ALNYLAM PHARMACEUTICALS, INC.
Form 424B5
January 20, 2015
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Filed Pursuant to Rule 424(b)(5)
Registration No. 333-185658

The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement relating to these securities has been filed with the Securities and Exchange Commission and is effective. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities, and we are not soliciting offers to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to completion, dated January 20, 2015

Preliminary Prospectus Supplement (To Prospectus dated December 21, 2012)

$450,000,000

Common Stock

We are offering up to $450,000,000 of our common stock.

Our common stock trades on the NASDAQ Global Select Market under the trading symbol ALNY . On January 16, 2015, the last reported sale price of our common stock on the NASDAQ Global Select Market was $100.77 per share.

	Per Share	Total
Public offering price	$	$
Underwriting discounts and commissions	$	$
Proceeds, before expenses, to us	$	$

We have granted the underwriters an option for a period of 30 days from the date of this prospectus supplement to purchase up to an additional $67,500,000 of our common stock at the public offering price, less the estimated underwriting discounts and commissions.

Genzyme Corporation, or Genzyme, one of our existing stockholders and collaboration partners, has exercised its right to purchase directly from us, in a concurrent private placement, the number of shares needed to maintain its current ownership percentage of our common stock of approximately 12%, at the public offering price. This sale of common stock to Genzyme will not be registered as part of this offering, though it will be consummated simultaneously with and subject to the closing of the public offering. We refer to this transaction as the concurrent private placement. Please read the section in this prospectus supplement entitled Underwriting for more information.

We estimate the expenses of this offering, excluding underwriting discounts and commissions, will be approximately $400,000.

Investing in our common stock involves risks. See Risk Factors beginning on page S-12 of this prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus supplement or the accompanying prospectus. Any representation to the contrary is a criminal offense.

The underwriters expect to deliver the shares to purchasers on or about January , 2015.

Joint book-running managers

J.P. Morgan **Deutsche Bank Securities**

January , 2015

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About this prospectus supplement

This document consists of two parts. The first part is this prospectus supplement, which describes the specific terms of this common stock offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein. The second part, the accompanying prospectus, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement and the information contained in the accompanying prospectus or any document incorporated by reference therein filed prior to the date of this prospectus supplement, you should rely on the information in this prospectus supplement; provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date for example, a document incorporated by reference in the accompanying prospectus the statement in the document having the later date modifies or supersedes the earlier statement.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference herein were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

We have not authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus supplement, the accompanying prospectus or in any free writing prospectus prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus supplement and the accompanying prospectus do not constitute an offer to sell, or a solicitation of an offer to purchase, the securities offered by this prospectus supplement and the accompanying prospectus in any jurisdiction to or from any person to whom or from whom it is unlawful to make such offer or solicitation of an offer in such jurisdiction. The information contained in this prospectus supplement or the accompanying prospectus, or incorporated by reference herein is accurate only as of the respective dates thereof, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or of any sale of our common stock. It is important for you to read and consider all information contained in this prospectus supplement and the accompanying prospectus, including the documents incorporated by reference herein and therein, in making your investment decision. You should also read and consider the information in the documents to which we have referred you in the sections entitled Where You Can Find More Information and Incorporation of Certain Information by Reference in this prospectus supplement and in the accompanying prospectus.

We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this

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prospectus supplement and the accompanying prospectus outside the United States. This prospectus supplement and the accompanying prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

Unless the context otherwise indicates, references in this prospectus to Alnylam, we, our, us, the Company and similar designations refer, collectively, to Alnylam Pharmaceuticals, Inc., a Delaware corporation, and its consolidated subsidiaries. Alnylam is a trademark of Alnylam Pharmaceuticals, Inc. Our logo, trademarks and service marks are property of Alnylam. All other trademarks or service marks appearing in this prospectus supplement are the property of their respective holders.

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Special note regarding forward-looking statements

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. All statements, other than statements of historical facts, that we include in this prospectus supplement, the accompanying prospectus and in the documents incorporated by reference into this prospectus supplement and the accompanying prospectus may be deemed forward-looking statements for purposes of the Securities Act and the Exchange Act. We use words such as believe, expect, anticipate, may, could, intend, will, plan, target, goal, anticipate, estimate, similar expressions to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These statements appear throughout this prospectus supplement, the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus and are statements regarding our current intent, belief or expectation, primarily with respect to our operations and related industry developments. Examples of these statements include, but are not limited to, statements regarding the following: our expected cash position as of December 31, 2014; the progress of our research and development programs; the timing and results of regulatory filings; our current and anticipated clinical trials and expectations regarding the enrollment in and the reporting of data from these trials; our expectations regarding potential product characteristics; market size for, and the successful commercialization of, the product candidates we are developing; our corporate collaborations, including potential future licensing fees and milestone and royalty payments; protection of our intellectual property; the outcome of litigation; the sufficiency of our cash resources; the timing and likelihood of regulatory approvals; and our operations and legal risks. We cannot guarantee that we actually will achieve the plans, intentions or expectations disclosed in our forward-looking statements and, accordingly, you should not place undue reliance on our forward-looking statements. There are a number of important factors that could cause actual results or events to differ materially from those expressed or implied by these forward-looking statements, including those discussed under Risk Factors and elsewhere in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus.

Any forward-looking statement speaks only as of the date on which it is made, and we disclaim any obligation to update any forward-looking statement to reflect events or circumstances after the date on which the statement is made or to reflect the occurrence of unanticipated events. New factors emerge from time to time, and it is not possible for us to predict which factors will arise. In addition, we cannot assess the impact of each factor on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements.

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Summary

This summary highlights information contained elsewhere in this prospectus supplement and the accompanying prospectus and in the documents we incorporate by reference. This summary does not contain all of the information that you should consider before deciding to invest in our common stock. You should read this entire prospectus supplement and the accompanying prospectus carefully, including the Risk Factors section contained in this prospectus supplement and our consolidated financial statements and the related notes and the other documents incorporated by reference herein.

Alnylam Pharmaceuticals, Inc.

Our business

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

Our broad pipeline of investigational RNAi therapeutics is focused in three Strategic Therapeutic Areas, or STArs: Genetic Medicines, for the treatment of rare diseases; Cardio-Metabolic Disease, focused on genetically validated, liver-expressed genes for cardio-metabolic diseases with high unmet need; and Hepatic Infectious Disease, addressing major global health challenges, including but not limited to the hepatitis B virus, or HBV.

Alnylam 2020 vision

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 across our three STArs:

- Genetic Medicines;
- Cardio-Metabolic Disease; and
- Hepatic Infectious Disease.

By the end of 2020, we expect to have three marketed RNAi products and ten RNAi therapeutic clinical programs, including four in late stages of development, across our three STArs.

STAr status and 2015 goals and objectives

Genetic Medicine STAr, investigational RNAi therapeutics for the treatment of rare diseases:

In our Genetic Medicine STAr, we are advancing a broad pipeline of investigational RNAi therapeutics for rare diseases and we intend to advance additional pre-clinical candidates toward an investigational new drug application, or IND, or IND equivalent, each year for the foreseeable

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future. 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 Corporation, a Sanofi company, or Genzyme, for commercialization in the rest of the world, subject to certain broader rights. Specifically, we plan to advance our Genetic Medicine STAr as follows:

Patisiran (ALN-TTR02), an intravenously delivered RNAi therapeutic targeting transthyretin, or TTR, in development for the treatment of TTR-mediated amyloidosis, or ATTR, in patients with familial amyloidotic polyneuropathy, or FAP, for which our APOLLO Phase 3 clinical trial is ongoing:

- Continue enrollment in our APOLLO Phase 3 study.
- Present data in mid-2015 from our ongoing Phase 2 open-label extension, or OLE, study with patisiran in patients with FAP.

Revusiran (ALN-TTRsc), a subcutaneously administered RNAi therapeutic targeting TTR in development for the treatment of ATTR in patients with TTR cardiac amyloidosis, including familial amyloidotic cardiomyopathy, or FAC, and senile systemic amyloidosis, or SSA, for which we recently initiated our ENDEAVOUR Phase 3 clinical trial for FAC:

- Continue enrollment in our ENDEAVOUR Phase 3 study.
- Present data in late 2015 from our ongoing Phase 2 OLE study in patients with TTR cardiac amyloidosis.
- Present results from our natural history study of patients with TTR cardiac amyloidosis in early 2015.

ALN-AT3, an RNAi therapeutic targeting antithrombin, or AT, in development for the treatment of hemophilia and rare bleeding disorders, or RBD, which is currently in a Phase 1 clinical trial and for which we recently reported early clinical data in January 2015:

- Continue enrollment in our Phase 1 study.
- Present additional Phase 1 data in mid- and late 2015, with complete data in late 2015.
- Start our Phase 2 study in late 2015.

ALN-CC5, an RNAi therapeutic targeting complement component C5, in development for the treatment of complement-mediated diseases, for which we have recently filed a clinical trial application, or CTA, for a Phase 1/2 clinical trial in healthy volunteers and patients with paroxysmal nocturnal hemoglobinuria, or PNH:

- Start our Phase 1/2 study in early 2015.

Present initial data from our Phase 1/2 study in mid-2015 and additional data in late 2015.

Initiate Part C of our Phase 1/2 study in patients with PNH in late 2015.

ALN-AS1, an RNAi therapeutic targeting aminolevulinate synthase-1, or ALAS-1, in development for the treatment of hepatic porphyrias, including acute intermittent porphyria, or AIP, for which we have recently filed a CTA for a Phase 1 clinical trial in AIP patients:

Start our Phase 1 study in mid-2015, with initial data expected in early 2016.

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Additional pre-clinical programs, including ALN-AAT targeting alpha-1 antitrypsin, or AAT, for the treatment of AAT deficiency-associated liver disease; ALN-GO1 targeting glycolate oxidase, or GO, for the treatment of primary hyperoxaluria type 1, or PH1; ALN-TMP targeting TMPRSS6 for the treatment of beta-thalassemia and iron-overload disorders; and other yet to be disclosed programs:

File an IND or IND equivalent for AAT in mid-2015.

Start a Phase 1 study in late 2015 for AAT.

Select a Development Candidate, or DC, in mid-2015 for ALN-GO1 to support an IND or IND equivalent filing in 2016.

Advance additional Genetic Medicine STAr programs to support two or more INDs in 2016.

Cardio-Metabolic Disease STAr, investigational RNAi therapeutics for the treatment of unmet needs in dyslipidemia, hypertension, diabetes and NASH:

ALN-PCSsc, a subcutaneously administered RNAi therapeutic targeting proprotein convertase subtilisin/kexin type 9, or PCSK9, for the treatment of hypercholesterolemia, which we are developing in collaboration with The Medicines Company, or MDCO, and for which we recently initiated a Phase 1 clinical study:

Continue enrollment in our Phase 1 study.

Present initial Phase 1 data in mid-2015.

Advance additional Cardio-Metabolic STAr programs to support at least one new IND in 2016.

Hepatic Infectious Disease STAr, investigational RNAi therapeutics for the treatment of infectious diseases with liver involvement:

ALN-HBV, a subcutaneously administered RNAi therapeutic targeting the HBV genome for the treatment of chronic HBV infection:

File an IND or IND equivalent in late 2015.

Advance additional Hepatic Infectious Disease STAr programs.

In early January 2015, we also announced that we expect to end 2014 with approximately $880 million in cash, cash equivalents and fixed income marketable securities.

Detailed recent developments in Genetic Medicine STAr

Phase 1 Data for ALN-AT3 in hemophila

In January 2015, we announced updated results from our ongoing Phase 1 study of ALN-AT3, a subcutaneously administered, investigational RNAi therapeutic targeting AT for the treatment of hemophilia and RBD. 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; 3:1 randomization of ALN-AT3: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 hemophilia A or B. 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

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assessment of clinical activity as determined by knockdown of circulating AT levels and increase in thrombin generation at pharmacologic doses of ALN-AT3.

Updated results were presented from the second dose cohort of hemophilia subjects which is now fully enrolled (n=3) where ALN-AT3 is administered subcutaneously once weekly for three weeks (qW x 3) at a low dose of 45 mcg/kg. All preliminary results are as of a data cut off on 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. Based on the essentially complete time course for AT knockdown from the first dose cohort receiving 15 mcg/kg (qW x 3), the effects of ALN-AT3 were also found to be highly durable, lasting about 60 days.

Initial evidence for the potential correction of the hemophilia phenotype was observed in the severe hemophilia A subjects. Specifically, ALN-AT3 administration resulted in thrombin generation increases of up to 334%. Increase in thrombin generation was closely correlated with degree of AT knockdown. When AT knockdown levels exceeded 50%, the mean increase in thrombin generation was 112 +/- 38% (p less than 0.05) relative to baseline. Thrombin generation is known to be a biomarker for bleeding frequency and severity in people with hemophilia, and the results achieved following ALN-AT3 administration are consistent with thrombin generation levels measured in mild hemophilia. Moreover, the observed maximal increase in thrombin generation in the hemophilia subjects (peak thrombin of 71 nM) remained at the low end of the range for peak thrombin levels in the healthy volunteers enrolled in Part A of the study (mean of 92 +/- 15 nM; range from 69-135nM). These data show that AT knockdown of up to 70% in hemophilia subjects should not lead to an excessive increase in thrombin generation beyond normal.

Further evaluation of the effects of ALN-AT3 employed the use of ROTEM® thromboelastometry, an established whole blood viscoelastic method which measures clotting time and clot strength following a physiologic coagulation stimulus; this assay method was available for a single severe hemophilia A subject in the second dose cohort, who happens to be the most advanced subject. ALN-AT3 administration was found to result in AT knockdown-dependent improvements in whole blood clotting in this subject. Finally, as of the current data cut-off date of January 6, 2015, this hemophilia subject was free of any bleeds for 47 days, which compares favorably to his physician-reported Annual Bleeding Rate (ABR) of 10-12 bleeds/year during use of on-demand therapy prior to enrolling in the study.

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). There have been no serious adverse events, no discontinuations, no injection site reactions, and no significant changes in physical exams, vital signs, or electrocardiography. Further, there have been no clinically significant changes in any laboratory parameter, including liver function tests, hematology, and coagulation measures. There have been no clinically significant increases in D-dimer, a marker of fibrin clot formation, or any thromboembolic events. The most common adverse event observed in hemophilia subjects was the occurrence of mild to moderate bleeds unrelated to study drug. All bleeds were successfully managed with replacement factor administration. In the second dose cohort and as of the data cut-off date, all five reported bleeds occurred on day 6 or earlier at low levels of AT knockdown with the exception of a trauma-related bleed in one subject at day 16, which was managed with a low, 1000 IU dose of Factor VIII.

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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.

Revusiran Phase 2 Data and Phase 3 Trial Initiation for TTR-mediated FAC

In December 2014, we announced the initiation of the 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 burden 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 class, Kansas City Cardiomyopathy Questionnaire (KCCQ), 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 2-to-1, revusiran to placebo, with revusiran administered subcutaneously at 500 mg daily for five days then weekly for 18 months. The 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 $p < 0.05$. 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 open-label extension (OLE) study. The ENDEAVOUR study is now enrolling patients. We achieved a $25 million milestone from Genzyme based on dosing of the first patient in the ENDEAVOUR study which is expected to be paid in the first quarter of 2015.

In November 2014, we presented positive initial results from our Phase 2 open-label, multi-dose study with revusiran in TTR cardiac amyloidosis patients. The revusiran pilot Phase 2 study was aimed at evaluating the safety, tolerability, pharmacodynamic, and preliminary clinical activity of revusiran in patients with FAC and SSA. The initial Phase 2 results presented were from 26 patients, including 14 diagnosed with FAC and 12 with SSA based on a data cutoff date of October 3, 2014. In this study, revusiran was found to be generally well tolerated in TTR cardiac amyloidosis patients. The most common adverse event was injection site reaction (23% of patients). 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. There were no other significant adverse events, discontinuations or other clinically significant laboratory abnormalities. Revusiran demonstrated clinical activity with an up to 98.2% knockdown of serum TTR, the disease causing protein, with a mean maximum knockdown of 87.2% +/- 9.1%. This included similar knockdown effects toward wild type and mutant TTR protein in V122I patients, who represent the most common FAC genotype. As expected following a five-week course of treatment, there were no significant changes observed in a number of exploratory clinical measurements.

Filed clinical trial applications for ALN-CC5 and ALN-AS1 Programs

In December 2014, we announced that we filed a CTA for ALN-CC5, an investigational RNAi therapeutic targeting complement C5 for the treatment of complement-mediated diseases. The CTA has recently been approved, and enables us to start a Phase 1/2 study. 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 healthy human volunteers; Part C will be a study in patients with PNH. We expect to present initial data from this Phase 1/2 study in mid- and late 2015. We also expect to enroll the first PNH patient in the study in late 2015.

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In January 2015, we announced that we filed a CTA for ALN-AS1, an investigational RNAi therapeutic targeting ALAS-1 for the treatment of hepatic porphyrias, including AIP. The CTA, when approved, will enable the start of a Phase 1 study that will be conducted initially in asymptomatic AIP patients with elevated levels of heme intermediates. We expect to start the ALN-AS1 Phase 1 study in mid-2015.

Detailed recent developments in Cardio-Metabolic Disease STAr

Filed CTA for ALN-PCSsc and Initiated Phase 1 Study

In October 2014, we announced that we filed a CTA for ALN-PCSsc, an investigational RNAi therapeutic targeting PCSK9 for the treatment of hypercholesterolemia. In December 2014, we announced that we initiated our Phase 1 study of ALN-PCSsc. The Phase 1 study is being performed in healthy adult volunteers with elevated LDL-C at baseline. The study is designed as a single ascending dose study, followed by a multiple dose study, which will include subjects on statin therapy. We expect to present initial data for ALN-PCSsc in mid-2015.

Detailed recent developments in Hepatic Infectious Disease STAr

Selected Development Candidate for ALN-HBV

In December 2014, we announced that we selected our DC for our ALN-HBV program. The DC employs our ESC-GalNAc-conjugate delivery platform that enables subcutaneous dose administration with high potency and durability and a wide therapeutic index. In a rodent model of HBV infection, the ALN-HBV DC demonstrated an up to 3.9 log10 reduction in HBV surface antigen, or HBsAg. We expect to file an IND or IND equivalent for ALN-HBV in late 2015.

Other recent developments

Additional Genzyme stock purchase

As set forth in the investor agreement between us and Genzyme, one of our existing stockholders and collaboration partners, 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 has exercised this right to purchase directly from us 196,251 shares of our common stock on January 22, 2015 at a price per share equal to the closing price of our common stock on the Nasdaq Global Select Market on such date. The sale of these shares to Genzyme will be consummated as a private placement and will not be registered in this offering.

Concurrent private placement

Genzyme also has exercised its right set forth in the investor agreement between us and Genzyme to purchase directly from us, in a concurrent private placement, the number of shares needed to maintain its current ownership percentage of our common stock of approximately 12%, at the public offering price. The sale of common stock to Genzyme will not be registered as part of this offering, though will be consummated simultaneously with and subject to the closing of the public offering. We refer to this transaction as the concurrent private placement. Please read the section in this prospectus supplement entitled Underwriting for more information.

Company information

We are a Delaware corporation. Our principal executive offices are located at 300 Third Street, Cambridge, Massachusetts 02142, and our telephone number at that address is (617) 551-8200. Our website address is *www.alnylam.com*. The information contained on our website is not incorporated by reference and should not be considered part of this prospectus supplement. We have included our website address in this prospectus supplement as an inactive textual reference only.

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The offering

Common stock offered	shares
Concurrent private placement	Genzyme Corporation, or Genzyme, one of our existing stockholders and collaboration partners, has exercised its right to purchase directly from us, in a concurrent private placement, the number of shares needed to maintain its current ownership percentage of our common stock of approximately 12%, at the public offering price. This sale of common stock to Genzyme will not be registered as part of this offering, though it will be consummated simultaneously with and subject to the closing of the public offering. We refer to this transaction as the concurrent private placement. Please read the section in this prospectus supplement entitled Underwriting for more information.
Common stock to be outstanding after this offering and the concurrent private placement	shares
Option to purchase additional shares offered to the underwriters	The underwriters have an option to purchase a maximum of an additional $67,500,000 of our common stock from us. The underwriters can exercise this option at any time within 30 days from the date of this prospectus supplement.
Use of Proceeds	We estimate that the net proceeds from this offering and the concurrent private placement will be approximately $493.1 million, based on an assumed public offering price of $100.77 per share (the last reported sale price of our common stock on the NASDAQ Global Select Market on January 16, 2015), after deducting estimated discounts and commissions for shares sold in the public offering and estimated offering expenses payable by us. We intend to use the net proceeds from this offering and the concurrent private placement for general corporate purposes, including research and development expenses, including clinical trial costs, potential acquisitions of new businesses, technologies or products that we believe have the potential to complement or expand our business, working capital, capital expenditures and general and administrative expenses. See Use of Proceeds.
Risk Factors	You should read the Risk Factors section of this prospectus supplement beginning on page S-12 for a discussion of factors to consider before deciding to purchase shares of our common stock.
NASDAQ Global Select Market symbol	ALNY

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The number of shares of our common stock to be outstanding after this offering and the concurrent private placement is based on 77,202,753 shares outstanding as of December 31, 2014, and excludes:

- 8,168,533 shares of common stock issuable upon the exercise of outstanding stock options at a weighted-average exercise price of $36.57 per share;
- 612,085 shares of common stock issuable upon the exercise of stock options granted to employees at a weighted-average exercise price of $96.45 per share that are contingent upon receiving stockholder approval of an amended and restated 2009 stock incentive plan in connection with our 2015 annual stockholder meeting;
- an aggregate of 536,529 additional shares of common stock reserved for future issuance under our 2009 stock incentive plan, our 2004 stock incentive plan and our 2004 employee stock purchase plan; and
- the expected sale of 196,251 shares of common stock to Genzyme on January 22, 2015 as described under Summary Other recent developments Additional Genzyme stock purchase above.

Except as otherwise noted, we have presented the information in this prospectus supplement assuming:

- no exercise by the underwriters of the option to purchase up to an additional $67,500,000 of our common stock in this offering;
- no sale of additional shares of our common stock to Genzyme as described in Underwriting based on the exercise by the underwriters of the option described in the previous bullet; and
- no exercise of outstanding stock options.

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Risk factors

Investing in our common stock involves significant risks. In deciding whether to invest, you should carefully consider the following risk factors, as well as the other information contained in this prospectus supplement, the accompanying prospectus and in our filings with the Securities and Exchange Commission, or the SEC, that we have incorporated by reference in this prospectus supplement and the accompanying prospectus. Any of the following risks could have a material adverse effect on our business, financial condition, results of operations and prospects and cause the value of our stock to decline, which could cause you to lose all or part of your investment. The risks and uncertainties we have described are not the only ones facing our company. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our business operations.

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

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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 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 September 30, 2014, we had an accumulated deficit of $935.2 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.

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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.

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.

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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, and paid us $23.0 million. This purchase allowed Genzyme to maintain its ownership level of approximately 12% of our outstanding common stock. Genzyme has also exercised its right to purchase shares based on 2014 compensatory issuances as described under Summary Other recent developments Additional Genzyme stock purchase and its right to purchase shares based on this offering as described under Underwriting. While the exercise of these rights by Genzyme has provided us with an additional $23.0 million in cash to date, and while we expect the exercise of these rights as described in the previous sentence, along with any exercise of Genzyme s rights in the future, will provide us with further additional cash, the March 2014 exercise caused, and any current or 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.

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. 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 September 30, 2014, we had $915.2 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

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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.

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 publically indicated that they no longer intend to invest in

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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 U.S. 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-PCSsc 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.

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

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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

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marketing capabilities outside of the U.S. 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 Pharmaceuticals Corporation, or TPC, and Protiva Biotherapeutics, Inc., a wholly owned subsidiary of TPC, and together with TPC, referred to as Tekmira, filed a civil complaint against us claiming, among other things, misappropriation of its confidential and proprietary information and trade secrets. As a result of the litigation, which was settled in November 2012, we were required to expend resources and management attention that would otherwise have been engaged in other activities. 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.

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

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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 good manufacturing practice, or 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 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 lipid nanoparticles, or 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 U.S. Food and Drug Administration, or 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

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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.

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.

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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 U.S. 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 U.S. 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 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

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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

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testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome, and the historical failure rate for product candidates is high. We currently have several programs in clinical development, including patisiran in a Phase 3 clinical trial, revusiran in a Phase 3 clinical trial, ALN-AT3 in a Phase 1 clinical trial and ALN-PCSsc in a Phase 1 clinical trial. Assuming regulatory clearance, we expect to initiate Phase 1 clinical trials for ALN-CC5 and ALN-AS1 during 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

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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 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;

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

conditions imposed on us by 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;

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.

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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 Risk Evaluation and Mitigation Strategy, or REMS, plan as part of a new drug application, or NDA, or after approval, which may impose further requirements or 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.

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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 recently 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;

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;

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the U.S. federal Health Insurance Portability and Accountability Act, or HIPAA, and Health Information Technology for Economic and Clinical Health, or HITECH, Act, which 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 The Centers for Medicare and Medicaid Services, or CMS, pursuant to the Patient Protection and Affordable Care Act, or PPACA. Under the National Physician Payment Transparency Program, manufacturers of medical devices, biological 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;

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

We currently expect that any drugs we develop may need to be administered under the supervision of a physician on an outpatient basis. Under currently applicable U.S. law, certain

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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 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.

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

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

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

The full effects of the U.S. healthcare reform legislation cannot be known until the new law is fully implemented through regulations or guidance issued by the 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.

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.

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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 United States Patent and Trademark Office, or USPTO, may commence interference proceedings involving our patents or patent applications. Any challenge to, finding of unenforceability or invalidation or circumvention of, our patents or patent applications, would be costly, would require significant time and attention of our management and could have a material adverse effect on our business.

Our pending patent applications may not result in issued patents. The patent position of pharmaceutical or biotechnology companies, including ours, is generally uncertain and involves complex legal and factual considerations. The standards that the USPTO and its foreign counterparts use to grant patents are not always applied predictably or uniformly and can change. Similarly, the ultimate degree of protection that will be afforded to biotechnology inventions, including ours, in the United States and foreign countries, remains uncertain and is dependent upon the scope of the protection decided upon by patent offices, courts and lawmakers. Moreover, there are periodic discussions in the Congress of the United States and in international jurisdictions about modifying various aspects of patent law. For example, the America Invents Act includes a number of changes to the patent laws of the United States. If any 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

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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 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, Cancer Research Technology Limited, or CRT, Isis, the Massachusetts Institute of Technology, or MIT, Whitehead Institute for Biomedical Research, or Whitehead, Max Planck Innovation GmbH (formerly known as Garching Innovation GmbH), or 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

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

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

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

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

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

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Foerderung Der Wissenschaften e.V. and Max Planck Innovation, together, Max Planck, Whitehead, MIT and The University of Massachusetts, or 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.

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.

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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 first 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 produc