards with performance targets that affect vesting and could be achieved after the requisite service period should be accounted for as performance conditions. As a result, performance targets are not reflected in estimating the award's grant date fair value. Stock-based compensation expense is recognized over the requisite service period if the achievement of the

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performance condition is probable. The standard is effective for interim and annual reporting periods beginning after December 15, 2015. Early adoption is permitted. We do not expect the standard will have an impact on our consolidated financial statements and related disclosures since our accounting for share-based payment awards with performance targets is consistent with this guidance.

3. SIGNIFICANT AGREEMENTS

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

	Year Ended December 31,		
	2014	2013	2012
Takeda	\$ 21,973	\$ 21,973	\$ 21,973
Monsanto	14,985	5,640	1,954
MDCO	10,753	4,604	
Roche/Arrowhead	1,000		37,318
Cubist		9,721	2,777
Other	1,850	5,229	2,703
Total net revenues from collaborators	\$ 50,561	\$ 47,167	\$ 66,725

Product Alliances*Genzyme Collaboration*

In January 2014, we entered into a global, strategic collaboration with Genzyme to discover, develop and commercialize RNAi therapeutics as Genetic Medicines to treat orphan diseases. The 2014 Genzyme collaboration superseded and replaced the previous collaboration between us and Genzyme entered into in October 2012 to develop and commercialize RNAi therapeutics targeting transthyretin, or TTR, for the treatment of TTR-mediated amyloidosis, or ATTR, including patisiran and revusiran, in Japan and the Asia-Pacific region.

2012 Genzyme Agreement

Under the 2012 Genzyme agreement, Genzyme paid us an upfront cash payment of \$22.5 million. We were also entitled to receive certain milestone payments under the 2012 Genzyme agreement. In the fourth quarter of 2013, we earned a milestone of \$7.0 million based upon the completion of a successful patisiran Phase 2 clinical trial and a milestone of \$4.0 million based upon the initiation of the Phase 3 clinical trial for patisiran.

Under the 2012 Genzyme agreement, the parties agreed to collaborate in the development and commercialization of licensed products, with Genzyme assuming primary responsibility in the Genzyme territory, which included Japan and the Asia-Pacific region, and us retaining primary responsibility in the rest of the world.

We determined that the deliverables under the 2012 Genzyme agreement included the license, a joint steering committee and any additional TTR-specific RNAi therapeutic compounds that comprised the ALN-TTR program. We also determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the license and undelivered joint steering committee and any additional TTR-specific RNAi therapeutic compounds did not have standalone value due to the specialized nature of the services to be provided by us. In addition, while Genzyme had the ability to grant sublicenses, it could not sublicense all or substantially all of its rights under the 2012 Genzyme agreement. The uniqueness of our services and the limited sublicense right were indicators that standalone value was not present in the arrangement. Therefore the deliverables were not separable and, accordingly, the license and undelivered services were treated as a single unit of accounting. We were unable to reasonably estimate the period of performance under the 2012 Genzyme agreement, as we were unable to estimate the timeline of our deliverables related to the deliverable for any

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additional TTR-specific RNAi therapeutic compounds. Through December 31, 2013, we had deferred all revenue, or \$33.5 million, under the 2012 Genzyme agreement.

2014 Genzyme Collaboration

In January 2014, we entered into the 2014 Genzyme collaboration. As noted above, the 2014 Genzyme collaboration superseded and replaced the 2012 Genzyme agreement.

The 2014 Genzyme collaboration is structured as an exclusive relationship for the worldwide development and commercialization of RNAi therapeutics in the field of Genetic Medicines, which includes our current and future Genetic Medicine programs that reach Human Proof-of-Principle Study Completion (as defined in the Genzyme master agreement), or Human POP, by the end of 2019, subject to extension to the end of 2021 in various circumstances. We will retain product rights in North America and Western Europe, referred to as the Alnylam Territory, while Genzyme will obtain exclusive rights to develop and commercialize collaboration products in the rest of the world, referred to as the Genzyme Territory, together with certain broader co-development/co-promote or worldwide rights for certain products. Genzyme's rights, described in detail below, are structured as an opt-in that is triggered upon achievement of Human POP. We maintain development control for all programs prior to Genzyme's opt-in and maintain development and commercialization control after Genzyme's opt-in for all programs in the Alnylam Territory.

Specifically, in addition to its regional rights for our current and future Genetic Medicine programs in the Genzyme Territory, Genzyme has the right to either (i) co-develop and co-promote ALN-AT3 for the treatment of hemophilia and other rare bleeding disorders in the Alnylam Territory, with us maintaining development and commercialization control, or (ii) obtain a global license to ALN-AS1 for the treatment of hepatic porphyrias. Genzyme may exercise this selection right upon the completion of Human POP for both the ALN-AT3 and ALN-AS1 programs. Finally, Genzyme has the right for a global license to a single, future Genetic Medicine program that was not one of our defined Genetic Medicine programs as of the effective date of the 2014 Genzyme collaboration. We will retain global rights to any RNAi therapeutic Genetic Medicine program that does not reach Human POP by the end of 2019, subject to certain limited exceptions. We retain full rights to all current and future RNAi therapeutic programs outside of the field of Genetic Medicines, including the right to form new collaborations.

Under the 2014 Genzyme collaboration, Genzyme's specific license rights include the following:

Regional license terms Upon opt-in, we will retain product rights in the Alnylam Territory, while Genzyme will obtain exclusive rights to develop and commercialize the product in the Genzyme Territory. Genzyme can elect this license for any of our current and future Genetic Medicine programs that complete Human POP by the end of 2019, subject to limited extension. Development costs for products once Genzyme exercises an option will be shared between Genzyme and us, with Genzyme responsible for twenty percent of the global development costs. Upon the effective date of the 2014 Genzyme collaboration, Genzyme expanded the scope of its regional license and collaboration for patisiran, an investigational RNAi therapeutic currently in a Phase 3 clinical trial, which was originally established under the 2012 Genzyme agreement. Genzyme will be required to make payments totaling up to \$50.0 million upon the achievement of certain patisiran development milestones. In addition, Genzyme will be required to make payments totaling up to \$75.0 million per product other than patisiran, including up to \$55.0 million in development milestones and \$20.0 million in commercial milestones. We could potentially earn the next patisiran milestone payment, ranging between \$5.0 million and \$20.0 million based on the geographic region, upon the achievement of specified events in connection with a regulatory filing or approval. Genzyme will also be required to pay tiered double-digit royalties up to twenty percent for each regional product based on annual net sales, if any, of such regional product by Genzyme, its affiliates and sublicensees.

Co-development/co-promote license terms Upon opt-in, we will retain product rights in the Alnylam Territory, while Genzyme will obtain exclusive rights to develop and commercialize the product in the Genzyme Territory, and will co-promote the product in the Alnylam Territory. Upon the effective date of

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the 2014 Genzyme collaboration, Genzyme expanded its regional rights for revusiran, an investigational RNAi therapeutic currently in a Phase 3 clinical trial, which were originally granted under the 2012 Genzyme agreement, to include a co-development/co-promote license and collaboration. Genzyme also has the right to elect a co-development/co-promote license and collaboration for ALN-AT3, if it does not elect a global license and collaboration for ALN-AS1. Development costs for co-development/co-promote products, once Genzyme exercises an option, will be shared between Genzyme and us, with Genzyme responsible for fifty percent of the global development costs. Genzyme will be required to make payments totaling up to \$75.0 million in development milestones for each of revusiran and ALN-AT3, if selected. In December 2014, we earned a development milestone payment of \$25.0 million based upon the initiation of the first global Phase 3 clinical trial for revusiran. We could potentially earn the next revusiran milestone payment, ranging between \$5.0 million and \$25.0 million based on the geographic region, upon the achievement of specified events in connection with regulatory approval. Genzyme will also be required to pay tiered double-digit royalties up to twenty percent for each co-development/co-promote product based on annual net sales, if any, in the Genzyme Territory for such co-development/co-promote product by Genzyme, its affiliates and sublicensees. The parties will share profits equally and we expect to book product sales in the Alnylam Territory.

Global license terms **Global license terms** Upon opt-in, Genzyme will obtain a worldwide license to develop and commercialize the product. Genzyme can elect a global license for ALN-AS1, if it does not elect a co-development/co-promote license for ALN-AT3. Genzyme will also have one right to a global license through 2019, subject to limited extension, for a future Genetic Medicine program that was not one of our defined Genetic Medicine programs as of the effective date of the 2014 Genzyme collaboration. Genzyme shall be responsible for one hundred percent of global development costs. Genzyme will be required to make payments totaling up to \$200.0 million per global product, including up to \$60.0 million in development milestones and \$140.0 million in commercial milestones. Genzyme will also be required to pay tiered double-digit royalties up to twenty percent for each global product based on annual net sales, if any, of each global product by Genzyme, its affiliates and sublicensees.

Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any additional milestone payments or any royalty payments from Genzyme under the 2014 Genzyme collaboration.

Under the master agreement, the parties will collaborate in the development of option products, with us leading development for all programs prior to Genzyme's opt-in and also leading development and commercialization for all programs in the Alnylam Territory after Genzyme's opt-in. If Genzyme does not exercise its option to license rights to a particular program, we will retain the exclusive right to develop and commercialize such program throughout the world, including the right to sublicense to third parties.

The 2014 Genzyme collaboration is governed by an alliance joint steering committee that is comprised of an equal number of representatives from each party. There will also be additional committees to manage various aspects of each regional, co-developed/co-promoted and global program. We and Genzyme intend to enter into supply agreements to provide for supply of collaboration products to Genzyme for clinical studies, and, at Genzyme's request, commercial sales. Genzyme also has certain rights to manufacture collaboration products. Additionally, Genzyme has certain limited opt-out rights, as specified in the master agreement, upon which products revert fully back to us with no further obligations to Genzyme.

The master agreement (including the license terms appended thereto) contains certain termination provisions, including for material breach by the other party. Unless terminated earlier pursuant to its terms, the master agreement will terminate upon the last to expire of any of the option periods under the master agreement or the license terms appended thereto.

Upon the closing of the equity transaction in February 2014, we sold to Genzyme 8,766,338 shares of our common stock and Genzyme paid \$700.0 million in aggregate cash consideration to us. As a condition to the closing of the equity transaction, Genzyme entered into an investor agreement with us. Under the investor agreement, until the earlier of the fifth anniversary of the expiration or earlier termination of the 2014 Genzyme

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collaboration and the date on which Genzyme and its affiliates cease to beneficially own at least 5% of our outstanding common stock, Genzyme and its affiliates are bound by certain standstill provisions. The standstill provisions include agreements not to acquire more than 30% of our outstanding common stock, call stockholder meetings, nominate directors other than those approved by our board of directors, subject to certain limited exceptions, or propose or support a proposal to acquire us. Further, Genzyme has agreed to vote, and cause its affiliates to vote, all shares of our voting securities they are entitled to vote, up to a maximum of 20% of our outstanding common stock, in a manner either as recommended by our board of directors or proportionally with the votes cast by our other stockholders, except with respect to certain change of control transactions or our liquidation or dissolution. Until Genzyme owns less than 7.5% of our outstanding common stock, subject to Genzyme's limited right to maintain its ownership percentage as described below, if we issue common stock or securities convertible into or exercisable for common stock to a third party that holds at least 30% of our outstanding common stock or, in connection with a collaboration or license transaction, to a third party that will initially hold at least the percentage of our outstanding common stock represented by the shares purchased by Genzyme at the closing of the equity transaction, we will offer Genzyme an opportunity to amend the standstill and voting provisions in the investor agreement to be consistent with the terms provided to such third party.

Under the investor agreement, Genzyme has also agreed not to dispose of any shares of common stock beneficially owned by it immediately after the closing of the stock purchase until the earlier of (i) December 31, 2019 (subject to extension by up to two years if Genzyme's option to select additional compounds under the master agreement is extended beyond December 31, 2019) and (ii) six months after the expiration or earlier valid termination of the collaboration, in each case subject to earlier termination in the event certain clinical activities under the collaboration fail to occur. Following the expiration of this lock-up period, Genzyme will be permitted to sell such shares of common stock subject to certain limitations, including volume and manner of sale restrictions. Notwithstanding the foregoing, following the two-year anniversary of the closing of the stock purchase, in the event that the market price per share of our common stock is at least 100% higher than the market price per share of our common stock at closing of the stock purchase (in each case based upon a ten-day trailing average), Genzyme may sell up to 25% of its initial shares, subject to certain restrictions on post-lock-up period dispositions as described above.

Under the investor agreement, following the lock-up period, Genzyme will have three demand rights to require us to conduct a registered underwritten public offering with respect to the shares of common stock beneficially owned by Genzyme immediately after the closing of the stock purchase. In addition, following the lock-up period, subject to certain conditions, Genzyme will be entitled to participate in registered underwritten public offerings by us if other selling stockholders are included in the registration.

The investor agreement provides that, until Genzyme owns less than 7.5% of our outstanding common stock, subject to Genzyme's limited right to maintain its ownership percentage as described herein, in connection with new issuances of common stock, subject to certain exceptions, Genzyme will be entitled to a right of first offer to participate proportionally to maintain its then-current ownership percentage of our common stock. If Genzyme is not entitled to a right of first offer with respect to a new issuance, Genzyme will have the opportunity, on a post-transaction basis, to purchase additional shares sufficient to maintain its pre-transaction ownership percentage of our common stock (subject to the same 7.5% ownership threshold).

Finally, in the event Genzyme and its affiliates acquire at least 20% or more of our outstanding common stock, Genzyme will be entitled to appoint one individual to our board of directors. Genzyme will also be entitled to certain information rights, including with respect to financial information in the event Genzyme or its affiliates require such information for its own financial reporting purposes. The rights and restrictions under the investor agreement are subject to termination upon the occurrence of certain events.

We recorded the issuance of 8,766,338 shares of our common stock under the stock purchase agreement using the price of our common stock on the date the shares were issued to Genzyme. Based on the common stock price of \$85.72, the fair value of the shares issued was \$751.5 million, which was \$51.5 million in excess of the proceeds received from Genzyme for the issuance of our common stock. This \$51.5 million is being amortized on a straight-line basis over the performance period, which is currently approximately six years as described

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below. In addition, due to intraperiod tax allocation rules, upon closing of the equity transaction we recorded a benefit from income taxes of \$15.2 million due to the Genzyme equity purchase being recorded in additional paid-in capital, net of tax. For the year ended December 31, 2014, we recorded a cumulative benefit from income taxes of \$20.7 million.

In accordance with the investor agreement, as a result of our issuance of shares in connection with our acquisition of Sirna Therapeutics, Inc., or Sirna, in March 2014, Genzyme exercised its right to purchase an additional 344,448 shares of our common stock for approximately \$23.0 million. In addition, in January 2015, in connection with our public offering, Genzyme exercised its right to purchase directly from us, in concurrent private placements, 744,566 shares of common stock at the public offering price resulting in approximately \$70.7 million in proceeds to us. The sales of common stock to Genzyme were not registered as part of the public offering, though they were consummated simultaneously with the public offering.

In addition, as part of these rights under our investor agreement with Genzyme, Genzyme has the right each January to purchase a number of shares of our common stock based on the number of shares we issued during the previous year for compensatory purposes. Genzyme exercised this right to purchase directly from us 196,251 shares of our common stock on January 22, 2015 for approximately \$18.3 million. The sale of these shares to Genzyme was consummated as a private placement. In each instance, the purchase by Genzyme described above allowed Genzyme to maintain its ownership level of our common stock of approximately 12%.

We determined that the deliverables for the programs Genzyme is currently collaborating with us on include the licenses to our patisiran and revusiran clinical programs, which licenses were delivered to Genzyme upon the closing date of the transaction, and the associated development activities, joint steering committee participation and information exchange for these clinical programs. We also determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the license and associated undelivered development activities, joint steering committee participation and information exchange activities did not have standalone value due to the specialized nature of the services to be provided by us. In addition, while Genzyme has the ability to grant sublicenses, it cannot sublicense all or substantially all of its rights under the 2014 Genzyme collaboration. The uniqueness of our services and the limited sublicense rights are indicators that standalone value is not present in the arrangement. Therefore the deliverables are not separable and, accordingly, the license and undelivered services were treated as a single unit of accounting. When multiple deliverables are accounted for as a single unit of accounting, we base our revenue recognition model on the final deliverable. Under the 2014 Genzyme collaboration, the last deliverables for patisiran and revusiran are expected to be completed within approximately six years.

We determined that the total cash received from Genzyme under the now superseded 2012 Genzyme agreement reflects consideration for certain of the performance obligations for ALN-TTR programs included in the 2014 Genzyme collaboration. Therefore we are recognizing the \$33.5 million of deferred revenue under the 2012 Genzyme agreement on a straight-line basis over the period of performance of the ALN-TTR programs, which, as noted above, is currently approximately six years. In addition, during the fourth quarter of 2014, we recognized as revenue a portion of the \$25.0 million milestone payment earned in December 2014 equal to the percentage of the performance period completed when the milestone was earned. As future consideration, including any milestones or reimbursement for development activities, are achieved, we will recognize as revenue a portion of these payments equal to the percentage of the performance period completed when the milestone or activities have been satisfied, multiplied by the amount of the payment. We will recognize the remaining portion of consideration received over the remaining performance period on a straight-line basis. At December 31, 2014, deferred revenue under the 2014 Genzyme collaboration was \$6.7 million.

We determined that the opt-in rights that Genzyme has for future Genetic Medicine programs represent separate and additional deliverables that Genzyme may receive from us in future periods. Upon each opt-in by Genzyme, we have determined that each program and the related activities will represent a single unit of accounting and, consistent with our accounting policies, we will base our revenue recognition period on the final deliverable associated with each future opt-in, if any.

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The Medicines Company Alliance

In February 2013, we and MDCO entered into a license and collaboration agreement pursuant to which we granted to MDCO an exclusive, worldwide license to develop, manufacture and commercialize RNAi therapeutics targeting PCSK9 for the treatment of hypercholesterolemia and other human diseases, including ALN-PCSsc. MDCO paid us an upfront cash payment of \$25.0 million. Upon achievement of certain events, we will be entitled to receive milestone payments, up to an aggregate of \$180.0 million, including up to \$30.0 million in specified development milestones, \$50.0 million in specified regulatory milestones and \$100.0 million in specified commercialization milestones. In addition, we will be entitled to royalties ranging from the low- to high- teens based on annual worldwide net sales, if any, of licensed products by MDCO, its affiliates and sublicensees, subject to reduction under specified circumstances. In December 2014, we earned a development milestone payment of \$10.0 million under the MDCO agreement based upon the initiation of our Phase 1 clinical trial for ALN-PCSsc. In addition, in December 2014, we earned \$4.8 million for reimbursement of costs incurred for certain development activities. We could potentially earn the next development milestone payment of \$20.0 million based upon the initiation of a pivotal study for ALN-PCSsc. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any additional milestone payments or any royalty payments from MDCO.

Under the MDCO agreement, we and MDCO will collaborate in the further development of ALN-PCSsc. We will retain responsibility for the development of ALN-PCSsc until Phase 1 Completion, as defined in the MDCO agreement, at our cost, up to an agreed upon initial development cost cap. MDCO will assume all other responsibility for the development and commercialization of ALN-PCSsc, at its sole cost. The collaboration between us and MDCO is governed by a joint steering committee comprised of an equal number of representatives from each party.

We are solely responsible for obtaining supply of finished product reasonably required for the conduct of our obligations under the initial development plan through Phase 1 Completion, and supplying MDCO with finished product reasonably required for the first Phase 2 clinical trial of ALN-PCSsc conducted by MDCO, at our expense, provided such costs do not exceed the development costs cap, subject to certain exceptions. After such time, MDCO will have the sole right and responsibility to manufacture and supply ALN-PCSsc for development and commercialization under the MDCO development plan, subject to the terms of the MDCO agreement. We and MDCO intend to enter into a supply and technical transfer agreement to provide for supply of ALN-PCSsc to MDCO within a specified time following the effective date of the MDCO agreement.

Unless terminated earlier in accordance with the terms of the agreement, the MDCO Agreement expires on a licensed product-by-licensed product and country-by-country basis upon expiration of the last royalty term for any licensed product in any country, where a royalty term is defined as the latest to occur of (1) the expiration of the last valid claim of patent rights covering a licensed product, (2) the expiration of the Regulatory Exclusivity, as defined in the MDCO Agreement, and (3) the twelfth anniversary of the first commercial sale of the licensed product in such country. We estimate that our fundamental RNAi patents covering licensed products under the MDCO Agreement will expire both in and outside of the United States generally between 2015 and 2028. We also estimate that our ALN-PCS product-specific patents covering licensed products under the MDCO Agreement in the United States and elsewhere will expire at the end of 2033. These patent rights are subject to potential patent term extensions and/or supplemental protection certificates extending such terms in countries where such extensions may become available. In addition, more patent filings relating to the collaboration may be made in the future.

Either party may terminate the MDCO Agreement in the event the other party fails to cure a material breach or upon patent-related challenges by the other party. In addition, MDCO has the right to terminate the agreement without cause at any time upon four months' prior written notice.

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

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We have determined that the significant deliverables under the MDCO agreement include the license, the joint steering committee, technology transfer obligations, development activities through Phase 1 Completion and supply of product for a Phase 2 clinical trial. We also determined that, pursuant to the accounting guidance governing revenue recognition on multiple element arrangements, the license and collective undelivered activities and services do not have standalone value due to the specialized nature of the activities and services to be provided by us. In addition, while MDCO has the ability to grant sublicenses, it must receive our prior written consent to sublicense all or substantially all of its rights. The uniqueness of our services and the limited sublicense right are indicators that standalone value is not present in the arrangement. Therefore the deliverables are not separable and, accordingly, the license and undelivered services are being treated as a single unit of accounting. When multiple deliverables are accounted for as a single unit of accounting, we base our revenue recognition pattern on the final deliverable. Under the MDCO agreement, all deliverables are expected to be completed within five years. We are recognizing revenue under the MDCO agreement on a straight-line basis over five years. We are not utilizing a proportional performance model since we are unable to reasonably estimate the level of effort to fulfill these obligations, primarily because the effort required under the development activities is largely unknown.

We received the upfront payment of \$25.0 million from MDCO in February 2013, which was initially recorded as deferred revenue. During the fourth quarter of 2014, we recognized as revenue a portion of the \$10.0 million milestone payment earned in December 2014 equal to the percentage of the performance period completed when the milestone was earned. During the fourth quarter of 2014, we also recognized as revenue a portion of the \$4.8 million expense reimbursement due to us under the terms of the MDCO agreement equal to the percentage of the performance period completed upon invoice date. As future consideration, including any milestones or reimbursement for development activities, are earned, we will recognize as revenue a portion of these payments equal to the percentage of the performance period completed when the milestone or service has been satisfied, multiplied by the amount of the payment. We will recognize the remaining portion of consideration received over the remaining performance period on a straight-line basis. At December 31, 2014, deferred revenue under the MDCO agreement was \$24.7 million.

Platform Alliances

Monsanto Alliance

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

Monsanto paid us \$29.2 million in upfront cash payments, and was also required to make near-term milestone payments to us upon the achievement of specified technology transfer and patent-related milestones. We were also entitled to receive additional funding for collaborative research efforts. In the aggregate, we had the ability to earn up to \$5.0 million in milestone payments and research funding under the Monsanto alliance. We received a total of \$4.0 million in milestone payments from Monsanto based upon the achievement of a specified patent-related event and the completion of technology transfer activities. In September 2014, we and Monsanto mutually determined not to pursue the discovery collaboration originally contemplated under the terms of the Monsanto agreement. Accordingly, Monsanto will not be required to pay us the final milestone of \$1.0 million. There are no remaining milestones under the Monsanto agreement. Monsanto is required to pay to us a percentage of specified fees from certain sublicense agreements Monsanto may enter into that include access to our intellectual property, as well as low single-digit royalty payments on worldwide, net sales by Monsanto, its affiliates and sublicensees of certain licensed products, as defined in the Monsanto agreement, if any. Due to the uncertainty of the application of RNAi technology in the field of agriculture, we may not receive any license fees or royalty payments from Monsanto.

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

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

Under the Monsanto agreement, the last deliverable expected to be completed was the discovery collaboration, which was originally to be completed within five years. Therefore, prior to the September 2014 amendment, we were recognizing revenue under the Monsanto agreement on a straight-line basis over five years. However, as a result of the September 2014 amendment, we have determined that the final deliverable in the collaboration is the technology transfer activities, know-how exchange and access to intellectual property controlled by us as of the date of the Monsanto agreement or during the 30 months thereafter, in the field of agriculture. Consequently, we are now recognizing the remaining deferred revenue of \$16.8 million at the date of the amendment on a prospective basis from September 2014 through February 2015, the date which is the end of the 30 month obligation, which excludes \$5.0 million related to a potential refund due to Monsanto under certain circumstances pursuant to the original terms of the Monsanto agreement. We will continue to recognize this revenue on a straight-line basis over the remaining obligation period. We cannot use a proportional performance model since we are unable to reasonably estimate the level of effort to fulfill these obligations, primarily because the potential effort required is unknown. At December 31, 2014, deferred revenue under the Monsanto agreement was \$10.6 million, of which \$5.6 million will be recognized through February 2015 and \$5.0 million will be recognized when the potential refund obligation ceases and can be considered fixed or determinable.

Takeda Alliance

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.

Takeda paid us an upfront payment of \$100.0 million and an additional \$50.0 million upon achievement of specified technology transfer milestones. In addition, for each RNAi therapeutic product developed by Takeda, its affiliates and sublicensees, we are entitled to receive specified development, regulatory and commercialization milestone payments, totaling up to \$171.0 million per product, together with a double-digit percentage royalty payment based on worldwide annual net sales, if any. The potential future milestone payments per product include up to \$26.0 million for the achievement of specified development milestones, up to \$40.0 million for the achievement of specified regulatory milestones and up to \$105.0 million for the achievement of specified commercialization milestones. We could potentially earn the next milestone payment of \$2.0 million based upon the achievement of a specified pre-clinical event by Takeda for an RNAi therapeutic product. Due to the

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uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any additional milestone payments or any royalty payments from Takeda.

Pursuant to the Takeda agreement, we and Takeda also agreed to collaborate on the research of RNAi therapeutics directed to one or two disease targets agreed to by the parties, subject to our existing contractual obligations with third parties. The collaboration is governed by a 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.

We have determined that the deliverables under the Takeda agreement include the license, the joint committees, the technology transfer activities and the services that we were obligated to perform under the research collaboration. We also 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. When multiple deliverables are accounted for as a single unit of accounting, we base our revenue recognition pattern on the final deliverable. Under the Takeda agreement, the last elements to be delivered are the joint technology transfer committee and joint delivery collaboration committee services, each of which has a life of no more than seven years.

We are recognizing the upfront payment of \$100.0 million and the technology transfer milestones of \$50.0 million, the receipt of which we believed was probable at the commencement of the collaboration, on a straight-line basis over seven years because we are unable to reasonably estimate the level of effort to fulfill these obligations, primarily because the effort required under the research collaboration is largely unknown, and therefore, cannot utilize a proportional performance model. As future milestones are achieved, if any, we will recognize as revenue a portion of the milestone payment equal to the percentage of the performance period completed when the milestone is achieved, multiplied by the amount of the milestone payment. At December 31, 2014, deferred revenue under the Takeda agreement was \$8.9 million. This remaining deferred revenue will be recognized in full through May 30, 2015.

Other Strategic License Agreements

Isis Collaboration and License Agreement

In January 2015, we and Isis entered into a second amended and restated strategic collaboration and license agreement. The 2015 Isis agreement provides for certain new exclusive target cross-licenses of intellectual property on four disease targets, providing each company with exclusive RNA therapeutic license rights for two programs, and extends the parties' existing non-exclusive technology cross-license, which was originally entered into in 2004 and was amended and restated in 2009, through April 2019.

Pursuant to the 2015 Isis agreement, Isis granted to us an exclusive, low single-digit royalty-bearing license to its chemistry, motif, mechanism and target-specific intellectual property for oligonucleotide therapeutics against two targets: antithrombin and aminolevulinic acid synthase-1. In exchange, we granted to Isis an exclusive, low single-digit royalty-bearing license to our chemistry, motif, mechanism and target-specific intellectual property for oligonucleotide therapeutics against two targets: Factor XI and apolipoprotein (a).

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In addition, under the 2015 Isis agreement, the parties agreed to extend the existing non-exclusive technology cross-license through April 2019. Specifically, Isis granted us a low single-digit royalty-bearing, non-exclusive license to new platform technology arising from May 2014 through April 2019 for double-stranded RNAi therapeutics. In turn, we granted Isis a low single-digit royalty-bearing, non-exclusive license to new platform technology arising from May 2014 through April 2019 for single-stranded antisense therapeutics. This broad, non-exclusive cross-license includes chemistry, motif and mechanism patents, but excludes patent claims on formulations, manufacturing and specific targets.

Under the original 2004 agreement, Isis licensed to us its patent estate related to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi products in exchange for a previously disclosed technology access fee, participation in fees for our partnering programs and future milestone and royalty payments from us for programs that incorporate Isis' intellectual property. We have the right to use Isis' intellectual property 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 double-stranded RNA products designed to work through an RNAi mechanism, except in the context of a collaboration in which Isis plays an active role.

In turn, under the original 2004 agreement, we non-exclusively licensed to Isis our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded antisense therapeutics, single stranded RNAi therapeutics and to research double-stranded RNAi compounds. Isis also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on a non-exclusive basis. We granted these licenses for RNAi therapeutics in exchange for option fees, and future milestone and royalty payments from Isis for RNAi programs that incorporate certain of our intellectual property.

In August 2012, we and Isis amended the agreement to provide certain terms for the discovery, development and commercialization of double-stranded RNA products by us or our sublicensees in the field of agriculture.

As set forth in the 2015 Isis agreement, under the original 2004 agreement, we paid Isis an upfront license fee of \$5.0 million and we agreed to pay Isis milestone payments, totaling up to approximately \$3.4 million, upon the occurrence of specified development and regulatory events, and low single-digit royalties on sales, if any, for each product that we or a collaborator develop 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 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. Isis agreed to pay us, per therapeutic target, a license fee of \$0.5 million, milestone payments for double-stranded RNAi products totaling approximately \$3.4 million, payable upon the occurrence of specified development and regulatory events, and low single-digit royalties on sales, if any, for each double-stranded RNAi or single-stranded RNAi product developed by Isis or a collaborator that utilizes our intellectual property. 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 Isis.

The term of 2015 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. Either party may terminate the 2015 Isis agreement on 90 days' prior written notice if the other party materially breaches the agreement and fails to cure the breach within the 90-day notice period and no substantial steps have otherwise been taken to cure the breach, provided, however, that neither party may terminate licenses granted to the other party to the extent necessary to develop or sell products that have at least reached investigational new drug-enabling studies (except for a party's uncured failure of its payment obligations). Either party may also terminate the agreement in the event the other party undergoes specified bankruptcy events.

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During the years ended December 31, 2014, 2013 and 2012, as result of certain payments received by us in connection with the Genzyme, MDCO and Monsanto alliances, we paid \$7.7 million, \$0.7 million and \$2.5 million to Isis, respectively. In addition, as of December 31, 2014, we owed Isis \$1.8 million for amounts incurred but not yet paid. These license fees were charged to research and development expense.

Asset acquisition

In-process research and development

In March 2014, we purchased from Merck Sharp & Dohme Corp., or Merck, all of Merck's right, title and interest in and to all of the outstanding shares of common stock of Sirna. Sirna possesses intellectual property and RNAi assets including early-stage pre-clinical therapeutic candidates, chemistry, and siRNA-conjugate and other delivery technologies that we intend to integrate into our platform for delivery of RNAi therapeutics.

At the closing of the transaction, we paid Merck \$25.0 million in cash and issued 2,142,037 shares of our common stock. We recorded this issuance using the price of our common stock on March 5, 2014, the date that these shares were issued to Merck. Based on the common stock price of \$81.36, the fair value of the shares issued was \$174.3 million. As a result of the cash payment and issuance of shares to Merck, we recorded a total of \$199.3 million to in-process research and development expense. We issued an additional 378,007 shares of common stock to Merck on May 19, 2014 upon the completion of certain technology transfer activities during the second quarter of 2014. In the first quarter of 2014, we recorded a liability of \$25.4 million associated with the then future obligation to issue these shares, based on the then current price of our common stock, which was also charged to in-process research and development expense. Upon completion of these technology transfer activities in the second quarter of 2014, we re-measured the expense recorded in connection with these shares using the then current price of our common stock, resulting in a credit of \$3.9 million. We recorded an expense of \$220.8 million to in-process research and development for the year ended December 31, 2014 as a result of this asset acquisition. In future periods, there will be no additional charges recorded to in-process research and development related to the purchase of the Sirna RNAi assets from Merck.

We accounted for this transaction as an acquisition of in-process research and development assets and recorded the entire amount to in-process research and development expense as we did not acquire any employees, manufacturing or other facilities, developed processes or clinical-stage assets as part of our acquisition of Sirna.

Pursuant to the Sirna agreement, Merck is also eligible to receive the following consideration from us: (i) up to an aggregate of \$10.0 million upon the achievement by us or our related parties of specified regulatory milestones for RNAi products covered by Sirna intellectual property, and (ii) up to an aggregate of \$105.0 million upon the achievement by us or our related parties of specified development and regulatory (\$40.0 million) and commercial (\$65.0 million) milestones associated with the clinical development progress of certain pre-clinical candidates discovered by Sirna, together with low single-digit royalties for our products and single-digit royalties for Sirna products, in each case based on annual worldwide net sales, if any, by us and our related parties of any such products. These amounts will be recorded as research and development expenses as incurred based on our accounting for this transaction as an asset acquisition.

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

Table of Contents**4. FAIR VALUE MEASUREMENTS**

The following tables present information about our assets that are measured at fair value on a recurring basis at December 31, 2014 and 2013, and indicate the fair value hierarchy of the valuation techniques we utilized to determine such fair value, in thousands:

Description	At December 31, 2014	Quoted Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents	\$ 56,203	\$ 56,203	\$	\$
Marketable securities (fixed income):				
Certificates of deposit	24,300		24,300	
Commercial paper	40,796		40,796	
Corporate notes	662,545		662,545	
Municipal debt securities	9,005		9,005	
U.S. government-sponsored enterprise securities	64,856		64,856	
U.S. treasury securities	5,248		5,248	
Marketable securities (Regulus equity holdings)	94,583	94,583		
Total	\$ 957,536	\$ 150,786	\$ 806,750	\$

Description	At December 31, 2013	Quoted Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents	\$ 32,571	\$ 32,571	\$	\$
Marketable securities (fixed income):				
Corporate notes	228,462		228,462	
U.S. government-sponsored enterprise securities	56,863		56,863	
Commercial paper	11,978		11,978	
Marketable securities (Regulus equity holdings)	45,452	45,452		
Total	\$ 375,326	\$ 78,023	\$ 297,303	\$

For the year ended December 31, 2014, there were no transfers between Level 1 and Level 2 financial assets. For the year ended December 31, 2013, we transferred \$45.5 million of marketable securities (equity holdings in Regulus) from Level 2 to Level 1 due to the increased volume in average daily trading on the NASDAQ stock market for these instruments. The carrying amounts reflected in our 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.

Table of Contents**5. MARKETABLE SECURITIES**

The following tables summarize the fair value, accumulated other comprehensive income and intraperiod tax allocation regarding our investment in Regulus available-for-sale marketable securities at December 31, 2014 and 2013, and for the activity recorded in the year, in thousands:

Description	At December 31, 2013	Sales of Regulus Shares During Year Ended December 31, 2014	All Other Activity During Year Ended December 31, 2014	Balance at December 31, 2014
Carrying value	\$ 12,449	\$ (514)	\$	\$ 11,935
Accumulated other comprehensive income, before tax	33,003	(2,081)	51,726	82,648
Investment in equity securities of Regulus Therapeutics Inc., as reported	\$ 45,452	\$ (2,595)	\$ 51,726	\$ 94,583
Accumulated other comprehensive income, before tax	\$ 33,003	\$ (2,081)	\$ 51,726	\$ 82,648
Intraperiod tax allocation recorded as a benefit from income taxes	(13,267)		(19,525)	(32,792)
Accumulated other comprehensive income, net of tax	\$ 19,736	\$ (2,081)	\$ 32,201	\$ 49,856

Description	At December 31, 2012	Sales of Regulus Shares During Year Ended December 31, 2013	All Other Activity During Year Ended December 31, 2013	Balance at December 31, 2013
Carrying value	\$ 12,449	\$	\$	\$ 12,449
Accumulated other comprehensive income, before tax	26,299		6,704	33,003
Investment in equity securities of Regulus Therapeutics Inc., as reported	\$ 38,748	\$	\$ 6,704	\$ 45,452
Accumulated other comprehensive income, before tax	\$ 26,299	\$	\$ 6,704	\$ 33,003
Intraperiod tax allocation recorded as a benefit from income taxes	(10,572)		(2,695)	(13,267)
Accumulated other comprehensive income, net of tax	\$ 15,727	\$	\$ 4,009	\$ 19,736

We obtain fair value measurement data for our marketable securities from independent pricing services. We perform 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, we perform our own review of prices received from the independent pricing services by comparing these prices to other sources and confirming those securities are trading in active markets.

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The following tables summarize our marketable securities, other than our holdings in Regulus noted above, at December 31, 2014 and 2013, in thousands:

		December 31, 2014		
	Amortized	Gross	Gross	Fair
	Cost	Unrealized	Unrealized	Value
		Gains	Losses	
Certificates of deposit (Due within 1 year)	\$ 24,300	\$	\$	\$ 24,300
Commercial paper (Due within 1 year)	40,785	11		40,796
Corporate notes (Due within 1 year)	449,044	14	(293)	448,765
Corporate notes (Due after 1 year through 2 years)	214,510		(730)	213,780
Municipal debt securities (Due after 1 year through 2 years)	9,002	3		9,005
U.S. government-sponsored enterprise securities (Due within 1 year)	13,069		(1)	13,068
U.S. government-sponsored enterprise securities (Due after 1 year through 2 years)	51,879		(91)	51,788
U.S. treasury securities (Due after 1 year through 2 years)	5,254		(6)	5,248
Total	\$ 807,843	\$ 28	\$ (1,121)	\$ 806,750

		December 31, 2013		
	Amortized	Gross	Gross	Fair
	Cost	Unrealized	Unrealized	Value
		Gains	Losses	
Commercial paper (Due within 1 year)	\$ 11,983	\$	\$ (5)	\$ 11,978
Corporate notes (Due within 1 year)	154,175	33	(46)	154,162
Corporate notes (Due after 1 year through 2 years)	74,312	23	(35)	74,300
U.S. government-sponsored enterprise securities (Due within 1 year)	26,553	8		26,561
U.S. government-sponsored enterprise securities (Due after 1 year through 2 years)	30,300	2		30,302
Total	\$ 297,323	\$ 66	\$ (86)	\$ 297,303

6. PROPERTY AND EQUIPMENT, NET

Property and equipment consist of the following at December 31, 2014 and 2013, in thousands:

		December 31,	
	Useful Life	2014	2013
Laboratory equipment	5 years	\$ 28,559	\$ 22,729
Computer equipment and software	3 years	4,440	4,261
Furniture and fixtures	5 years	1,999	1,793
Leasehold improvements	*	30,853	28,953
Construction in progress		1,982	28
		67,833	57,764
Less: accumulated depreciation		(46,093)	(41,316)
		\$ 21,740	\$ 16,448

* Shorter of asset life or lease term

During the years ended December 31, 2014, 2013 and 2012, we recorded \$5.0 million, \$6.1 million and \$4.6 million, respectively, of depreciation expense related to our property and equipment.

Table of Contents**7. COMMITMENTS AND CONTINGENCIES*****Purchase Commitments***

We have future purchase commitments totaling \$104.5 million at December 31, 2014, of which \$59.3 million is expected to be incurred in 2015 and \$45.2 million is expected to be incurred past 2015. These commitments are related to purchase orders, clinical and pre-clinical agreements, and other purchase commitments for goods or services that we are likely to continue, regardless of the fact that they were cancelable at December 31, 2014.

Technology License Commitments

We have licensed from third parties the rights to use certain technologies in our research processes as well as in any products we may develop including these licensed technologies. In accordance with the related license agreements, we are required to make certain fixed payments to the licensor or a designee of the licensor over various agreement terms. Many of these agreement terms are consistent with the remaining lives of the underlying intellectual property that we have licensed. At December 31, 2014, we were committed to make the following fixed, estimated and cancelable payments under existing license agreements, in thousands:

Year Ending December 31,	
2015	\$ 7,379
2016	724
2017	744
2018	754
2019	762
Thereafter	8,592
Total	\$ 18,955

Operating Leases

We lease office and laboratory space located at 300 Third Street, Cambridge, Massachusetts, for our corporate headquarters and primary research facility under a non-cancelable real property lease agreement, or the Third Street Lease, with ARE-MA Region No. 28 LLC, or the Landlord. Under the Third Street Lease, we lease a total of approximately 129,000 square feet of office and laboratory space. The term of the Third Street Lease was set to expire in September 2016. In March 2014, we and the Landlord amended the Third Street Lease to extend the term for an additional five years, through September 30, 2021. Under the amended Third Street Lease, we have the option to extend the term for one additional five-year period. As a result of the extension of the term of the Third Street Lease, our operating lease obligations through 2021 increased by \$37.8 million.

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

We received \$1.9 million, \$0.2 million and \$1.8 million in leasehold improvement incentives from BMR during the years ended December 31, 2014, 2013 and 2012, respectively. These leasehold improvement incentives are being accounted for as a reduction in rent expense ratably over the BMR Lease term. The balance from these leasehold improvement incentives is included in current portion of deferred rent and deferred rent, net of current portion, in the consolidated balance sheets at December 31, 2014 and 2013.

Total rent expense, including operating expenses, under our real property leases was \$8.9 million, \$4.9 million and \$6.4 million for the years ended December 31, 2014, 2013 and 2012, respectively.

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

Year Ending December 31,	
2015	\$ 6,810
2016	6,994
2017	7,535
2018	7,387
2019	7,608
Thereafter	13,845
Total	\$ 50,179

Litigation*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 Gesellschaft Zur Foerderung Der Wissenschaften e.V. and Max Planck Innovation GmbH, together, Max Planck, the Whitehead Institute for Biomedical Research, or Whitehead, the Massachusetts Institute of Technology, or MIT, and the University of Massachusetts, or UMass, claiming a professor at Utah is the sole inventor or, in the alternative, a joint inventor, of the Tuschl patents. 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. In June 2012, the Court denied both motions to dismiss. We, Max Planck, Whitehead, MIT and UMass filed an appeal of the Court's ruling on the motion to dismiss for lack of jurisdiction and a motion requesting that the Court stay the case pending the outcome of the appeal. In July 2012, the Court stayed discovery in the case pending the outcome of the defendants' appeal. In August 2013, the United States Court of Appeals for the Federal Circuit, or CAFC, affirmed the lower Court's ruling, in a split decision. In September 2013, we filed a petition with the CAFC for rehearing or rehearing en banc. In November 2013, the CAFC denied our petition for rehearing or rehearing en banc and remanded the case back to the lower Court. In February 2014, we filed a petition for writ of certiorari from the Supreme Court and a motion to stay the lower Court proceedings pending a decision from the Supreme Court on our petition. The lower Court granted our motion to stay the proceedings, however, in June 2014 the Supreme Court denied our petition for certiorari and remanded the case back to the United States District Court for the District of Massachusetts for trial, which is now scheduled to begin on November 2, 2015.

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. We have not recorded an estimate of the possible loss associated with this legal proceeding due to the uncertainties related to both the likelihood and the amount of any possible loss or range of loss.

Our accounting policy for accrual of legal costs is to recognize such expenses as incurred.

Tekmira Settlement Agreement

On November 12, 2012, we, Tekmira Pharmaceuticals Corporation, or TPC, Protiva Biotherapeutics, Inc., a wholly owned subsidiary of TPC, or Protiva, and together with TPC, Tekmira, and Acuitas Therapeutics Inc. (formerly AICana Technologies, Inc.), or Acuitas, entered into a settlement agreement and general release resolving all ongoing litigation, as well as a patent interference proceeding between us and Protiva. The terms of the settlement agreement include mutual releases and dismissal with prejudice of all claims and counterclaims between the parties. In addition, as part of the settlement agreement, the parties agreed to a covenant not to sue one another in the future on matters released under the settlement agreement, as well as substantial liquidated

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damages to be paid by any party that breaches such covenant. The parties also agreed to resolve any future disputes that may arise over the three years following the settlement through binding arbitration.

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

Contemporaneously with the execution of the settlement agreement, we and Tekmira restructured our contractual relationship and entered into a cross-license agreement that superseded the prior license and manufacturing agreements among us, TPC and Protiva. In connection with this restructuring, we incurred a \$65.0 million charge to operating expenses for the year ended December 31, 2012. Specifically, we made a one-time payment of \$30.0 million to Tekmira for the termination of, and our release from, all of our obligations under the manufacturing agreement with TPC, including without limitation the obligations to obtain materials and/or services from TPC. Further, we elected to buy-down certain future potential milestone and royalty payments due to Tekmira for certain of our RNAi therapeutics, formulated using lipid nanoparticle, or LNP, technology. Specifically, pursuant to the cross-license agreement, we made a one-time payment of \$35.0 million to Tekmira, which amount constituted payment for the termination of the 2008 license agreements with TPC and Protiva and the parties' rights and obligations thereunder, as well as the buy-down of certain milestone payments and the significant reduction of royalty rates for ALN-VSP, ALN-PCS02 and patisiran. In addition, under the 2012 cross-license agreement, we were obligated to pay TPC an aggregate of \$10.0 million in contingent milestone payments related to advancement of ALN-VSP and patisiran, which now represent the only potential milestones due to Tekmira for ALN-VSP, ALN-PCS02 and patisiran LNP-based RNAi therapeutics. In the fourth quarter of 2013, we paid TPC \$5.0 million in connection with the initiation of the patisiran Phase 3 clinical trial. With respect to the second \$5.0 million milestone, in August 2013, we initiated binding arbitration proceedings to resolve a disagreement with TPC regarding the achievement by TPC of this milestone under the parties cross-license agreement relating to the manufacture of ALN-VSP clinical trial material for use in China. We currently expect that the Tekmira arbitration hearing will be held in the second quarter of 2015. Our policy is to expense these potential milestones when incurred and record them as research and development expense. A description of our cross-license agreement with Tekmira is included in Part I, Item 1, "Delivery-Related Licenses and Collaborations - Tekmira," of this annual report on Form 10-K.

Indemnifications

Licensors indemnification In connection with our license agreements with Max Planck relating to the Tuschl I and Tuschl 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 the Max Planck indemnification agreement, we are responsible for paying the costs of any litigation relating to the license agreements or the underlying intellectual property rights, including the costs associated with certain litigation regarding the Tuschl patents, which was settled during 2011, as well as certain costs associated with defending the University of Utah litigation described above. In connection with our research agreement with Acuitas, we agreed to indemnify Acuitas for certain legal costs, subject to certain exceptions and limitations, associated with the Tekmira litigation described above. These indemnification costs were charged to general and administrative expense. We are also 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. Such indemnification obligations are usually in effect from the date of execution of the applicable agreement for a period equal to the applicable statute of limitations.

Our maximum potential future liability under any such indemnification provisions is uncertain. However, to date, other than certain costs associated with certain previously settled litigation related to the Tuschl patents and the Tekmira litigation described above, and certain ongoing defense costs related to the University of Utah litigation also described above, we have not incurred material costs to defend lawsuits or settle claims related to these indemnification provisions. We have determined that the estimated aggregate fair value of our potential liabilities under all such indemnification provisions is minimal and have not recorded any liability related to such indemnification provisions at December 31, 2014 or 2013.

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8. STOCKHOLDERS EQUITY

Preferred Stock

We have authorized up to 5,000,000 shares of preferred stock, \$0.01 par value per share, for issuance. The preferred stock will have such rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, as shall be determined by our Board of Directors upon its issuance. At December 31, 2014 and 2013, there were no shares of preferred stock outstanding.

Stockholder Rights Agreement

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

Public Offerings

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

In January 2013, we sold an aggregate of 9,200,000 shares of our common stock through an underwritten public offering at a price to the public of \$20.13 per share. As a result of this offering, we received aggregate net proceeds of approximately \$173.6 million, after deducting underwriting discounts and commissions and other estimated offering expenses of approximately \$11.6 million.

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In January 2015, we sold an aggregate of 5,447,368 shares of our common stock through an underwritten public offering at a price to the public of \$95.00 per share. As a result of the offering, which included the full exercise of the underwriters' option to purchase additional shares, we received aggregate net proceeds of approximately \$496.4 million, after deducting underwriting discounts and commissions and other estimated offering expenses of approximately \$21.1 million.

9. STOCK INCENTIVE PLANS

Stock Plans

In June 2009, our stockholders approved an amendment and restatement of our 2004 Stock Incentive Plan, or the Amended and Restated 2004 Plan, which replaced our 2004 Stock Incentive Plan, as amended, or the 2004 Plan. At December 31, 2014, the Amended and Restated 2004 Plan provided for the granting of stock options to purchase up to 12,366,485 shares of common stock. Prior to the adoption of the Amended and Restated 2004 Plan, we were authorized to grant both stock options and restricted stock awards under the 2004 Plan. As of the effective date of the Amended and Restated 2004 Plan, we may only grant stock options under the Amended and Restated 2004 Plan, provided that the terms and conditions of any restricted stock awards outstanding under the 2004 Plan will continue to be governed by the Amended and Restated 2004 Plan.

In June 2009, our stockholders also approved our 2009 Stock Incentive Plan, or the 2009 Plan. The 2009 Plan provides for the granting of stock options, restricted stock awards and units, stock appreciation rights and other stock-based awards. In June 2013, our stockholders approved an amendment to the 2009 Plan, which increased the number of shares of common stock authorized for issuance from 2,200,000 to 5,900,000. The 2009 Plan has a fungible share pool. Any award that is not a full value award is counted against the authorized share limits specified in the 2009 Plan as one share for each share of common stock subject to the award, and all full value awards, defined in the 2009 Plan as restricted stock awards or other stock-based awards, are counted as one and a half shares for each one share of common stock subject to such full value award. In addition, the 2009 Plan includes a non-employee director stock option program under which each eligible non-employee director is entitled to (1) a grant of an option to purchase 30,000 shares of common stock upon his or her initial appointment to the Board of Directors, or such other amount as the Board of Directors deems appropriate, and (2) a subsequent annual grant of an option to purchase 15,000 shares of common stock based on continued service, provided the non-employee director has served as a director for at least six months and is serving as a director immediately prior to and following such annual grant. Stock options granted by us to non-employee directors upon their appointment to the Board of Directors vest as to one-third of such shares on each of the first, second and third anniversaries of the date of grant, and those granted annually thereafter vest in full on the first anniversary of the date of grant. During 2014, the Compensation Committee of our Board of Directors approved an amendment to the 2009 Plan to provide that upon retirement or resignation, non-employee Directors would have three months to exercise any outstanding stock option awards, unless such non-employee Director has five or more years of service, in which case such non-employee Director will have the lesser of five years or the remainder of the stock option term post-retirement or resignation to exercise such awards.

At December 31, 2014, an aggregate of 9,317,147 shares of common stock were reserved for issuance under our stock plans, including outstanding stock options to purchase 8,168,533 shares of common stock, 941,583 of common stock available for additional equity awards and 207,031 shares available for future grant under our 2004 Employee Stock Purchase Plan, or the 2004 ESPP, excluding 612,085 shares of common stock granted in December 2014 that are subject to and contingent upon receiving stockholder approval of an amendment and restatement of our 2009 Plan in connection with our 2015 annual stockholder meeting. Each option shall expire within ten years of issuance. Stock options granted by us to employees generally vest as to 25% of the shares on the first anniversary of the grant date and 6.25% of the shares at the end of each successive three-month period until fully vested. Performance-based stock options granted to employees vest as to one-third of the shares upon the achievement of each of three specific clinical development and regulatory events, as approved by our compensation committee.

Table of Contents**Stock-Based Compensation**

The following table summarizes stock-based compensation expense by type of award during the three years ended December 31, 2014, in thousands:

	2014	2013	2012
Stock-based compensation expense by type of award:			
Stock options	\$ 24,603	\$ 13,839	\$ 8,739
Performance-based stock options	4,960		
Restricted stock awards	1,068	3,420	2,436
ESPP share issuances	392	261	241
Non-employee stock options	2,038	3,183	944
	\$ 33,061	\$ 20,703	\$ 12,360

The following table summarizes our unrecognized stock-based compensation expense, net of estimated forfeitures, at December 31, 2014 by type of awards, excluding performance-based stock options, and the weighted-average period over which that expense is expected to be recognized:

	At December 31, 2014	
	Unrecognized Expense, Net of Estimated Forfeitures (in thousands)	Weighted-average Recognition Period (in years)
Type of award:		
Stock options	\$ 59,854	2.62
Restricted stock awards	1,571	3.46
ESPP share issuances	197	0.33

Valuation Assumptions for Stock Options

The fair value of stock options, at date of grant, based on the following assumptions, was estimated using the Black-Scholes option-pricing model. Our expected stock-price volatility assumption is based on the historical volatility of our publicly traded stock. The expected life assumption is based on our historical data. The dividend yield assumption is based on the fact that we have never paid cash dividends and have no present intention to pay cash dividends. The risk-free interest rate used for each grant is equal to the zero coupon rate for instruments with a similar expected life.

	2014	2013	2012
Risk-free interest rate	1.7-2.3%	1.0-2.0%	0.8-1.0%
Expected dividend yield			
Expected option life	5.5-7.5 years	5.6 years	5.6-5.9 years
Expected volatility	53-57%	55-56%	57%

Table of Contents**Stock Option Activity**

The following table summarizes the activity of our stock option plans, excluding stock options granted in December 2014, subject to and contingent upon stockholder approval of an amendment and restatement of our 2009 Plan, and performance-based stock options:

	Number of Options (in thousands)	Weighted- average Exercise Price	Weighted- average Remaining Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding, December 31, 2013	8,245	\$ 22.06		
Granted	1,352	75.77		
Exercised	(1,982)	14.83		
Cancelled	(85)	35.32		
Outstanding, December 31, 2014	7,530	\$ 33.46	6.32	\$ 478,506
Exercisable at December 31, 2014	4,736	\$ 21.44	4.86	\$ 357,891
Vested or expected to vest at December 31, 2014	7,292	\$ 32.53	6.23	\$ 470,149

The weighted-average fair value of stock options granted was \$39.08, \$26.33 and \$8.68 per share for the years ended December 31, 2014, 2013 and 2012, respectively. The intrinsic value of stock options exercised was \$126.5 million, \$57.9 million and \$4.8 million for the years ended December 31, 2014, 2013 and 2012, respectively. We satisfy stock option exercises with newly issued shares of our common stock.

Performance-Based Stock Options

During 2013, we began granting performance-based stock options to employees that vest as to one-third of the shares upon the achievement of each of three specific clinical development and regulatory events, as approved by our Compensation Committee. The following table summarizes the activity of our performance-based stock options, excluding stock options granted in December 2014 subject to and contingent upon stockholder approval of an amendment and restatement of our 2009 Plan:

	Number of Options (in thousands)	Weighted- average Exercise Price	Weighted- average Remaining Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding, December 31, 2013	468	\$ 63.00		
Granted	194	96.45		
Exercised	(5)	63.00		
Cancelled	(18)	63.00		
Outstanding, December 31, 2014	639	\$ 73.15	9.05	\$ 15,237
Exercisable at December 31, 2014	150	\$ 63.00	8.40	\$ 5,100

On December 12, 2014, we achieved the first performance criteria of the December 18, 2013 grant of performance-based stock options and the stock option was vested as one-third of the performance-based portion of the grant. The weighted-average grant date fair value of the first tranche of the December 18, 2013 performance-based stock option was \$32.26 per share. During the fourth quarter of 2014, we determined the first performance criteria of the December 18, 2013 grant was probable and began to record expense, which was recognized in full as of December 12, 2014. As of the grant date and December 31, 2014, we have determined that the remaining performance criteria of all outstanding performance-based stock options reflected in the table above are not probable. As a result, we have not recorded stock-based compensation expense for these performance-based stock options. The intrinsic value of performance-based stock options exercised was \$0.1

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million for the year ended December 31, 2014. We satisfy performance-based stock option exercises with newly issued shares of our common stock.

Contingent Stock Option Awards

On December 17, 2014, the Compensation Committee of our Board of Directors approved the grant of stock options to purchase 612,085 shares of our common stock, at an exercise price of \$96.45 per share, to members of our management team. These stock option grants were approved subject to and contingent upon approval by our stockholders at our 2015 annual meeting of an amendment and restatement of our 2009 Plan, to, among other things, increase the shares authorized for issuance thereunder. One-half of the contingent stock options granted are time-based stock options and one-half are performance-based stock options. In no event will the contingent stock options be exercised before approval of the amended and restated 2009 Plan by our stockholders; and in the event that the amended and restated 2009 Plan is not approved by the stockholders at the 2015 annual meeting, the contingent stock options shall immediately terminate and be of no further force or effect. If the stockholders approve the amended and restated 2009 Plan, the grant-date fair value of the contingent stock options would be based on a Black-Scholes valuation model based on the fair market value of the stock on the date of such stockholder approval. No stock-based compensation expense was recorded in 2014 relating to this contingent stock option grant.

Restricted Stock Awards

In October 2010, we granted 113,370 shares of our restricted stock to certain employees. These restricted stock awards were valued at \$1.4 million on the grant date. These restricted stock awards vested ratably over an approximate three-year period. In May 2011, we granted an aggregate of 229,806 shares of performance-based restricted stock awards to our employees, excluding our leadership team. These restricted stock awards were valued at \$2.3 million on the grant date and had a contractual term of five years. The vesting of these awards was predicated on our achievement of certain clinical development goals. These awards have vested in full due to the achievement of these goals in 2011 and 2013.

In January 2012, as part of our post-restructuring retention program, we granted an aggregate of 508,928 shares of restricted stock to our retained employees, excluding our chief executive officer and president and chief operating officer. These restricted stock awards were valued at \$5.3 million on the grant date and vested in full on the second anniversary of the grant date.

The following table summarizes the activity of our restricted stock awards, including restricted stock and restricted stock units:

	Number of Restricted Stock Awards (in thousands)	Weighted- average Grant Date Fair Value
Unvested at December 31, 2013	500	\$ 10.69
Granted	29	68.28
Vested	(499)	10.59
Forfeited		
Unvested at December 31, 2014	30	\$ 68.02

The total fair value of restricted stock awards that vested during the years ended December 31, 2014, 2013 and 2012 (measured on the date of vesting) was \$44.4 million, \$5.8 million and \$1.5 million, respectively.

Employee Stock Purchase Plan

In 2004, we adopted the 2004 ESPP with 315,789 shares authorized for issuance. In June 2010, our stockholders approved an amendment to the 2004 ESPP, which increased the shares authorized for issuance from

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315,789 shares to 715,789 shares. Under the 2004 ESPP, each offering period is six months, at the end of which employees may purchase shares of common stock through payroll deductions made over the term of the offering. The per-share purchase price at the end of each offering period is equal to the lesser of 85% of the closing price of our common stock at the beginning or end of the offering period. We issued 21,938, 45,141 and 73,590 shares during the years ended December 31, 2014, 2013 and 2012, respectively, and at December 31, 2014, 207,031 shares were available for issuance under the 2004 ESPP.

The weighted-average fair value of stock purchase rights granted as part of the 2004 ESPP was \$17.03, \$11.49 and \$2.82 per share for the years ended December 31, 2014, 2013 and 2012, respectively. The fair value was estimated using the Black-Scholes option-pricing model. During the three years ended December 31, 2014, we used a weighted-average stock-price volatility of 55%, expected option life assumption of six months and a risk-free interest rate of 0.1%.

10. INCOME TAXES

The domestic and foreign components of loss before income taxes are as follows, in thousands:

	2014	2013	2012
Domestic	\$ (372,137)	\$ (81,109)	\$ (116,400)
Foreign	(28,467)	(10,811)	(186)
Loss before income taxes	\$ (400,604)	\$ (91,920)	\$ (116,586)

Deferred income taxes reflect the tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting and income tax purposes. We establish a valuation allowance when uncertainty exists as to whether all or a portion of the net deferred tax assets will be realized. We have allocated the valuation allowance between current and non-current deferred tax assets and liabilities. As a result of this allocation, we have recorded a long term deferred tax asset of \$31.7 million and a corresponding short term deferred tax liability of \$31.7 million on the balance sheet. Components of the net deferred tax (liability) asset at December 31, 2014 and 2013 are as follows, in thousands:

	2014	2013
Deferred tax assets:		
Net operating loss carryforwards	\$ 176,789	\$ 124,797
Research and development credits	38,204	23,902
AMT credits	788	788
Foreign tax credits	3,196	3,196
Capitalized research and development and start-up costs	19,246	16,214
Deferred revenue	14,273	37,273
Deferred compensation	24,516	21,706
Intangible assets	17,637	2,210
Partnership interest	689	689
Other	5,871	4,885
Total deferred tax assets	301,209	235,660
Deferred tax liabilities:		
Intangible assets		(7)
Unrealized gain on available-for-sale securities	(32,793)	(13,267)
Deferred tax asset valuation allowance	(268,416)	(222,393)
Net deferred tax liability	\$	\$ (7)

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The benefit from income taxes for the years ended December 31, 2014, 2013 and 2012 are as follows, in thousands:

	2014	2013	2012
U.S.:			
Current	\$	\$ 34	\$ 52
Deferred	(40,209)	(2,695)	(10,572)
Total U.S.	(40,209)	(2,661)	(10,520)
Foreign:			
Current			
Deferred		(34)	(52)
Total Foreign		(34)	(52)
Benefit from income taxes	\$ (40,209)	\$ (2,695)	\$ (10,572)

Our effective income tax rate differs from the statutory federal income tax rate as follows for the years ended December 31, 2014, 2013 and 2012:

	2014	2013	2012
At U.S. federal statutory rate	35.0%	35.0%	35.0%
State taxes, net of federal effect	1.8	4.3	4.9
Stock-based compensation	(0.2)	0.8	(0.7)
Tax credits	3.5	8.5	4.2
Orphan drug credit addback	(0.6)	(2.7)	
Other permanent items		(0.3)	(1.6)
Foreign rate differential	(2.5)	(4.1)	(0.1)
In-process research and development	(19.4)		
Tax basis in intangible assets as a result of Sirna transaction	4.2		
Valuation allowance	(11.8)	(38.5)	(32.6)
Effective income tax rate	10.0%	3.0%	9.1%

We have evaluated the positive and negative evidence bearing upon the realizability of our deferred tax assets. We have concluded, in accordance with the applicable accounting standards, that it is more likely than not that we may not realize the benefit of all of our deferred tax assets. Accordingly, we have recorded a valuation allowance against the deferred tax assets that management believes will not be realized. We reevaluate the positive and negative evidence on a quarterly basis. The valuation allowance increased by \$46.0 million, \$29.7 million and \$38.3 million for the years ended December 31, 2014, 2013 and 2012 respectively, due primarily to additional operating losses. Increases to the valuation allowance were partially offset by decreases related to the recognition of deferred revenue.

For the years ended December 31, 2014, 2013 and 2012, we recorded a tax benefit of \$40.2 million, \$2.7 million and \$10.6 million, respectively. For the years ended December 31, 2014, 2013 and 2012, we recorded unrealized gains on our investments in available-for-sale securities in other comprehensive income and additional paid-in capital. The benefit of \$19.5 million, \$2.7 million and \$10.6 million for the years ended December 31, 2014, 2013 and 2012, respectively, is due to the recognition of corresponding income tax expense associated with the increase in the value of our investment in Regulus that we carried at fair market value during the same period. In addition, for the year ended December 31, 2014, we recorded a benefit of \$20.7 million due to the difference between the fair value of stock and the cash proceeds received from Genzyme for the issuance of our common stock calculated at the closing date of the transaction. The corresponding income tax expense has

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been recorded in other comprehensive income and additional paid-in capital, respectively. Intraperiod tax allocation rules require us to allocate our provision for income taxes between continuing operations and other categories of earnings, such as other comprehensive income and additional paid-in capital. In periods in which we have a year-to-date pre-tax loss from continuing operations and pre-tax income in other categories of earnings, such as other comprehensive income and additional paid-in capital, we must allocate the tax provision to the other categories of earnings. We then record a related tax benefit in continuing operations.

The deferred tax assets above exclude \$83.5 million of net operating losses and \$0.4 million of federal and state research and development credits related to tax deductions from the exercise of stock options subsequent to the adoption of the 2006 accounting standard on stock-based compensation. This amount represents an excess tax benefit and has not been included in the gross deferred tax assets.

At December 31, 2014, we had federal and state net operating loss carryforwards of \$639.3 million and \$701.8 million, respectively. These amounts will reduce future taxable income that will expire at various dates through 2034. At December 31, 2014, federal and state research and development credit carryforwards were \$32.3 million and \$10.1 million, respectively, available to reduce future tax liabilities that expire at various dates through 2034. At December 31, 2014, foreign tax credit carryforwards were \$3.2 million available to reduce future tax liabilities that expire in 2017. At December 31, 2014, alternative minimum tax credits of \$0.8 million are available to reduce future regular tax liabilities to the extent such regular tax less other non-refundable credits exceeds the tentative minimum tax. Ownership changes, as defined in the Internal Revenue Code, including those resulting from the issuance of common stock in connection with our public offerings, may limit the amount of net operating loss that can be utilized to offset future taxable income or tax liability. We have determined that based on the value of Alnylam, in the event there was an annual limitation under Section 382, all net operating loss and tax credit carryforwards would still be available to offset taxable income.

At December 31, 2014, 2013 and 2012, we had no unrecognized tax benefits that, if recognized, would favorably impact our effective income tax rate in future periods.

The tax years 2010 through 2014 remain open to examination by major taxing jurisdictions to which we are subject, which are primarily in the United States, as carryforward attributes generated in years past may still be adjusted upon examination by the Internal Revenue Service or state tax authorities if they have or will be used in a future period. We have not recorded any interest and penalties on any unrecognized tax benefits since its inception.

11. REGULUS

In September 2007, we and Isis established Regulus, a company focused on the discovery, development and commercialization of microRNA therapeutics, a potential new class of drugs to treat the pathways of human disease. Regulus, which initially was established as a limited liability company, converted to a C corporation in January 2009 and changed its name to Regulus Therapeutics Inc. Regulus operates as an independent company with a separate board of directors, scientific advisory board and management team. We currently own approximately 12% of Regulus outstanding common stock.

In consideration for our and Isis' initial interests in Regulus, each party granted Regulus exclusive licenses to its intellectual property for certain microRNA therapeutic applications as well as certain patents in the microRNA field. In addition, we made an initial cash contribution to Regulus of \$10.0 million, resulting in us and Isis making approximately equal aggregate initial capital contributions to Regulus. In March 2009, we and Isis each purchased \$10.0 million of Series A preferred stock of Regulus.

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

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Summary results of Regulus' statements of comprehensive loss for the nine months ended September 30, 2012 are presented in the tables below, in thousands:

	Nine months ended September 30, 2012
Statements of Comprehensive Loss Data:	
Net revenues	\$ 9,462
Operating expenses	17,733
Loss from operations	(8,271)
Other expense	(2,289)
Income tax benefit	28
Net loss	\$ (10,532)

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

Based upon our ownership percentage of 17% after the initial public offering, as well as a review of qualitative factors, we did not believe that we had the ability to exercise significant influence over the operating decisions and financial policies of Regulus and therefore discontinued the equity method of accounting for Regulus at September 30, 2012. We determined that the period between September 30, 2012 and the date on which Regulus' closed its initial public offering was immaterial for additional equity method accounting. Accordingly, beginning in October 2012, we accounted for our investment in Regulus as an available-for-sale marketable security due to its readily determinable fair value. As a result of the issuance of additional common stock by Regulus, we recognized a gain of \$16.1 million. This amount was recorded as other income in our consolidated statements of comprehensive loss for the year ended December 31, 2012. Our carrying amount in Regulus increased to \$12.4 million following the initial public offering, which became the initial basis of our investment in Regulus under the accounting standard for marketable securities. In addition, we recorded \$15.7 million as an unrealized gain in other comprehensive income, net of an intraperiod tax benefit of \$10.6 million during the year ended December 31, 2012. After sales of our investment in Regulus during 2014, our carrying amount in Regulus decreased to \$11.9 million at December 31, 2014.

12. ACCRUED EXPENSES

Accrued expenses consist of the following at December 31, 2014 and 2013, in thousands:

	At December 31, 2014	2013
Compensation and related	\$ 7,357	\$ 4,822
Clinical trial and manufacturing	5,548	2,933
Consulting and professional services	3,886	2,135
Pre-clinical	3,081	1,004
Other	3,808	3,266
	\$ 23,680	\$ 14,160

13. RESTRUCTURING

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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.

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

14. QUARTERLY FINANCIAL DATA (UNAUDITED)

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

	March 31, 2014	Three Months Ended		December 31, 2014
		June 30, 2014	September 30, 2014	
		(In thousands, except per share data)		
Revenues	\$ 8,275	\$ 7,295	\$ 10,972	\$ 24,019
Operating expenses	277,339	52,300	56,171	69,731
Net loss	(250,943)	(44,074)	(43,989)	(21,389)
Net loss per common share basic and diluted	\$ (3.70)	\$ (0.58)	\$ (0.58)	\$ (0.28)
Weighted-average common shares basic and diluted	67,786	75,835	76,408	76,957

	March 31, 2013	Three Months Ended		December 31, 2013
		June 30, 2013	September 30, 2013	
		(In thousands, except per share data)		
Revenues	\$ 18,642	\$ 8,687	\$ 8,991	\$ 10,847
Operating expenses	28,446	29,999	41,225	40,439
Net loss	(9,013)	(18,169)	(29,686)	(32,357)
Net loss per common share basic and diluted	\$ (0.15)	\$ (0.29)	\$ (0.48)	\$ (0.51)
Weighted-average common shares basic and diluted	59,173	61,661	62,416	62,909

The increase in operating expenses for the three months ended March 31, 2014 resulted from a \$224.7 million charge to in-process research and development expense in connection with the purchase of the Sirna RNAi assets from Merck. During the three months ended June 30, 2014, we recorded a credit of \$3.9 million to in-process research and development expense, resulting in \$220.8 million in-process research and development expense recorded for the year ended December 31, 2014 as a result of this asset acquisition. See Note 3, Significant Agreements, for further information.

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

None.

ITEM 9A. CONTROLS AND PROCEDURES

Our management, with the participation of our chief executive officer and vice president of finance and treasurer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2014. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2014, our chief executive officer and vice president of finance and treasurer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

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

No change in our internal control over financial reporting occurred during the fiscal quarter ended December 31, 2014 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

None.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by this item is incorporated herein by reference to the information contained under the sections captioned

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

ITEM 11. EXECUTIVE COMPENSATION

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

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

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

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

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

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

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

PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

(a) (1) Financial Statements

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

	Page
<u>Management's Annual Report on Internal Control Over Financial Reporting</u>	101
<u>Report of Independent Registered Public Accounting Firm</u>	102
<u>Consolidated Balance Sheets at December 31, 2014 and 2013</u>	103
<u>Consolidated Statements of Comprehensive Loss for the Years Ended December 31, 2014, 2013 and 2012</u>	104
<u>Consolidated Statements of Stockholders' Equity for the Years Ended December 31, 2014, 2013 and 2012</u>	105
<u>Consolidated Statements of Cash Flows for the Years Ended December 31, 2014, 2013 and 2012</u>	106
<u>Notes to Consolidated Financial Statements</u>	107
(a) (2) List of Schedules	

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

(a) (3) List of Exhibits

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

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SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this Report to be signed on its behalf by the undersigned, thereunto duly authorized, on February 13, 2015.

ALNYLAM PHARMACEUTICALS, INC.

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

Pursuant to the requirements of the Securities Exchange Act of 1934, the Report has been signed below by the following persons on behalf of the Registrant and in the capacities indicated as of February 13, 2015.

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

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Amy W. Schulman

/s/ Phillip A. Sharp, Ph.D.

Director

Phillip A. Sharp, Ph.D.

/s/ Kevin P. Starr

Director

Kevin P. Starr

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EXHIBIT INDEX

Exhibit No.	Exhibit
2.1 *	Stock Purchase Agreement dated as of January 10, 2014 by and among the Registrant, Sirna Therapeutics, Inc., Merck Sharp & Dohme Corp., and solely for the purposes of certain specified provisions, Merck & Co., Inc. (filed as Exhibit 2.1 to the Registrant's Quarterly Report on Form 10-Q filed on May 9, 2014 (File No. 001-36407) for the quarterly period ended March 31, 2014 and incorporated herein by reference)
3.1	Restated Certificate of Incorporation of the Registrant (filed as Exhibit 3.1 to the Registrant's Quarterly Report on Form 10-Q filed on August 11, 2005 (File No. 000-50743) for the quarterly period ended June 30, 2005 and incorporated herein by reference)
3.2	Amended and Restated Bylaws of the Registrant (filed as Exhibit 3.4 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
4.1	Specimen certificate evidencing shares of common stock (filed as Exhibit 4.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
4.2	Rights Agreement dated as of July 13, 2005 between the Registrant and EquiServe Trust Company, N.A., as Rights Agent, which includes as Exhibit A the Form of Certificate of Designations of Series A Junior Participating Preferred Stock, as Exhibit B the Form of Rights Certificate and as Exhibit C the Summary of Rights to Purchase Preferred Stock (filed as Exhibit 4.1 to the Registrant's Current Report on Form 8-K filed on July 14, 2005 (File No. 000-50743) and incorporated herein by reference)
10.1**	2002 Employee, Director and Consultant Stock Plan, as amended, together with forms of Incentive Stock Option Agreement, Non-qualified Stock Option Agreement and Restricted Stock Agreement (filed as Exhibit 10.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.2**	2003 Employee, Director and Consultant Stock Plan, as amended, together with forms of Incentive Stock Option Agreement, Non-qualified Stock Option Agreement and Restricted Stock Agreement (filed as Exhibit 10.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.3**	Amended and Restated 2004 Stock Incentive Plan (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on August 8, 2014 (File No. 001-36407) for the quarterly period ended June 30, 2014 and incorporated herein by reference)
10.4**	Forms of Incentive Stock Option Agreement and Nonstatutory Stock Option Agreement under 2004 Stock Incentive Plan, as amended (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on August 8, 2014 (File No. 001-36407) for the quarterly period ended June 30, 2014 and incorporated herein by reference)
10.5**	2009 Stock Incentive Plan, as amended (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed on August 8, 2014 (File No. 001-36407) for the quarterly period ended June 30, 2014 and incorporated herein by reference)
10.6**	Forms of Incentive Stock Option Agreement and Nonstatutory Stock Option Agreement under 2009 Stock Incentive Plan (filed as Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q filed on August 8, 2014 (File No. 001-36407) for the quarterly period ended June 30, 2014 and incorporated herein by reference)
10.7**	Form of Restricted Stock Agreement under 2009 Stock Incentive Plan (filed as Exhibit 10.5 to the Registrant's Quarterly Report on Form 10-Q filed on August 8, 2014 (File No. 001-36407) for the quarterly period ended June 30, 2014 and incorporated herein by reference)
10.8**	Form of Director Nonstatutory Stock Option Agreement under 2009 Stock Incentive Plan (filed as Exhibit 10.6 to the Registrant's Quarterly Report on Form 10-Q filed on August 8, 2014 (File No. 001-36407) for the quarterly period ended June 30, 2014 and incorporated herein by reference)

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Exhibit No.	Exhibit
10.9**	2004 Employee Stock Purchase Plan, as amended (filed as Appendix A to the Registrant's Definitive Proxy Statement on Schedule 14A filed on April 20, 2010 (File No. 000-50743) and incorporated herein by reference)
10.10**	Letter Agreement between the Registrant and John M. Maraganore, Ph.D. dated October 30, 2002 (filed as Exhibit 10.7 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.11**	Letter Agreement between the Registrant and Barry E. Greene dated September 29, 2003 (filed as Exhibit 10.10 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.12**	Consulting Agreement dated as of March 1, 2006 by and between the Registrant and Phillip A. Sharp, Ph.D., as amended (filed as Exhibit 10.16 to the Registrant's Annual Report on Form 10-K filed on February 19, 2013 (File No. 000-50743) for the year ended December 31, 2012 and incorporated herein by reference)
10.13**	Consulting Agreement dated as of April 20, 2012 by and between the Registrant and Dennis A. Ausiello, M.D. (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on April 23, 2012 (File No. 000-50743) and incorporated herein by reference)
10.14	Lease, dated as of September 26, 2003 by and between the Registrant and Three Hundred Third Street LLC (filed as Exhibit 10.15 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.15	First Amendment to Lease, dated March 16, 2006, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on March 17, 2006 (File No. 000-50743) and incorporated herein by reference)
10.16	Second Amendment to Lease, dated June 26, 2009, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q filed on August 7, 2009 (File No. 000-50743) for the quarterly period ended June 30, 2009 and incorporated herein by reference)
10.17	Third Amendment to Lease, dated May 11, 2010, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on August 5, 2010 (File No. 000-50743) for the quarterly period ended June 30, 2010 and incorporated herein by reference)
10.18	Fourth Amendment to Lease, dated November 4, 2011, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.19 to the Registrant's Annual Report on Form 10-K filed on February 13, 2012 (File No. 000-50743) for the year ended December 31, 2011 and incorporated herein by reference)
10.19	Fifth Amendment to Lease, dated March 27, 2014, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.5 to the Registrant's Amendment No. 1 to its Quarterly Report on Form 10-Q/A filed on January 9, 2015 (File No. 001-36407) for the quarterly period ended March 31, 2014 and incorporated herein by reference)
10.20	Lease entered into as of February 10, 2012 by and between BMR-Fresh Pond Research Park LLC and the Registrant (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on May 3, 2012 (File No. 000-50743) for the quarterly period ended March 31, 2012 and incorporated herein by reference)
10.21	Co-exclusive License Agreement between Garching Innovation GmbH (now known as Max Planck Innovation GmbH) and Alnylam U.S., Inc. dated December 20, 2002, as amended by Amendment dated July 8, 2003 together with Indemnification Agreement by and between Garching Innovation GmbH (now known as Max Planck Innovation GmbH) and Alnylam Pharmaceuticals, Inc. effective April 1, 2004 (filed as Exhibit 10.19 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)

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Exhibit No.	Exhibit
10.22	Co-exclusive License Agreement between Garching Innovation GmbH (now known as Max Planck Innovation GmbH) and Alnylam Europe, AG dated July 30, 2003 (filed as Exhibit 10.20 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.23	Agreement between the Registrant, Garching Innovation GmbH (now known as Max Planck Innovation GmbH), Alnylam U.S., Inc. and Alnylam Europe AG dated June 14, 2005 (filed as Exhibit 10.8 to the Registrant's Quarterly Report on Form 10-Q filed on August 11, 2005 (File No. 000-50743) for the quarterly period ended June 30, 2005 and incorporated herein by reference)
10.24	Confidential Settlement Agreement and Mutual Release entered into as of March 14, 2011 by and between Max-Planck-Gesellschaft zur Förderung der Wissenschaften e. V., Max-Planck-Innovation GmbH and the Registrant, on the one hand, and Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, and the University of Massachusetts, on the other hand (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on May 5, 2011 (File No. 000-50743) for the quarterly period ended March 31, 2011 and incorporated herein by reference)
10.25	Exclusive License Agreement for Tuschl II United States Patents and Patent Applications dated as of March 14, 2011, by and between the Registrant and University of Massachusetts (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed on May 5, 2011 (File No. 000-50743) for the quarterly period ended March 31, 2011 and incorporated herein by reference)
10.26	Amendment to Co-Exclusive License Agreement dated as of March 14, 2011, by and between the Registrant, on the one hand, and Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology and Max-Planck-Innovation GmbH (filed as Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q filed on May 5, 2011 (File No. 000-50743) for the quarterly period ended March 31, 2011 and incorporated herein by reference)
10.27	Research Collaboration and License Agreement effective as of October 12, 2005 by and between the Registrant and Novartis Institutes for BioMedical Research, Inc. (filed as Exhibit 10.23 to the Registrant's Annual Report on Form 10-K filed on March 2, 2009 (File No. 000-50743) for the quarterly and annual period ended December 31, 2008 and incorporated herein by reference)
10.28	License and Collaboration Agreement, entered into as of July 8, 2007, by and among F. Hoffmann-La Roche, Ltd, Hoffmann-La Roche Inc. (which assigned its rights and obligations to Arrowhead Research Corporation), the Registrant and, for limited purposes, Alnylam Europe AG (filed as Exhibit 10.26 to the Registrant's Annual Report on Form 10-K filed on March 2, 2009 (File No. 000-50743) for the quarterly and annual period ended December 31, 2008 and incorporated herein by reference)
10.29	License and Collaboration Agreement entered into as of May 27, 2008 by and among Takeda Pharmaceutical Company Limited and the Registrant (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on August 8, 2008 (File No. 000-50743) for the quarterly period ended June 30, 2008 and incorporated herein by reference)
10.30	Amended and Restated License and Collaboration Agreement, entered into as of January 1, 2009, by and among the Registrant, Isis Pharmaceuticals, Inc. and Regulus Therapeutics Inc. (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed on May 8, 2009 (File No. 000-50743) for the quarterly period ended March 31, 2009 and incorporated herein by reference)
10.31	Founding Investor Rights Agreement entered into as of January 1, 2009, by and among Regulus Therapeutics Inc., Isis Pharmaceuticals, Inc. and the Registrant (filed as Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q filed on May 8, 2009 (File No. 000-50743) for the quarterly period ended March 31, 2009 and incorporated herein by reference)

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Exhibit No.	Exhibit
10.32	Sublicense Agreement dated effective January 8, 2007 among the Registrant and INEX Pharmaceuticals Corporation (now Tekmira Pharmaceuticals Corporation, as successor in interest) (filed as Exhibit 10.38 to the Registrant's Annual Report on Form 10-K filed on February 18, 2011 (File No. 000-50743) for the year ended December 31, 2010 and incorporated herein by reference)
10.33	Sponsored Research Agreement dated as of July 27, 2009 by and among the Registrant, The University of British Columbia and Acuitas Therapeutics Inc. (formerly AICana Technologies, Inc.) (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on June 29, 2011 (File No. 000-50743) and incorporated herein by reference)
10.34	Supplemental Agreement effective July 27, 2009 by and among the Registrant, Tekmira Pharmaceuticals Corporation, Protiva Biotherapeutics Inc., The University of British Columbia and Acuitas Therapeutics Inc. (formerly AICana Technologies, Inc.) (filed as Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed on June 29, 2011 (File No. 000-50743) and incorporated herein by reference)
10.35	Amendment No. 1, dated as of July 27, 2011, to the Sponsored Research Agreement dated as of July 27, 2009 by and among the Registrant, The University of British Columbia and Acuitas Therapeutics Inc. (formerly AICana Technologies, Inc.) (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on November 3, 2011 (File No. 000-50743) for the quarterly period ended September 30, 2011 and incorporated herein by reference)
10.36	License and Collaboration Agreement dated as of August 27, 2012 by and among Monsanto Company and the Registrant (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on November 5, 2012 (File No. 000-50743) for the quarterly period ended September 30, 2012 and incorporated herein by reference)
10.37	Letter Agreement dated September 5, 2014 by and among the Registrant and Monsanto Company (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on November 6, 2014 (File No. 001-36407) for the quarterly period ended September 30, 2014 and incorporated herein by reference)
10.38	Cross-License Agreement dated as of November 12, 2012 by and among the Registrant, Tekmira Pharmaceuticals Corporation and Protiva Biotherapeutics Inc. (filed as Exhibit 10.50 to the Registrant's Annual Report on Form 10-K filed on February 19, 2013 (File No. 000-50743) for the year ended December 31, 2012 and incorporated herein by reference)
10.39	Settlement Agreement and General Release entered into as of November 12, 2012 by and among Tekmira Pharmaceuticals Corporation, Protiva Biotherapeutics Inc., the Registrant and Acuitas Therapeutics Inc. (formerly AICana Technologies, Inc.) (filed as Exhibit 10.51 to the Registrant's Annual Report on Form 10-K filed on February 19, 2013 (File No. 000-50743) for the year ended December 31, 2012 and incorporated herein by reference)
10.40	License and Collaboration Agreement dated as of February 3, 2013 by and among The Medicines Company and the Registrant (filed as Exhibit 10.2 to the Registrant's Amendment No. 1 to its Quarterly Report on Form 10-Q/A filed on July 26, 2013 (File No. 000-50743) for the quarterly period ended March 31, 2013 and incorporated herein by reference)
10.41	Master Services Agreement dated as of January 15, 2010 between Medpace, Inc. and the Registrant, as amended, together with Task Order No. 10 thereto, dated July 2, 2013 (filed as Exhibit 10.49 to the Registrant's Annual Report on Form 10-K filed on February 20, 2014 (File No. 000-50743) for the year ended December 31, 2013 and incorporated herein by reference)
10.42	Stock Purchase Agreement dated as of January 11, 2014 by and between the Registrant and Genzyme Corporation (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on May 9, 2014 (File No. 001-36407) for the quarterly period ended March 31, 2014 and incorporated herein by reference)

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Exhibit No.	Exhibit
10.43	Investor Agreement dated as of February 27, 2014 by and between the Registrant and Genzyme Corporation (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed on May 9, 2014 (File No. 001-36407) for the quarterly period ended March 31, 2014 and incorporated herein by reference)
10.44	Master Collaboration Agreement dated as of January 11, 2014 by and between the Registrant and Genzyme Corporation, including the Regional, Global and Co-Co License Terms Appended thereto (filed as Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q filed on May 9, 2014 (File No. 001-36407) for the quarterly period ended March 31, 2014 and incorporated herein by reference)
12#	Computation of Consolidated Ratios of Earnings/Deficiencies to Fixed Charges
21.1#	Subsidiaries of the Registrant
23.1#	Consent of PricewaterhouseCoopers LLP, an Independent Registered Public Accounting Firm
31.1#	Certification pursuant to Section 302 of the Sarbanes-Oxley Act of 2002, Rule 13(a)- 14(a)/15d-14(a), by Principal Executive Officer
31.2#	Certification pursuant to Section 302 of the Sarbanes-Oxley Act of 2002, Rule 13(a)- 14(a)/15d-14(a), by Principal Financial Officer
32.1#	Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, by Principal Executive Officer
32.2#	Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, by Principal Financial Officer
101#	The following materials from Registrant's Annual Report on Form 10-K for the year ended December 31, 2014, formatted in XBRL (Extensible Business Reporting Language): (i) the Consolidated Balance Sheets, (ii) the Consolidated Statements of Comprehensive Loss, (iii) the Consolidated Statements of Stockholders' Equity, (iv) the Consolidated Statements of Cash Flows and (v) Notes to Consolidated Financial Statements.

* Schedules, exhibits and similar supporting attachments or agreements to the Stock Purchase Agreement are omitted pursuant to Item 601(b)(2) of Regulation S-K. The Registrant agrees to furnish a supplemental copy of any omitted schedule or similar attachment to the Securities and Exchange Commission upon request.

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

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

Filed herewith.