ALNYLAM PHARMACEUTICALS, INC.
Form 10-K
February 15, 2017

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2016

OR

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to

Commission File Number 001-36407

ALNYLAM PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	77-0602661
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)

300 Third Street, Cambridge, MA 02142

(Address of Principal Executive Offices) (Zip Code)

Registrant’s telephone number, including area code: (617) 551-8200

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock, $0.01 par value per share	The Nasdaq Global Select Market

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes No

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes No

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes No

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

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

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

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

The aggregate market value of the registrant's common stock, $0.01 par value per share ("Common Stock"), held by non-affiliates of the registrant, based on the last sale price of the Common Stock at the close of business on June 30, 2016, was $4,703,804,453. For the purpose of the foregoing calculation only, all directors and executive officers of the registrant are assumed to be affiliates of the registrant.

At January 31, 2017, the registrant had 86,013,785 shares of Common Stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2017 annual meeting of stockholders, which the registrant intends to file pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year end of December 31, 2016, are incorporated by reference into Part II, Item 5 and Part III of this Form 10-K.

ALNYLAM PHARMACEUTICALS, INC.

ANNUAL REPORT ON FORM 10-K

For the Year Ended December 31, 2016

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

PART I

ITEM 1. BUSINESS

Overview

We are a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. RNAi is a naturally occurring biological pathway within cells for selectively silencing and regulating the expression of specific genes. Since many diseases are caused by the inappropriate activity of specific genes, the ability to silence genes selectively through RNAi could provide a new way to treat a wide range of human diseases. We believe that drugs that work through RNAi have the potential to become a broad new class of innovative medicines, and that this potential new drug class is similar to the opportunity created with other major biological discoveries such as recombinant DNA and monoclonal antibodies. Using our intellectual property and expertise, we are developing what we believe to be a reproducible and modular platform to develop RNAi therapeutics for a variety of human diseases.

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

Specifically, our broad pipeline of investigational RNAi therapeutics is focused in three Strategic Therapeutic Areas, or “STArs:” Genetic Medicines, with multiple product candidates for the treatment of rare diseases; Cardio-Metabolic Diseases, with product candidates directed toward genetically validated, liver-expressed disease targets for unmet needs in cardiovascular and metabolic diseases; and Hepatic Infectious Diseases, with product candidates designed to address the major global health challenges of hepatic infectious diseases, beginning with hepatitis B and hepatitis D viral infections. We are focused on advancement of our Alnylam 2020 strategy for the development and commercialization of RNAi therapeutics as a potential new class of innovative medicines. Specifically, our goal is to

achieve, by the end of 2020, a company profile with three marketed products and ten RNAi therapeutic clinical programs, including four in late stages of development, across our three STArs.

Our most advanced investigational RNAi therapeutic in development, patisiran, targets the transthyretin, or TTR, gene for the treatment of patients with polyneuropathy due to hereditary TTR-mediated amyloidosis, or hATTR amyloidosis. We expect to report top-line data from our ongoing APOLLO Phase 3 study of patisiran in mid-2017. Assuming that the APOLLO data are positive, we plan to submit our first new drug application, or NDA, and marketing authorization application, or MAA, for patisiran by the end of 2017. We expect to advance additional investigational RNAi therapeutics into Phase 3 development during 2017, including fitusiran, for the treatment of hemophilia and rare bleeding disorders, and givosiran (ALN-AS1), for the treatment of acute hepatic porphyrias. Given our plans for patisiran and the expected progress of our other late stage development programs, during 2016 we were focused on expanding our manufacturing, commercial and medical affairs capabilities to support our transition from a development-stage company toward a multi-product, commercial-stage biopharmaceutical company. For example, as a result of significant efforts in 2016, our manufacturing facility for patisiran formulated bulk drug product is now fully operational and ready for the potential launch of patisiran. In addition, we commenced construction of a manufacturing facility in Norton, Massachusetts for drug substance, including siRNAs and siRNA conjugates, for clinical and commercial use. We also expanded our global footprint with the establishment of our European headquarters in Zug, Switzerland, as well as the opening of a new development and commercial hub in Maidenhead, United Kingdom. Lastly, we continued to build our commercial and medical affairs teams in preparation for the potential launch of patisiran in 2018, which we plan to market in the United States, Canada and Western Europe.

Finally, based on our expertise in RNAi therapeutics and broad intellectual property estate, we have formed alliances with leading pharmaceutical and life sciences companies to support our development and commercialization efforts, including Sanofi Genzyme, the specialty care global business unit of Sanofi, and The Medicines Company, or MDCO.

RNAi Therapeutics – A Potential New Class of Innovative Medicines

RNAi is a natural biological pathway that occurs within cells to selectively silence the activity of specific genes. The discovery of RNAi first occurred in plants and worms in 1998, and two of the scientists who made this discovery, Dr. Andrew Fire and Dr. Craig Mello, received the 2006 Nobel Prize for Physiology or Medicine.

RNAi therapeutics harness the natural RNAi pathway to silence disease-associated genes and knock down production of disease-causing proteins, representing the opportunity to create a potential new class of innovative medicines. This potential new drug class is similar to the opportunity created with other major biological discoveries such as recombinant DNA and monoclonal antibodies. RNAi therapeutics also have a distinct mechanism of action, acting "upstream" of today's medicines. Specifically, RNAi therapeutics achieve their biological effects through a highly potent, catalytic mechanism. This unique mechanism of action confers a number of attributes that we believe have the potential to provide meaningful differentiation and distinct value for our investigational RNAi therapeutics relative to other drug classes.

Key Features of Alnylam Investigational RNAi Therapeutics Potential Attributes for Differentiation and Value
• Potential to silence any disease-associated gene, including so-called "undruggable" targets, where conventional therapeutic modalities (e.g., small molecule drugs and biologics) have not been successful
• Demonstrated potential in clinical trials to achieve robust clinical activity with up to 99 percent target gene knockdown in some cases
• Clamped pharmacodynamic effect that has potential to provide improved and consistent efficacy compared with intermittent and transient effects often achieved with other drug classes
• Demonstrated durability of effect in clinical trials that enables once-monthly, once-quarterly and, in some cases, possible bi-annual dose regimens
• Ability to achieve subcutaneous dose administration with our proprietary GalNAc-conjugate delivery platform
• Potential for room temperature stability, avoiding the inconveniences, costs and global challenges of a cold chain distribution

We believe that the combination of these attributes represents a very promising profile for our investigational therapeutics, even in competitive markets. We have reported on our advances in developing RNAi therapeutics as potential drugs in a large number of peer-reviewed publications and many scientific meetings, including publications by Alnylam scientists in the journals Nature, Nature Medicine, Nature Biotechnology, Cell, Proceedings of the National Academy of Sciences, the New England Journal of Medicine and The Lancet.

Our Product Platform

We are leading the translation of RNAi as a potential new class of innovative medicines, with a focus on development and commercialization of investigational RNAi therapeutics in three STArs: Genetic Medicines; Cardio-Metabolic Diseases; and Hepatic Infectious Diseases. With RNAi therapeutics, we believe that we have created a reproducible and modular platform for drug discovery, development and commercialization of innovative medicines.

Alnylam Reproducible and Modular Platform Strategic Framework for Innovative Medicines	
	• High unmet need population
1 Genetically validated, liver-expressed target gene	• Opportunity for highly competitive profile
	• Delivery with GalNAc-conjugate platform • Blood- or urine-based
2 Biomarker for human proof-of-concept in Phase 1	• Informative disease correlation
	• Establish dose/regimen for late stage development • Clinical development plans with established endpoints
3 Definable path to potential approval and market	• Demonstrable value for payors

Delivery of RNAi Therapeutics

In recent years, a tremendous amount of progress has been made in effectively delivering RNAi therapeutics to targeted organs and cells, and we believe Alnylam has been the leader of this advancement. This delivery success is now enabling execution on our product strategy and our Alnylam 2020 strategy.

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

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

We have extensive human safety experience with our investigational RNAi therapeutics, with over 1,000 patients or volunteers dosed for up to three years of treatment in over ten clinical programs. Our data demonstrates that to date,

RNAi therapeutics have been generally well tolerated with minimal platform-related safety findings. These findings, set forth below, occur at a low incidence and are monitorable. They are also generally asymptomatic and reversible even with continued dosing. Based on data as of December 2016, these findings include:

- Low incidence (2.2 percent) of generally mild, asymptomatic, reversible liver function test increases greater than three times the upper limit of normal, or ULN
- Low incidence (15.2 percent) of generally mild, transient injection site reactions, or ISRs

In our view, this is an acceptable tolerability profile in the high unmet need indications that we pursue.

In October 2016, we announced our decision to discontinue development of revusiran. Revusiran is an investigational therapeutic approach for the treatment of cardiomyopathy due to hATTR amyloidosis, which utilized our STC-GalNAc-conjugate delivery platform. Our decision followed the recommendation of the revusiran ENDEAVOUR Phase 3 study Data Monitoring Committee, or DMC, to suspend dosing and the observation of an imbalance in mortality in revusiran-treated patients (N=17) as compared to those on placebo (N=2). This breakdown has been updated since October 2016 to reflect data available to us as of December 2016.

We are conducting a comprehensive evaluation of the revusiran data and expect this evaluation will take some time to complete, as uncertainty remains regarding the cause of the findings that led to the discontinuation of the revusiran program. Findings as of December 2016 showed that mortality events in the ENDEAVOUR trial were concentrated in the study patients with more advanced, end-stage heart failure.

Based on the ongoing evaluation there continues to be no evidence of any broader platform issue. The decision to discontinue development of revusiran did not affect patisiran or any of our other investigational RNAi therapeutic programs in development. The DMC for the APOLLO Phase 3 study of patisiran met at our request following our decision to discontinue development of revusiran, and recommended continuation of the APOLLO Phase 3 trial without modification.

We believe RNAi therapeutics represent a simplified and efficient new class of investigational medicines. We have achieved human proof of concept in multiple clinical trials of our investigational candidates, providing strong support for our approach to drug development. Moreover, we believe that our reproducible and modular platform will support our achievement of our 2020 strategy, such that by the end of 2020, we can grow into a multi-product commercial stage company with a deep and sustainable pipeline that can fuel continued growth for the future.

Our Product Pipeline

Our broad pipeline of investigational RNAi therapeutics is focused in three STArs: Genetic Medicines; Cardio-Metabolic Diseases; and Hepatic Infectious Diseases. The following is a summary of our product development programs as of January 31, 2017, that identifies those programs in which we have achieved human proof of concept, or POC, by demonstrating target gene knockdown and/or additional evidence of activity in clinical studies, the development stage of our programs and our commercial rights to such programs:

We have spent substantial funds over the past three years to develop our product pipeline and expect to continue to do so in the future. We incurred research and development costs of $382.4 million in 2016, $276.5 million in 2015 and $190.2 million in 2014.

The investigational therapeutics described below are in various stages of clinical development and the scientific information included about these therapeutics is preliminary and investigative. None of Alnylam's investigational therapeutics have been approved by the United States Food and Drug Administration, or FDA, European Medicines Agency, or EMA, or any other health authority and no conclusions can or should be drawn regarding the safety or efficacy of these therapeutics.

Late Stage Clinical Development Programs

Patisiran — Hereditary TTR-Mediated Amyloidosis

Patisiran, our most advanced investigational RNAi therapeutic in development, targets the TTR gene for the treatment of patients with polyneuropathy due to hATTR amyloidosis. hATTR amyloidosis is a progressively debilitating and often fatal disease caused by deposition of TTR in peripheral tissues. TTR protein is produced primarily in the liver and is normally a carrier of vitamin A. We believe TTR is a suitable target for an RNAi therapeutic formulated to maximize delivery to liver cells, which are the primary source of TTR synthesis. In hATTR amyloidosis, mutations in TTR result in the accumulation of damaging toxic deposits of the wild-type and mutant protein in several body organs and tissues, including the peripheral nervous system, heart and/or gastrointestinal tract. Our hATTR amyloidosis program targets wild-type and all known mutant forms of TTR, including the V30M and V122I mutations, which are the major mutations of hATTR amyloidosis, and therefore it represents a potential therapeutic approach for the treatment of all forms of hATTR amyloidosis.

hATTR amyloidosis represents a major unmet medical need with significant morbidity and mortality as an orphan, or rare, disease. Based on our analysis of the available patient and market data, we estimate that hATTR amyloidosis affects approximately 50,000 people worldwide. An estimated 10,000 people are typically classified as having predominant polyneuropathy symptoms and an estimated 40,000 people are classified as having predominant cardiomyopathy symptoms. We believe that our APOLLO and ENDEAVOUR Phase 3 studies, which targeted patients with polyneuropathy symptoms and cardiomyopathy symptoms, respectively, demonstrated that there is significant overlap between the two symptomatic presentations. Over 50 percent of patients in APOLLO had cardiac involvement at baseline and a significant percentage of ENDEAVOUR patients had polyneuropathy symptoms at baseline.

Patients with polyneuropathy due to hATTR amyloidosis have a mean life expectancy of five to 15 years from symptom onset, and the only approved treatment options for early stage disease are liver transplantation and TTR stabilizers such as tafamidis, a small molecule stabilizer of the TTR protein that has been approved for hATTR amyloidosis patients with early stage polyneuropathy in the European Union, or EU, certain countries in Latin America and Japan, where it is approved for all stages of disease. In some countries, patients may also be treated with diflunisal, a commercially available non-steroidal anti-inflammatory agent, which has been used off-label for the treatment of hATTR amyloidosis. The mean survival for patients with cardiomyopathy due to hATTR amyloidosis is approximately 2.5 to five years following diagnosis, and treatment is currently limited to supportive care. Although limited treatment options are available, there remains a significant need for novel therapeutics to treat patients with hATTR amyloidosis.

Our APOLLO Phase 3 clinical trial for patisiran is ongoing and we expect to report top-line data from APOLLO in mid-2017. Assuming that the APOLLO data are positive, we expect to submit an NDA and MAA for patisiran by the end of 2017.

- APOLLO Phase 3 Clinical Trial. In November 2013, we initiated our ongoing APOLLO Phase 3 clinical trial of patisiran. The APOLLO Phase 3 clinical trial is a randomized, double-blind, placebo-controlled, global study designed to evaluate the efficacy and safety of patisiran in hATTR amyloidosis patients. The primary endpoint of the

study is the difference in the change in the modified composite Neuropathy Impairment Score (NIS), termed "mNIS+7," between patisiran and placebo at 18 months. The mNIS+7 score is an evaluation of muscle weakness, sensory and autonomic function, and nerve conductance across a 304-point scale, where neuropathy progression leads to an increased score over time. Secondary endpoints include: the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) score; Neuropathy Impairment Score, or NIS-weakness; modified body mass index, or mBMI; timed ten-meter walk; and the COMPASS-31 autonomic symptom score. The trial was designed to enroll 200 hATTR amyloidosis patients with a baseline NIS in the range of five to 130, which represents patients with Stage 1 or Stage 2 familial amyloidotic polyneuropathy, or FAP. Patients were randomized two-to-one, patisiran-to-placebo, with patisiran administered at 0.30 mg/kg once every three weeks for 18 months by intravenous infusion. The study was designed with 90 percent power to conservatively detect as little as a 37.5 percent difference in change in mNIS+7 between treatment groups, with a two-sided alpha of 0.05. The placebo mNIS+7 progression rate was derived from an Alnylam analysis of natural history data from 283 hATTR amyloidosis patients. Patients completing the APOLLO Phase 3 clinical trial are eligible to enroll in a Phase 3 open-label extension, or OLE, study, called the APOLLO-OLE. In January 2016, we completed enrollment in our APOLLO study with a total of 225 hATTR amyloidosis patients with Stage 1 or Stage 2 disease, significantly exceeding the original anticipated enrollment of 200.

- Phase 2 OLE Clinical Trial. We have completed a Phase 2 clinical trial of patisiran. Patients participating in the Phase 2 study were eligible to participate in a Phase 2 OLE study with patisiran. The ongoing patisiran Phase 2 OLE study is an open-label, multi-center trial designed to evaluate the long-term safety and tolerability of patisiran administration. Patisiran is being administered once every three weeks at a dose of 0.30 mg/kg by intravenous infusion. The study is measuring a number of clinical endpoints every six months, including mNIS+7. In July 2016, we reported preliminary 24-month clinical data from this ongoing Phase 2 OLE study. The results for patients (N=24) who reached the 24-month endpoint as of a data cut off of May 12, 2016 showed a mean decrease of 6.7 points from baseline in mNIS+7 after 24 months of treatment. This compares favorably to an estimated mean increase (worsening) in mNIS+7 of 26 to 30 points at 24 months based upon analyses of historical data sets in untreated patients with polyneuropathy due to hATTR amyloidosis with similar baseline neurologic impairment. Similar results were seen in patients with or without concomitant use of TTR tetramer stabilizers. In a new analysis, over 70 percent of patients showed either improvement or no change in mNIS+7 at 24 months. In addition, patisiran administration was associated with statistically significant mean improvements in nerve fiber density from sweat gland biopsy samples from both the distal thigh and distal leg (p less than 0.01 for both), as read histologically in a blinded manner by a central lab. Over the 24-month period, hATTR amyloidosis patients with polyneuropathy with associated cardiac involvement (N=11) showed stability in their cardiac biomarkers, echocardiographic measures, and 10-meter walk test (i.e., gait speed). Serum TTR levels were also measured throughout the Phase 2 OLE study, and showed serum TTR reduction of up to 97 percent, a mean maximal reduction of 93 percent, and a mean reduction of 84 percent at 24 months.

In July 2016, we also presented the results of an exploratory analysis examining the relationship between the degree of serum TTR reduction with subsequent changes in mNIS+7. In the analysis, the degree of TTR reduction on Day 17 after the first dose of patisiran was compared to changes in mNIS+7 at 6, 12, 18 and 24 months. There was a positive correlation between the degree of serum TTR reduction and changes in mNIS+7. Specifically, greater degrees of TTR reduction resulted in greater levels of mNIS+7 improvement.

In the Phase 2 OLE study, patisiran administration was found to be generally well tolerated in patients with polyneuropathy due to hATTR amyloidosis out to 25 months, with no drug-related serious adverse events, or SAEs, reported through the data transfer date. The most common drug-related or possibly drug-related adverse events, or AEs, were flushing (22.2 percent) and infusion-related reactions (18.5 percent), all of which were mild in severity and did not result in any discontinuations. There were nine reports of SAEs in six patients, all of which were unrelated to study drug, including two deaths as previously reported. There were no clinically significant changes in liver function tests, renal function, or hematologic parameters, including platelet counts.

We expect to report 36-month data from the patisiran Phase 2 OLE study in late 2017.

The Committee for Orphan Medicinal Products, or COMP, of the EMA has designated patisiran as an orphan medicinal product for the treatment of ATTR amyloidosis. In addition, the FDA provided Orphan Drug Designation to patisiran as a therapeutic approach for the treatment of ATTR amyloidosis. The FDA has also granted Fast Track designation to patisiran for the treatment of hATTR amyloidosis with polyneuropathy.

In January 2014, we entered into the 2014 Sanofi Genzyme collaboration, which is an exclusive relationship for the worldwide development and commercialization of RNAi therapeutics in the field of Genetic Medicines, which includes our current and future Genetic Medicine programs that reach human proof-of-principal study completion, or Human POP, by the end of 2019, subject to extension to the end of 2021 in various circumstances. Under this collaboration, we are leading development and commercialization of patisiran in the United States, Canada and Western Europe while Sanofi Genzyme will develop and commercialize the product in the Sanofi Genzyme Territory. The 2014 Sanofi Genzyme collaboration is described below under the heading “Strategic Alliances.”

Fitusiran — Hemophilia and Rare Bleeding Disorders

Fitusiran is a subcutaneously administered, investigational RNAi therapeutic targeting antithrombin, or AT, for the treatment of hemophilia A and B and rare bleeding disorders, or RBD. Fitusiran is designed to lower levels of AT with the goal of promoting sufficient thrombin generation to prevent bleeding in patients with hemophilia and RBD. AT, also known as "antithrombin III" and "SERPINC1," is a liver expressed plasma protein and member of the “serpin” family of proteins that acts by inactivating thrombin and other coagulation factors. AT plays a key role in normal hemostasis by helping to limit the process of fibrin clot formation. However, in hemophilia, insufficient thrombin generation results in impaired fibrin clot formation. Lowering AT in the hemophilia setting may promote the generation of sufficient levels of thrombin needed to form an effective fibrin clot and prevent bleeding. This rationale is supported by human genetic data suggesting that co-inheritance of thrombophilic mutations, including AT deficiency, may ameliorate bleeding in hemophilia. We believe this approach is a unique and innovative strategy for preventing bleeding in people with hemophilia.

Hemophilia is an inherited bleeding disorder characterized by recurrent bleeding episodes, typically into the joints and muscles. Recurrent bleeding into joints results in arthritis and joint damage, reducing mobility and often requiring joint replacement surgeries. There are approximately 200,000 persons diagnosed with hemophilia worldwide. Hemophilia A, or HA, is defined by loss-of-function mutations in factor VIII and hemophilia B, or HB, is defined by a loss-of-function mutation in factor IX. In patients with hemophilia, a deficiency in plasma proteins factor VIII or factor IX prevents the generation of thrombin to levels that are sufficient to prevent or stop bleeding. Other RBD are defined by deficiencies of blood coagulation factors, including Factors II, V, VII, X and XI. Based on our analysis of the available patient and market data, we estimate that there are approximately 1,000 persons worldwide with a severe bleeding phenotype because of these conditions. The goal of treatment for persons living with hemophilia is to prevent bleeding, establish prompt management of bleeds, and manage the complications of bleeding and treatment. Current guidelines recommend management of hemophilia with regular intravenous infusions of recombinant or human-derived clotting factors. The most serious treatment-related complication is the development of antibodies, known as inhibitors, to replacement factor. Inhibitor development can occur in both HA and HB, impacting as many as one-third of people with severe HA, and persons in this inhibitor subset become refractory to standard replacement therapy. There exists a significant need for novel therapeutics to treat people living with hemophilia and RBD.

We believe fitusiran has the potential to prevent bleeding in severe HA and HB patients and in patients with other RBD. We are evaluating fitusiran in an ongoing Phase 1 study in HA and HB patients, with and without inhibitors, as well as in a Phase 2 OLE study. We plan to initiate our ATLAS Phase 3 program in early 2017. Subject to continued diligence and health authority feedback, the ATLAS program is expected to consist of three separate Phase 3 clinical trials: ATLAS-INH in severe HA and HB patients with inhibitors; ATLAS-A/B in severe HA and HB patients without inhibitors; and, ATLAS-PPX in severe HA and HB patients with or without inhibitors, switching from prophylactic factor or bypassing agent therapy to fitusiran prophylaxis.

- Phase 1/Phase 2 OLE Clinical Trials. The ongoing Phase 1 clinical trial of fitusiran is a single- and multi-dose, dose-escalation study comprised of four parts. Part A - which is complete - was a randomized, single-blind, placebo-controlled, single-dose, dose-escalation study (N=4 per cohort; 3:1 randomization of drug:placebo) in healthy volunteers. This part of the study was completed after the first dose cohort received a single subcutaneous dose of fitusiran at 30 micrograms per kilogram, or mcg/kg. Part B of the study - which is also complete - was an open-label, multi-dose, dose-escalation study that enrolled 12 patients with severe HA or HB. Patients in Part B received three weekly subcutaneous injections of fitusiran at doses of 15, 45, or 75 mcg/kg. Part C of the study - which has completed dosing - is an open-label, multi-dose, dose escalation study that enrolled 18 patients with moderate or severe hemophilia A or B without inhibitors. Twelve patients in Part C received three monthly subcutaneous doses of fitusiran at doses of 225, 450, 900, or 1800 mcg/kg. In addition, six patients in Part C received three fixed monthly subcutaneous doses of fitusiran at 80 mg. Part D of the study is designed to enroll up to 18 patients with inhibitors. Patients in Part D received three fixed monthly subcutaneous doses of fitusiran at 50 mg or 80 mg. The primary objective of Parts B, C, and D of the study is to evaluate the safety and tolerability of multiple doses of subcutaneously administered fitusiran in patients with hemophilia, with and without inhibitors. Secondary objectives include assessment of clinical activity as determined by lowering of plasma AT levels and increase in thrombin generation at pharmacologic doses of fitusiran. In addition, exploratory analyses of bleeding are being performed.

Patients with and without inhibitors who complete dosing in the Phase 1 trial are eligible to roll over into the fitusiran Phase 2 OLE study.

- Phase 1 Data – HA and HB Patients with Inhibitors. In December 2016, we reported interim results, as of the data cut-off date of October 6, 2016, from Part D of our ongoing fitusiran Phase 1 study in patients with HA or HB with inhibitors who were enrolled in two separate dose cohorts of 50 mg, once-monthly (N=6) or 80 mg, once-monthly (N=10). Treatment with fitusiran resulted in potent and dose-dependent lowering of AT and increases in thrombin generation. In an exploratory analysis of bleeding events, a median annualized bleeding rate, or ABR, of zero was

achieved for patients in combined dose cohorts in the observation period, compared to the pre-study median ABR of 31.

- Phase 2 OLE Data – HA and HB Patients without Inhibitors. In December 2016, we reported results, as of the data cut-off date of October 6, 2016, from our ongoing Phase 2 fitusiran OLE study in 16 HA or HB patients without inhibitors. All patients were previously enrolled in the fitusiran Phase 1 study, receiving 3 weekly or 3 monthly subcutaneous doses ranging from 45 mcg/kg to 1800 mcg/kg. In the Phase 2 OLE study, fitusiran was administered subcutaneously once-monthly at two fixed dose levels, 50 mg (N=8) and 80 mg (N=8), with patients receiving up to 14 months of continuous dosing. Both dose levels achieved mean AT lowering of approximately 80 percent and mean increases in thrombin generation levels approaching the lower end of the range observed in normal healthy individuals in Part A of the Phase 1 study. In an exploratory post hoc analysis of bleed events, fitusiran achieved a median overall ABR of 1.0, over a median observation period of 5.7 months, compared to a median pre-study ABR of 4.0.

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- Safety. As of the data cut-off date of October 6, 2016, a total of 41 HA or HB patients were exposed to fitusiran in our ongoing Phase 1 and Phase 2 OLE studies. Fitusiran was generally well tolerated with the longest period of exposure of up to 14 months of continuous treatment. There were no drug-related SAEs and no thromboembolic events or laboratory evidence of pathologic clot formation through the data cut-off date. One non-inhibitor patient discontinued due to an AE described as non-cardiac chest pain considered severe and possibly related to study drug. The majority of AEs were mild or moderate in severity, with the most common AEs consisting of mild ISRs in 17 patients (41 percent). Asymptomatic and reversible alanine aminotransferase, or ALT, increases greater than three times ULN, without concurrent elevations in bilirubin greater than two times ULN, were observed in seven patients (17 percent); six of these patients had a medical history of hepatitis C infection. All breakthrough bleed events were successfully managed with standard replacement factor or bypassing agents.

Fitusiran has received Orphan Drug Designation for HA and HB in the United States and the EU.

In September 2015, Sanofi Genzyme elected to opt into a regional license for fitusiran and began funding the program under the regional license terms in January 2016. In November 2016, Sanofi Genzyme elected to expand its regional rights and opt-in to co-develop and co-commercialize fitusiran in the United States, Canada and Western Europe, in addition to developing and commercializing the product in the Sanofi Genzyme Territory. In connection with the exercise of this right, Sanofi Genzyme paid us in January 2017 for their incremental share of co-development costs incurred from January 2016 to September 2016 in accordance with the 2014 Sanofi Genzyme collaboration. The 2014 Sanofi Genzyme collaboration is described below under the heading “Strategic Alliances.”

Inclisiran (ALN-PCSsc) — Hypercholesterolemia

Inclisiran is a subcutaneously administered, investigational RNAi therapeutic targeting proprotein convertase subtilisin/kexin type 9, or PCSK9, for the treatment of hypercholesterolemia. PCSK9 is a protein involved in the regulation of low-density lipoprotein receptor, or LDL receptor, levels on hepatocytes and the metabolism of LDL cholesterol, or LDL-C, which is commonly referred to as “bad” cholesterol. PCSK9 is produced by the liver and circulates in the bloodstream. Both intracellular and extracellular PCSK9 reduce the liver’s capacity to absorb LDL-C by decreasing LDL receptor levels. Published case reports have shown individuals with loss-of-function genetic mutations in PCSK9 have decreased blood cholesterol levels and a dramatically reduced risk of coronary artery disease, or CAD, including myocardial infarction or heart attack.

Hypercholesterolemia is a condition characterized by very high levels of cholesterol in the blood which is known to increase the risk of CAD, the leading cause of death in the United States. Some forms of hypercholesterolemia can be treated through dietary restrictions, lifestyle modifications (e.g., exercise and smoking cessation) and medicines such as statins. However, many patients with hypercholesterolemia are unable to lower their LDL-C to a level which reduces the risk of major cardiovascular events with lifestyle modifications and statins alone. In addition, high-risk subpopulations such as familial hypercholesterolemia patients, acute coronary syndrome patients and other statin intolerant patients often have residual risk of adverse cardiovascular outcomes that would benefit from more efficacious treatment. Severe forms of hypercholesterolemia are estimated to affect millions of patients worldwide, and as a result, there is a significant need for novel therapeutics to treat patients with hypercholesterolemia whose disease is inadequately managed by existing therapies.

In February 2013, we and MDCO entered into a license and collaboration agreement pursuant to which we granted to MDCO an exclusive, worldwide license to develop, manufacture and commercialize RNAi therapeutics targeting PCSK9 for the treatment of hypercholesterolemia and other human diseases. Under the terms of the agreement, we

were responsible for conducting certain pre-clinical studies, as well as the Phase 1 clinical study of inclisiran, and MDCO is responsible for leading and funding development from Phase 2 forward, as well as potential commercialization. Under the terms of the agreement with MDCO, the development leadership of inclisiran has now transferred from us to MDCO. A description of our agreement with MDCO is included below under the heading "Strategic Alliances."

MDCO is conducting ORION-1, an ongoing Phase 2 clinical trial of inclisiran. In addition, in January 2017, MDCO announced the initiation of the ORION-2 study of inclisiran in patients with homozygous familial hypercholesterolemia, or HoFH, as well as the ORION-3 study, which is a Phase 2 OLE cross-over study for patients completing the ongoing ORION-1 study. Based on interim results from ORION-1, MDCO has announced its intention to progress inclisiran into Phase 3 development.

- ORION-1 Phase 2 Clinical Trial. In November 2016, we and MDCO reported positive initial data from a randomized, double-blind, placebo-controlled Phase 2 clinical study of inclisiran, known as ORION-1, being conducted by MDCO. Among 189 randomized and treated patients who had been followed for 180 days or more by the interim data cut-off date of October 25, 2016, a single 300 mg subcutaneous injection of inclisiran achieved mean LDL-C reductions of 59 percent at Day 60, which were durable to Day 90 (mean 50 percent) and Day 180 (mean 43

percent and up to 81 percent). Two 300 mg injections of inclisiran - one given on Day 1 and one on Day 90 - achieved a mean LDL-C reduction of 57 percent at Day 120, which was durable to Day 180 (mean 52 percent and up to 81 percent). All differences relative to placebo in these 189 patients were statistically significant ($p < 0.0001$). Inclisiran represents the largest safety experience for one of our investigational RNAi therapeutics to date. As of the data cut-off date of October 25, 2016 (N=501), inclisiran was generally well tolerated and no material safety issue was observed, including no significant elevations of liver enzymes considered related to study medication and no neuropathy or change in renal function. The overall incidence of treatment emergent AEs was 54 percent both in patients randomized to placebo and in patients randomized to inclisiran, with no differences between inclisiran doses. ISRs with inclisiran were infrequent (observed in 3.2 percent of patients), mild or moderate, and transient. One fatal myocardial infarction was reported as unrelated to study drug, and one patient with ALT greater than three times ULN was attributed to concomitant statin use.

In January 2017, MDCO reported positive top-line results from its interim analysis with Day 180 follow-up for all 501 patients enrolled in the ORION-1 Phase 2 study. As reported by MDCO, in the interim analysis, inclisiran continued to demonstrate significant and durable LDL-C reduction, supporting the potential for a low-volume dosing regimen of two or three injections per year. Inclisiran was well tolerated and no material safety issue, including no investigational drug-related elevation of liver enzymes, neuropathy or change in renal function, was observed. ISRs with inclisiran were infrequent, mild or moderate, and transient.

Data from our Phase 1 study of inclisiran were published in the New England Journal of Medicine Jan. 2017.

Early Stage Clinical Development Programs

Givosiran — Acute Hepatic Porphyrias

Givosiran is a subcutaneously administered, investigational RNAi therapeutic targeting aminolevulinate synthase-1, or ALAS-1, for the treatment of acute hepatic porphyrias, or AHPs. The porphyrias are a family of rare metabolic disorders predominately caused by a genetic mutation in one of the eight enzymes responsible for heme biosynthesis. AHPs constitute a subset of porphyrias that are characterized by acute neurovisceral attacks and in some instances, skin manifestations. The enzyme deficiency in AHP occurs within the liver, and includes acute intermittent porphyria, or AIP, hereditary coproporphyria, variegate porphyria and hereditary delta-aminolevulinic acid dehydratase deficiency which is extremely rare. The initial focus of the givosiran program is on AIP, the most common AHP, which is an ultra-rare disease caused by loss of function mutations in porphobilinogen deaminase, or PBGD, that can result in the upstream accumulation of toxic heme intermediates, including aminolevulinic acid, or ALA, and porphobilinogen, or PBG. Exposure of AIP patients to certain drugs, dieting or hormonal changes can trigger strong induction of ALAS-1, the first and rate-limiting enzyme in the pathway, which can lead to accumulation of the toxic heme intermediates that precipitate disease symptoms. Patients with one of the AHPs can have acute and/or recurrent attacks that are characterized by severe abdominal pain, paresis or paralysis, neuropsychiatric manifestations, cutaneous lesions and, in some instances, death if untreated or if treatment is delayed. In addition, more than 50 percent of AHP patients report chronic porphyria symptoms, most commonly pain, while not having acute attacks.

It is estimated that approximately 5,000 patients in the United States and Europe suffer sporadic AIP attacks annually, and approximately 1,000 patients are afflicted with recurrent, debilitating attacks. The only approved treatments for acute attacks are preparations of heme derived from human blood. Heme requires administration through a large vein or central venous catheter and is associated with a number of side effects including thrombophlebitis, coagulation abnormalities, headaches and hypersensitivity reactions. While heme is not approved for prophylactic use (i.e., the prevention of acute attacks), it is sometimes used in this manner in patients who experience recurrent attacks. Chronic administration of heme has been found to result in renal insufficiency, iron overload, systemic infections (due to the requirement for central venous access) and, in some instances, tachyphylaxis. In addition, given the short half-life of

hemin (10.8 hours), its beneficial effect on the toxic precursors ALA and PBG is short lived. As a result, patients may require hemin infusions as frequently as bi-weekly and often have significant chronic symptoms in between infusions. There is a clear unmet need for new therapies for AIP that could be both safer and more effective and more convenient to administer than available therapies.

Givosiran has the potential to be a prophylactic approach for the prevention of recurrent attacks, as well as a therapy for the treatment of acute porphyria attacks. We are evaluating givosiran in an ongoing Phase 1 study and expect to present additional data from Part C of this study in mid-2017. We plan to initiate a Phase 3 clinical trial for givosiran in late 2017, subject to communications with regulatory authorities.

- Phase 1 Givosiran Study. The Phase 1 study is being conducted in three parts. Parts A and B, which have completed dosing, were randomized (3:1, drug:placebo), single-blind, single-dose (Part A) and multi-dose (Part B), dose-escalation studies, designed to enroll up to a total of 40 “asymptomatic high excreter,” or ASHE, subjects with a

defined mutation in the PBGD gene and elevated urinary levels of ALA and PBG, but no current porphyria attacks. The primary objective of Parts A and B was to evaluate safety and tolerability of single and multiple subcutaneous doses of givosiran. Secondary objectives included evaluation of clinical activity for givosiran as measured by reduction in plasma and urinary levels of ALA and PBG. Exploratory objectives include the impact of givosiran on liver ALAS-1 messenger RNA, or mRNA, as measured from serum or urinary exosomal mRNA preparations. Part C, initiated in February 2016, is a randomized (3:1, drug:placebo), double-blind, multi-dose study in up to 20 AIP patients who experience recurrent porphyria attacks. Patients are initially followed in a three-month run-in phase, where the number and frequency of porphyria attacks and levels of ALA and PBG are measured prospectively. Patients who experience at least one porphyria attack during the run-in phase are then eligible to enter the six-month treatment phase of the study, where they are randomized to receive two once-quarterly doses or four once-monthly doses of placebo or givosiran. During the treatment phase, the effects of placebo or givosiran on the number and frequency of porphyria attacks, as well as on the levels of ALA and PBG, are measured prospectively and then compared to run-in phase results. Additional measures include safety, tolerability, hospitalizations, use of hemin, levels of ALAS-1 mRNA, and givosiran pharmacokinetics. Following the treatment phase, all patients are eligible to receive givosiran in an OLE study.

We reported interim data from Parts A and B of our Phase 1 study in September 2016. Results as of the data transfer date of June 28, 2016 showed that givosiran administration resulted in rapid, dose-dependent and durable silencing of liver ALAS-1 mRNA in both Part A (N=20) and Part B (N=8) of the trial. In addition, data showed rapid and dose-dependent lowering of ALA and PBG of up to 95 percent. Reductions in ALA and PBG were highly durable, with effects lasting for over ten months after a single dose. Givosiran continued to be generally well tolerated in ASHE subjects as of the data transfer date. There were three SAEs that were all deemed to be unlikely related to study drug. With the exception of one AE that was severe and unrelated to study drug, all other AEs were mild or moderate in severity, most commonly including abdominal pain, diarrhea, hypoesthesia, nasopharyngitis, pruritis and rash. There were no clinically significant changes in vital signs, electrocardiograms, clinical laboratory parameters, or physical examination.

In December 2016, we reported positive initial clinical activity results for givosiran from Cohorts 1 and 2 of Part C of our Phase 1 study. Data included unblinded results for Cohort 1 (N=4, 2.5 mg/kg given once-quarterly) and aggregated, blinded results for Cohort 2 (N=4, 2.5 mg/kg given once-monthly) given that the patients in Cohort 2 were still in the treatment phase of the study. Consistent with results in ASHE patients, givosiran administration resulted in robust and durable lowering of ALA and PBG. In Cohort 1, givosiran administration resulted in meaningful reductions in the number and frequency of porphyria attacks. Specifically, as compared with the run-in phase, there was a 74 percent mean decrease in the annualized attack rate and a 75 percent mean reduction in annualized hemin administration. In addition, the maximum attack-free interval (i.e., the greatest period of time between porphyria attacks) was a mean of approximately 10.5 times that observed during the run-in phase. Favorable treatment effects in all three parameters were seen in each of the givosiran-treated patients. In contrast, the single placebo patient in Cohort 1 showed a generally similar number and frequency of porphyria attacks and a generally similar amount of hemin usage during the run-in and treatment phases. Finally, the aggregated blinded data for Cohort 2 patients, with approximately three months of treatment phase data, provided additional evidence of clinical activity. Specifically, as compared with the run-in phase, Cohort 2 patients receiving placebo or givosiran showed a 50 percent mean reduction in annualized attack rate and a 76 percent mean reduction in annualized hemin doses administered; the maximum attack-free interval was a mean of approximately 2.4 times that observed during the run-in phase.

As of the data transfer on November 7, 2016, there were no drug-related SAEs reported in Cohorts 1-4. In Cohort 3, which remains blinded, one death was reported after the data transfer date due to acute pancreatitis, complicated by a pulmonary embolism; the death was considered to be unlikely related to givosiran or placebo by the investigator and the study's Safety Review Committee. In Cohorts 1 and 2, there were no discontinuations due to AEs. Possibly or definitely related AEs reported in two or more cases were ISRs and myalgia; all of these events were mild. There were no other clinically significant changes in vital signs, electrocardiograms, clinical laboratory parameters or physical

examination.

Givosiran has received Orphan Drug Designation in the United States and the EU for the treatment of AHPs.

During 2016, Sanofi Genzyme elected not to opt into the development and commercialization of givosiran in the Sanofi Genzyme Territory, providing us with full global control of the program for further development and commercialization, if approved. The 2014 Sanofi Genzyme collaboration is described below under the heading “Strategic Alliances.”

Other Early Stage Clinical Programs

ALN-CC5 — Complement-Mediated Diseases

- Subcutaneously administered, investigational RNAi therapeutic targeting the C5 component of the complement pathway for the treatment of complement-mediated diseases. The complement system plays a central role in immunity as a protective mechanism for host defense, but its dysregulation results in life-threatening complications in a broad range of human diseases including paroxysmal nocturnal hemoglobinuria, or PNH, atypical hemolytic-uremic syndrome, or aHUS, myasthenia gravis, neuromyelitis optica and membranous nephropathy, amongst others. Complement component 5, which is predominantly expressed in liver cells, is a genetically and clinically validated target.
- Dosing completed in a Phase 1/2 clinical trial. The Phase 1/2 trial was conducted in three parts. Parts A and B were randomized (3:1, drug:placebo), double-blind, placebo-controlled, single ascending dose, or SAD, and multiple ascending dose, or MAD, studies, respectively, which enrolled 56 healthy adult volunteers. These parts of the study were designed to evaluate safety and tolerability of single and multiple subcutaneous doses of ALN-CC5. In December 2016, we reported new results from Part C of the Phase 1/2 trial, which provided evidence that ALN-CC5-mediated knockdown of serum C5 has the potential to enable effective sparing of dose level and frequency of eculizumab in patients with PNH. As of the data transfer date of October 13, 2016, results showed that PNH patients who had previously been naive to eculizumab (N=3) achieved sustained control of disease hemolysis by achieving normalization of LDH to less than or at approximately 1.5 times ULN for up to six months while on a spared eculizumab regimen of 600 mg every four weeks (normal dose for eculizumab 900 mg every two weeks). For patients who entered the study on background eculizumab (N=3), effective disease control with normalization of LDH to less than or at approximately 1.5 times ULN was achieved for up to five months while on a spared regimen of 900 mg eculizumab dosed every four weeks. Using an assay for eculizumab plasma levels, both sparing regimens achieved stable eculizumab trough levels greater than 100 mcg/mL during the five to six month period.
- ALN-CC5 generally well tolerated in patients with PNH after multiple doses for up to 16 weeks of dosing. As of the data transfer date of October 13, 2016, there were no SAEs or discontinuations due to AEs in the study, and the majority of reported AEs were mild or moderate in severity. One patient had a mild injection site reaction which was deemed possibly or definitely related to study drug, and one patient had a severe AE reported as hepatoxicity, which was asymptomatic grade 3 transaminitis, transient and without increase in total bilirubin. Further, under the ongoing pharmacodynamic effects of ALN-CC5, the transaminase elevations returned to baseline and the patient remained in the study.
- During 2016, Sanofi Genzyme elected not to opt into the development and commercialization of ALN-CC5 in the Sanofi Genzyme Territory, providing us with full global control of the program for further development and commercialization, if approved. The 2014 Sanofi Genzyme collaboration is described below under the heading "Strategic Alliances."

ALN-GO1 — Primary Hyperoxaluria 1

- Subcutaneously administered, investigational RNAi therapeutic, for the treatment of primary hyperoxaluria type 1, or PH1, an ultra-rare inherited orphan disease in which the lack of a particular liver enzyme causes the body to produce excess amounts of a substance called oxalate. This leads to a buildup of insoluble calcium oxalate, causing kidney failure and further organ damage for some patients in infancy and most patients by their mid-twenties. About 50 percent of patients will have kidney failure by age 15, and about 80 percent will have end stage renal disease by age 30. ALN-GO1 targets the gene for glycolate oxidase, GO, an enzyme that works upstream of the defect in PH1 patients, and is designed to starve the pathway of substrate for oxalate production with the goal of preventing its associated pathology. Current treatment options are very limited, and include frequent renal dialysis or combined organ transplantation of liver and kidneys, a procedure with high morbidity that is limited due to organ availability. Although a small minority of patients respond to vitamin B6 supplementation, there are no approved pharmaceutical therapies for PH1.
- Dosing in a randomized, single-blind, placebo-controlled Phase 1/2 clinical trial ongoing. Part A is a single-dose study that enrolled 32 healthy adult volunteers. Part B will be a multi-dose study designed to enroll up to a total of 20 patients with PH1. The primary objective is to evaluate safety and tolerability of single and multiple subcutaneous doses of ALN-GO1. In September 2016, we reported initial data (N=32) as of the data transfer dates on August 17, 2016 (for safety) and September 2, 2016 (for pharmacodynamic activity). ALN-GO1 administration resulted in dose-dependent and statistically significant (nominal two-sided p values less than 0.05) increases from baseline in plasma and urinary glycolate as compared to placebo, with up to an 8-fold increase in plasma glycolate in the highest dose cohort. The effects of ALN-GO1 were highly durable, with levels sustained through 85 days at the highest dose, supportive of a once-monthly and possibly once-quarterly subcutaneous dose regimen.
- Single doses of ALN-GO1 were shown to be generally well tolerated in healthy adult volunteers. There were no SAEs reported. AEs were reported in 88 percent (N=21) of ALN-GO1 treated subjects and 63 percent (N=5) of placebo treated subjects. Common AEs occurring in greater than 10 percent of ALN-GO1 treated subjects included nasopharyngitis (N=6), headache (N=5), and transient injection site pain (N=4). All AEs were mild to moderate with the exception of one subject in the lowest dose cohort who had transient, asymptomatic creatine phosphokinase elevation which was unrelated to study drug.
- ALN-GO1 has been granted Orphan Drug Designation in the United States and the EU for the treatment of PH1.

ALN-TTRsc02 — TTR-Mediated Amyloidosis

- Subcutaneously administered, investigational RNAi therapeutic targeting TTR for the treatment of ATTR amyloidosis; represents an extension of our program for ATTR amyloidosis.
- Phase 1 randomized, placebo-controlled, single ascending-dose study in healthy volunteers ongoing. Data (N=48) reported in December 2016 demonstrated that single subcutaneous doses of ALN-TTRsc02 achieved robust serum TTR reduction of up to 98.4 percent (mean max of 97.1 ± 0.5 percent), with durability for well over four months. At a dose of 50 mg, ALN-TTRsc02 achieved a mean TTR reduction at day 90 of 86.2 percent. Based on these results, we believe that a once-quarterly, fixed dose of 25 to 50 mg of ALN-TTRsc02 could achieve clamped and potentially clinically-meaningful reductions of TTR exceeding 80 percent.
- Generally well tolerated in healthy volunteers, with no SAEs and no discontinuations due to AEs. All AEs reported were mild or moderate in severity and included transient ISRs (redness and pain), pruritus, cough, nausea, fatigue and abdominal pain. No clinically significant changes were reported in hematologic or laboratory parameters (e.g., liver function tests), vital signs or physical exams.

ALN-HBV — Hepatitis B Virus (HBV)

- Subcutaneously administered, investigational RNAi therapeutic, ALN-HBV, targeting the hepatitis B virus, or HBV, genome for the treatment of chronic hepatitis B. Chronic HBV infection is the most common serious liver infection in the world. Worldwide, two billion people (one out of three people) have been infected with HBV and an estimated 240 - 290 million people have become chronically infected. The clinical manifestations are severe. Nearly 25 percent

of chronic HBV patients develop serious liver diseases such as cirrhosis, fibrosis and hepatocellular carcinoma. An estimated one million people die each year from HBV infection and its complications worldwide; about 5,000 of those are in the United States. Despite the use of nucleoside analog inhibitors of viral DNA synthesis and interferon therapies, the cure rate for chronic HBV infection is less than ten percent. Reduction in HBV surface antigen, or HBsAg, levels of over 0.5 $\log_{10}$ is the single best predictor of immunologic cure. We believe an RNAi therapeutic

inhibiting all steps of the HBV life cycle and silencing tolerogenic viral antigens has the potential to achieve a "functional cure."

- Phase 1/2 randomized, single-blind, placebo-controlled study is ongoing. Part A is a single-dose study designed to enroll up to a total of 24 normal healthy volunteers. Part B will be a single-dose study designed to enroll up to a total of 28 patients with chronic HBV infection. Part C will be a multi-dose study designed to enroll up to a total of 48 patients with chronic HBV infection. The primary objective of the study is to evaluate safety and tolerability of single and multiple subcutaneous doses of ALN-HBV. Our ALN-HBV program derives from our 2014 acquisition of the RNAi assets of Merck Sharp & Dohme Corp., or Merck, including Sirna Therapeutics, Inc., or Sirna.

Our Collaboration and Licensing Strategy

Our business strategy is to develop and commercialize a broad pipeline of RNAi therapeutic products directed towards our three STArs: Genetic Medicines; Cardio-Metabolic Diseases; and Hepatic Infectious Diseases. As part of this strategy, we have entered into, and expect to enter into additional, collaboration and licensing agreements as a means of obtaining resources, capabilities and funding to advance our investigational RNAi therapeutic programs.

Our collaboration strategy is to form alliances that create significant value for ourselves and our collaborators in the advancement of RNAi therapeutics as a potential new class of innovative medicines. Specifically, with respect to our Genetic Medicine pipeline, we formed a broad strategic alliance with Sanofi Genzyme in 2014 pursuant to which we retain development and commercial rights for our current and future Genetic Medicine products in the United States, Canada and Western Europe, and Sanofi Genzyme will develop and commercialize our current and future Genetic Medicine products for which it elects to opt-in, in the rest of the world, 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 development and commercialization rights. We currently have a global alliance with MDCO for the development and commercialization of our inclisiran program.

We also have entered into license agreements to obtain rights to intellectual property in the field of RNAi. In addition, because delivery of RNAi therapeutics has historically been an important objective of our research activities, we have entered into various collaboration and licensing arrangements with other companies and academic institutions to gain access to delivery technologies, including various LNP delivery technologies.

Strategic Alliances

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

Product Alliances.

Sanofi Genzyme. In January 2014, we entered into a global, strategic collaboration with Sanofi Genzyme to discover, develop and commercialize RNAi therapeutics as Genetic Medicines to treat orphan diseases. The 2014 Sanofi Genzyme collaboration is structured as an exclusive relationship for the worldwide development and commercialization of RNAi therapeutics in the field of Genetic Medicines, which includes our current and future Genetic Medicine programs that reach Human POP by the end of 2019, subject to extension to the end of 2021 in various circumstances. We will retain product rights in the United States, Canada and Western Europe, referred to as the Alnylam Territory, while Sanofi Genzyme will obtain exclusive rights to develop and commercialize collaboration products in the rest of the world, referred to as the Sanofi Genzyme Territory, together with certain broader co-development/co-commercialize or worldwide rights for certain products. Sanofi Genzyme's rights are structured as

an opt-in that is triggered upon achievement of Human POP. We maintain development control for all programs prior to Sanofi Genzyme's opt-in and maintain development and commercialization control after Sanofi Genzyme's opt-in for all programs in the Alnylam Territory.

Upon the closing of the equity transaction in February 2014, we sold to Sanofi Genzyme 8,766,338 shares of our common stock and Sanofi Genzyme paid $700.0 million in aggregate cash consideration to us. As a condition to the closing of the equity transaction, Sanofi Genzyme entered into an investor agreement with us containing provisions regarding Sanofi Genzyme's holding and "standstill" obligations, additional purchase, voting and registration rights, as well as certain other rights and obligations of the parties.

For more information regarding the 2014 Sanofi Genzyme collaboration, including its ongoing financial and accounting impact on our business, please read Note 3, Significant Agreements, to our consolidated financial statements included in Part II, Item 8, "Financial Statements and Supplementary Data," of this annual report on Form 10-K.

The Medicines Company. In February 2013, we and MDCO entered into a license and collaboration agreement pursuant to which we granted to MDCO an exclusive, worldwide license to develop, manufacture and commercialize RNAi therapeutics targeting PCSK9 for the treatment of hypercholesterolemia and other human diseases. Under the MDCO agreement, we had responsibility for the development of inclisiran until Phase 1 Completion, as defined in the MDCO agreement, at our cost. In late 2015, MDCO assumed responsibility for all development and commercialization of inclisiran, at its sole cost, and is advancing inclisiran into late stage development. For more information regarding the MDCO agreement, including its ongoing financial and accounting impact on our business, please read Note 3, Significant Agreements, to our consolidated financial statements included in Part II, Item 8, "Financial Statements and Supplementary Data," of this annual report on Form 10-K.

Platform Alliances.

Monsanto Company. In August 2012, we and Monsanto Company, or Monsanto, entered into a license and collaboration agreement, pursuant to which we granted to Monsanto a worldwide, exclusive, royalty bearing right and license, including the right to grant sublicenses, to our RNAi platform technology and intellectual property controlled by us as of the date of the Monsanto agreement or during the 30 months thereafter, in the field of agriculture. The Monsanto agreement also included the transfer of technology from us to Monsanto and initially included a collaborative research project. Under the Monsanto agreement, Monsanto will be our exclusive collaborator in the agriculture field for a ten-year period. For more information regarding the Monsanto agreement, including its ongoing financial and accounting impact on our business, please read Note 3, Significant Agreements, to our consolidated financial statements included in Part II, Item 8, "Financial Statements and Supplementary Data," of this annual report on Form 10-K.

Takeda Pharmaceutical Company Limited. In May 2008, we entered into a license and collaboration agreement with Takeda Pharmaceutical Company Limited, or Takeda, to pursue the development and commercialization of RNAi therapeutics. Under the Takeda agreement, we granted to Takeda a non-exclusive, worldwide, royalty-bearing license to our intellectual property, including delivery-related intellectual property, controlled by us as of the date of the Takeda agreement or during the five years thereafter, to develop, manufacture, use and commercialize RNAi therapeutics, subject to our existing contractual obligations to third parties. The license initially is limited to the fields of oncology and metabolic disease and may be expanded at Takeda's option to include other therapeutic areas, subject to specified conditions. For more information regarding the Takeda agreement, including its ongoing financial and accounting impact on our business, please read Note 3, Significant Agreements, to our consolidated financial statements included in Part II, Item 8, "Financial Statements and Supplementary Data," of this annual report on Form 10-K.

Other Strategic License Agreements.

Ionis Pharmaceuticals, Inc. (formerly Isis Pharmaceuticals, Inc.). In January 2015, we and Ionis Pharmaceuticals, Inc., or Ionis, entered into a second amended and restated strategic collaboration and license agreement, which we further amended in July 2015. The 2015 Ionis agreement provides for certain new exclusive target cross-licenses of intellectual property on eight disease targets, providing each company with exclusive RNA therapeutic license rights for four programs, and extends the parties' existing non-exclusive technology cross-license, which was originally entered into in 2004 and was amended and restated in 2009, through April 2019. Under the original agreement, Ionis licensed to us its patent estate related to antisense motifs and mechanisms and oligonucleotide chemistry for

double-stranded RNAi products. In turn, we non-exclusively licensed to Ionis our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded antisense therapeutics, single stranded RNAi therapeutics and to research double-stranded RNAi compounds. Ionis also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on a non-exclusive basis. For more information regarding the 2015 Ionis agreement, including its ongoing financial and accounting impact on our business, please read Note 3, Significant Agreements, to our consolidated financial statements included in Part II, Item 8, “Financial Statements and Supplementary Data,” of this annual report on Form 10-K.

Intellectual Property Licenses

In December 2002, we entered into a co-exclusive license with Max Planck Innovation GmbH (formerly known as Garching Innovation GmbH), or Max Planck Innovation, for the worldwide rights to use and sublicense certain patented technology to develop and commercialize therapeutic products and related applications. We also obtained the rights to use, without the right to sublicense, the technology for all diagnostic uses other than for the purposes of therapeutic monitoring. We were also given the right to acquire the remaining 50 percent exclusive rights, which right we exercised upon our acquisition of Ribopharma AG in July 2003. In June

2005, we entered into an amendment to our agreement with Max Planck Innovation that secured our exclusivity to use and sublicense certain patented technology to develop and commercialize therapeutic products and related applications.

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

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

Delivery-Related License Agreements

Arbutus. In November 2012, we, Arbutus Biopharma Corporation, or ABC (formerly Tekmira Pharmaceuticals Corporation), and Protiva Biotherapeutics, Inc., a wholly owned subsidiary of ABC, and together with ABC, referred to as Arbutus, agreed to restructure our existing contractual relationship. In connection with this restructuring, the parties entered into a cross-license agreement that superseded the prior license and manufacturing agreements among us.

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

In addition, we elected to buy out our manufacturing obligations to ABC with respect to our LNP-based pipeline programs. We made a one-time payment of $30.0 million to ABC for the termination of, and our release from, all of our obligations under the manufacturing agreement. We also have the right to manufacture and have manufactured our LNP-based RNAi therapeutics, which right may be sublicensed to our collaborators.

Further, pursuant to the 2012 cross-license agreement, we made a one-time payment of $35.0 million to ABC, which amount included a license termination payment, as well as the buy-down of certain milestone payments and the significant reduction of royalty rates for certain LNP-based products, including patisiran. In addition, we agreed to pay ABC an aggregate of $10.0 million in contingent milestone payments related to advancement of ALN-VSP and patisiran, representing the only remaining milestone obligations for these products. In December 2013, we paid to ABC $5.0 million in connection with the initiation of our APOLLO Phase 3 clinical trial for patisiran, fulfilling one of these milestone obligations. With respect to the second $5.0 million milestone, in August 2013, we initiated binding arbitration proceedings to resolve a disagreement with ABC regarding the achievement by ABC of this milestone under our cross-license agreement relating to the manufacture of ALN-VSP clinical trial material for use in China. The Arbutus arbitration hearing was held in May 2015. In March 2016, the arbitration panel ruled in our favor and as

a result, no milestone payment is due to Arbutus at this time. The grounds on which Arbutus could appeal this ruling were limited and Arbutus did not appeal by the June 8, 2016 deadline.

Under the 2012 cross-license agreement, Arbutus has three exclusive and ten non-exclusive licenses to research, develop and commercialize RNAi therapeutics directed to up to thirteen gene targets. Arbutus may sublicense these rights on a product-by-product basis. We are eligible to receive from Arbutus up to an aggregate of $8.5 million in milestone payments for RNAi therapeutics directed to nine of the targets for which we have granted licenses to Arbutus, together with single-digit royalties on annual product sales, if any, of RNAi therapeutic products directed to all thirteen of the targets for which we have granted licenses to Arbutus. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any additional milestone payments or any royalty payments from Arbutus.

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

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

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

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

Patents and Proprietary Rights

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

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

We believe that no other company possesses a portfolio of such broad and exclusive rights to the patents and patent applications required for the commercialization of RNAi therapeutics. Our intellectual property estate for RNAi therapeutics includes over 3,400 active cases and over 1,400 granted or issued patents, of which over 500 are issued or granted in the United States, the EU, including by the European Patent Office, or EPO, and Japan. Given the importance of our intellectual property portfolio to our business operations, we intend to vigorously enforce our rights and defend against challenges that have arisen or may arise in this area.

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

In this category, we include United States and certain foreign patents and patent applications that claim key aspects of siRNA architecture and RNAi-related mechanisms. Specifically included are patents and patent applications covering

targeted cleavage of mRNA directed by RNA-like oligonucleotides and double-stranded RNAs of particular lengths and particular structural features, such as blunt and/or overhanging ends, as well as various types and patterns of chemical modifications. Our strategy has been to secure exclusive rights where possible and appropriate to key patents and patent applications that we believe cover fundamental aspects of RNAi.

The following table lists patents and/or patent applications to which we have secured rights that we regard as being fundamental for the use of siRNAs as therapeutics.

Patent Licensor/Owner	Subject Matter	First Priority Date	Inventors	Status	Expiration Date*	Alnylam Rights
Ionis	Inactivation of target mRNA	6/6/1997	S. Crooke	EP 0928290 Additional applications pending in the U.S. and several foreign jurisdictions	6/6/2017	Exclusive rights for therapeutic purposes related to siRNAs**
Carnegie Institution of Washington	Double-stranded RNAs to induce RNAi	12/23/1997	A. Fire, C. Mello	U.S. 6,506,559, U.S. 7,560,438, U.S. 7,538,095, U.S. 7,622,633, U.S. 8,580,754, U.S. 8,283,329 & U.S. 9,102,939 Additional applications pending in the U.S. and several foreign jurisdictions	12/18/2018	Non-exclusive rights for therapeutic purposes
Medical College of Georgia Research Institute, Inc.	Methods for inhibiting gene expression using double-stranded RNA	1/28/1999	Y. Li, M. Farrell, M. Kirby	U.S. 7,888,325 & U.S. 8,148,345 AU 776150 (Australia)	1/28/2020	Exclusive rights

				Additional applications pending in the U.S., Europe and Canada		
Alnylam	Small double-stranded RNAs as therapeutic products	1/30/1999	R. Kreutzer, S. Limmer	U.S. 7,763,590, U.S. 7,829,697 & U.S. 7,994,309 EP 1798285, EP 2363479, EP 1144623, EP 1214945 (revoked/under appeal), EP 1550719 (revoked/under appeal), CA 2359180 (Canada), AU 778474 (Australia), ZA 2001/5909 (South Africa), DE 20023125 U1, DE 10066235 & DE 10080167 (Germany) Additional applications pending in the U.S. and several foreign jurisdictions	1/29/2020	Owned
Alnylam	Medicament for inhibiting the expression of a target gene and medicament for treating a tumor disease	1/9/2001	R. Kreutzer, S. Limmer, H-P.Vornlocher, P. Hadwiger,	U.S. 7,868,160 & U.S. 8,143,390	1/9/2022	Owned

			A. Geick, M. Ocker, C. Herold, D. Schuppan	EP 1799270 & EP 1349927 (opposed and maintained in amended form)		
Alnylam	Method for inhibiting the expression of a wide variety of oncology target genes with double-stranded RNA between 15-49 nucleotides	1/9/2001	R. Kreutzer, S. Limmer, P. Hadwiger	U.S. 8,273,870, U.S. 8,546,143 & U.S. 9,074,213 EP 1352061 (opposed, maintained with no further right to appeal)	1/9/2022	Owned
Alnylam	Composition and methods for inhibiting a target nucleic acid with double-stranded RNA of between 20-49 base pairs wherein at least one end is blunt	1/9/2001	R. Kreutzer, St. Limmer, Sy. Limmer, P. Hadwiger	U.S. 14/737,304 (allowed)	1/9/2022	Owned

Patent Licensor/Owner	Subject Matter	First Priority Date	Inventors	Status	Expiration Date*	Alnylam Rights
Alnylam	Composition and methods for inhibiting a target nucleic acid with double-stranded RNA	4/21/1999	C. Pachuk, C. Satishchandran	EP 1171586, AU 781598 (Australia) Additional applications pending in the U.S. and several foreign jurisdictions	4/19/2020	Owned
Cancer Research Technology Limited	RNAi uses in mammalian oocytes, preimplantation embryos and somatic cells (EP only: wherein the RNAi compound is at least 25 base pairs)	11/19/1999	M. Zernicka-Goetz, F. Wianny, M.J. Evans, D.M. Glover	EP 1230375 (revoked/successfully appealed and granted in amended form), SG 89569 (Singapore), AU 774285 (Australia) Additional applications pending in the U.S. and several foreign jurisdictions	11/17/2020	Exclusive rights for therapeutic purposes
Massachusetts Institute of Technology, Whitehead Institute for Biomedical Research, Max Planck Gesellschaft, University of Massachusetts ***	Mediation of RNAi by small RNAs 21-23 base pairs long with claims directed to compositions, methods of use and manufacture	3/30/2000	D.P. Bartel, P.A. Sharp, T. Tuschl, P.D. Zamore	U.S. 8,790,922, U.S. 8,742,092, U.S. 8,632,997, U.S. 8,552,171, U.S. 8,420,391, U.S. 8,394,628, U.S. 8,957,157, U.S. 9,012,138, U.S. 9,012,621 & U.S. 9,193,753 EP 1309726 (opposed and maintained in amended form/under appeal), EP 2028278 (opposed), EP 2345742, EP 2360253 (opposed) & EP	3/30/2021	Exclusive rights for therapeutic purposes***

				2361981 (opposed), AU 2001249622 (Australia), NZ 522045 (New Zealand), KR 08724437 & KR 10-0909681 (Korea) Additional applications pending in the U.S. and several foreign jurisdictions		
Massachusetts Institute of Technology, Whitehead Institute, University of Massachusetts, Max Planck Gesellschaft (U.S.)**** Max Planck Gesellschaft (ex-U.S.), European Molecular Biology Laboratory (ex-U.S.)*****	Synthetic and chemically modified siRNAs as therapeutic products including patents with claims including those directed to double-stranded RNA of between 19 to 23 or 19 to 25 nucleotides, with and without a 3' overhang; claims directed to double-stranded RNA of between 19 to 52 nucleotides with a 3' overhang; claims directed to double-stranded RNA of 14 to 24 base pairs or up to 25 base pairs with at least one nucleotide analogue, along with methods of	12/1/2000 (EP), 4/24/2004 and 4/27/2004	T. Tuschl, S. Elbashir, W. Lendeckel, M. Wilm#, R. Lührmann# #EMBL inventors	U.S. 7,056,704, U.S. 7,078,196, U.S. 8,329,463, U.S. 8,372,968, U.S. 8,362,231, U.S. 8,445,237, U.S. 8,765,930, U.S. 8,778,902, U.S. 8,796,016, U.S. 8,853,384, U.S. 8,895,721, U.S. 8,933,044, U.S. 8,895,718 & U.S. 8,993,745 EP 1407044 (opposed and maintained in amended form/under appeal), EP 1873259, EP 2348133, EP 2348134 & EP 2351852 (opposed), AU 2002235744 (Australia), ZA 2003/3929 (South Africa), SG 96891 (Singapore), NZ 52588 (New Zealand), JP 4 095 895 (opposed and maintained), JP 4 494	11/29/2021	Exclusive rights for therapeutic purposes****

using and making such double-stranded RNA	392 (Japan), RU 2322500 (Russia), CN 1568373 (China)
	Additional applications pending in the U.S. and several foreign jurisdictions

Patent Licensor/Owner	Subject Matter	First Priority Date	Inventors	Status	Expiration Date*	Alnylam Rights
Alnylam	Methods for inhibiting a target nucleic acid via the introduction of a vector encoding a double-stranded RNA	1/31/2001	T. Giordano, C. Pachuk, C. Satishchandran	U.S. 9,051,566 AU 785395 (Australia) Additional applications pending in the U.S., Australia and Canada	1/31/2021	Owned
Stanford University	RNAi uses in vivo in mammalian liver	7/23/2001	M.A. Kay, A.P. McCaffrey	U.S. 9,018,179 EP 1409506, AU 2002326410 (Australia) Additional applications pending in the U.S. and several foreign jurisdictions	7/23/2021	Exclusive rights for therapeutic purposes
Alnylam	Claims directed to carbohydrate conjugates linked to siRNA	4/17/2003	M. Manoharan	U.S. 7,723,509, U.S. 7,745,608, U.S. 7,851,615, U.S. 8,017,762, U.S.	9/21/2024	Owned

				8,507,661, U.S. 8,344,125, U.S. 8,796,436, U.S. 8,865,677 & U.S. 8,426,377 Additional applications pending in the U.S. and several foreign jurisdictions		
Alnylam	Claims directed to GalNAc-conjugated siRNA	12/4/2007	M. Manoharan	U.S. 8,106,022, U.S. 8,450,467, U.S. 8,828,956 & U.S. 9,370,581 Additional applications pending in the U.S. and several foreign jurisdictions	12/4/2028	Owned
Sirna******	Claims directed to highly chemically modified oligonucleotides with granted claims directed to double-stranded RNA of between 18 and 24 nucleotides with various combinations of chemical	2/20/2002	J. McSwiggen	U.S. 7,923,547, U.S. 7,956,176, U.S. 7,989,612, U.S. 8,232,383, U.S. 8,268,986, U.S. 8,236,944,	2/20/2023-2028	Owned

modifications	U.S. 8,272,979, U.S. 8,273,866, U.S. 8,242,257, U.S. 8,618,277, U.S. 8,846,894, U.S. 8,648,185 & U.S. 9,181,551	
	EP 1423406 (opposed and maintained), EP 2287306 (opposed and maintained in amended form), EP 2278004 (opposed, opposition withdrawn), EP 1627061, EP 1458741 (opposed, opposition withdrawn) & EP 1931781,	
	AU 2003216324, AU 2006203725, CA 2526831 (Canada), JP 49481631	
	Additional cases pending in the US and Europe	

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

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

*** We hold exclusive rights to the interest owned by three co-owners. The University of Massachusetts, or UMass, licensed its interest separately to Sirna. In March 2014, we acquired Sirna from Merck, thus we now hold exclusive rights.

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

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

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

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

We believe that the Crooke patent series, issued in several countries around the world, covers the use of modified oligonucleotides to achieve enzyme-mediated cleavage of a target mRNA. We have obtained rights to the Crooke patents for use with double-stranded RNA products, through a license agreement with Ionis. Under the terms of our agreement, Ionis agreed not to grant licenses under these patents to any other organization for double-stranded RNA products designed to work through an RNAi mechanism, except in the context of a collaboration in which Ionis plays an active role. Our agreement with Ionis was amended and restated in January 2015 to, among other things, extend the license for an additional five years, through April 2019.

Through our acquisition of Ribopharma AG, now known as Alnylam Europe, we own the entire Kreutzer-Limmer patent portfolio, which includes pending applications in the United States and many countries worldwide.

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

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

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

The other pending patent applications listed in the table above either provide further coverage for structural features of siRNAs or relate to the use of siRNAs in mammalian cells. For some of these, we have exclusive rights, and for others, we have non-exclusive rights. In addition, in December 2008, we acquired the intellectual property assets of

Nucleonics, Inc., a privately held biotechnology company. This acquisition included over 100 active patent filings, including 15 patents that have been granted worldwide, of which five have been granted in the United States and Europe. With this acquisition, we obtained patents and patent applications with early priority dates, notably the “Li & Kirby,” “Pachuk I” and “Giordano” patent families, that cover broad structural features of RNAi therapeutics, thus extending the breadth of our fundamental intellectual property.

Intellectual Property Related to Chemical Modifications

Our amended and restated collaboration and license agreement with Ionis provided us with rights to practice the inventions covered by over 200 issued patents worldwide, as well as rights based on future chemistry patent applications through April 2014 for use with double-stranded RNA products. In January 2015, we entered into a second amended and restated agreement with Ionis to extend our rights to future chemistry applications through April 2019. These patents expire both in and outside the United States generally between 2015 and 2035, subject to any potential patent term extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available. These inventions cover chemical modifications we may wish to incorporate into double-stranded RNA therapeutic products designed to work through an RNAi

mechanism. Under the terms of our agreement, Ionis agreed not to grant licenses under these patents to any other organization for double-stranded RNA products designed to work through an RNAi mechanism, except in the context of a collaboration in which Ionis plays an active role.

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

With the combination of the technology we have licensed from Ionis, various patents in the Tuschl II patent series and our own patent application filings, we possess issued claims that cover methods of making siRNAs that incorporate any of various chemical modifications, including the use of phosphorothioates, 2'-O-methyl and/or 2'-fluoro modifications and modifications such as those found in locked and unlocked (acyclic) nucleotides. These modifications are believed to be important for achieving "drug-like" properties for RNAi therapeutics. We hold exclusive worldwide rights to these claims for RNAi therapeutics.

In addition to the above, in March 2014, we acquired the RNAi assets from Merck, which included intellectual property developed at Sirna and Merck. The acquired patent portfolio includes the "McSwiggen" patent families with issued and pending claims covering highly chemically modified oligonucleotide compositions, both single- and double-stranded and independent of 5' and 3' architecture. A total of thirteen patents have granted in the United States with claims directed to various combinations of chemical modifications to double-stranded RNA of between 18 and 24 nucleotides. Notably, U.S. 8,273,866 was granted in September 2012 with significant patent term adjustment extending the expiration of this patent to mid-2028. EP423406 was granted in September 2010 with claims directed to double-stranded RNA of between 18 and 24 nucleotides with ten or more chemical modifications on the pyrimidine residues of the sense and/or antisense strand. As indicated in the chart above, four additional EP patents have granted with claims to various combinations of chemically modified compositions comprising double-stranded RNA of between 18 and 24 nucleotides and methods of making and using such combinations. In November 2015, U.S. 9,181,551 granted with claims directed to highly modified double-stranded RNA molecules comprising a ligand, with dependent claims wherein the ligand is chosen from a ligand for a cellular receptor, a protein localization sequence, an antibody, a nucleic acid aptamer, a vitamin, a co-factor, a phospholipid, a cholesterol, a polyamine, a galactose, a galactosamine, a folate, an N-acetyl-galactosamine (wherein the N-acetylgalactosamine is a mono-antennary, bi-antennary or a tri-antennary galactosamine). Additional dependent claims are directed to highly modified double-stranded RNA with modified nucleotides, including but not limited to unlocked (acyclic) and locked nucleotides.

Intellectual Property Related to the Delivery of siRNAs to Cells

We also pursue internal research and collaborative approaches regarding the delivery of siRNAs to mammalian cells. These approaches include exploring technology that may allow delivery of siRNAs to cells through the use of cholesterol and carbohydrate conjugation, cationic lipids, peptide and antibody-based targeting, and polymer conjugations. Our collaborative efforts have included working with academic and corporate third parties to examine specific embodiments of these various approaches to delivery of siRNAs to appropriate cell tissue, and in-licensing and/or acquiring the most promising technology.

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

The acquisition of Sirna also accelerated our overall efforts to develop and commercialize siRNA delivery technologies, including GalNAc-siRNA conjugate technology. As part of the Sirna acquisition, we obtained several patent families directed to various conjugate technologies including “tetra-GalNAc” compositions and methods. The tetra-GalNAc cases are pending worldwide and will expire May 1, 2033. Also included were patent families directed to novel lipid compositions and formulations that are pending worldwide and set to expire May 31, 2031.

In addition to the Sirna delivery technology, we have a license from UBC and Arbutus in the field of RNAi therapeutics to intellectual property covering cationic liposomes and their use to deliver nucleic acid to cells. The issued United States patents and foreign counterparts, including the Semple (U.S. Patent No 6,858,225) and Wheeler (U.S. Patent No. 6,815,432) patents, cover compositions, methods of making and methods of using cationic liposomes to deliver agents, such as nucleic acid molecules, to cells. These patents expire both in and outside the United States on October 30, 2017 and June 7, 2015, respectively, subject to any potential patent term extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available.

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

Intellectual Property Related to siRNAs Directed to Specific Targets

We have filed a number of patent applications claiming specific siRNAs directed to various gene targets that correlate to specific diseases. While there may be a significant number of competing applications filed by other organizations claiming siRNAs to treat the same gene target, we were among the first companies to focus and file on RNAi therapeutics, and thus, we believe that a number of our patent applications may predate competing applications that others may have filed. Reflecting this, in August 2005, the EPO granted a broad patent, which we call the Kreutzer-Limmer II patent, with 103 allowed claims on therapeutic compositions, methods and uses comprising siRNAs that are complementary to mRNA sequences in over 125 disease target genes. In July 2009, the EPO ruled in our favor in an opposition proceeding related to the Kreutzer-Limmer II patent. The decision had been appealed by Sirna and was subsequently withdrawn upon our acquisition of Sirna. No further appeal before the EPO is available. The Kreutzer-Limmer II patent will expire on January 9, 2022, subject to any potential patent term extensions and/or supplemental protection certificates extending such term extensions in countries where such extensions may become available. Some of these claimed gene targets are being pursued by our development and pre-clinical programs, such as those expressed by viral pathogens including RSV and influenza virus. In addition, the claimed targets include oncogenes, cytokines, cell adhesion receptors, angiogenesis targets, apoptosis and cell cycle targets, and additional viral disease targets, such as hepatitis C virus and HIV. The Kreutzer-Limmer II patent series is pending in the United States and many foreign countries. Granted U.S. patent 8,618,277 obtained in the Sirna acquisition and set to expire February 20, 2023, contains claims directed to a highly chemically modified double-stranded siRNA of between 18-24 nucleotides specifically targeting the hepatitis B virus in a sequence independent manner. Moreover, a patent in the Tuschl II patent series, U.S. Patent No. 7,078,196, claims methods of preparing siRNAs that mediate cleavage of an mRNA in mammalian cells and, therefore, covers methods of making siRNAs directed toward any and all target genes. We hold exclusive worldwide rights to these claims for RNAi therapeutics.

In 2016, we were granted U.S. Patent Nos. 9,370,581, 9,370,582 and 9,352,048 containing claims that broadly cover single- or double-stranded RNA therapeutic molecules conjugated with any bi or triantennary ligand (including but not limited to GalNAc) independent of length, specifically inhibiting TTR, PCSK9 or HBV, respectively, wherein the HBV-specific RNA molecule is fully chemically modified.

Intellectual Property Related to Our Development Candidates

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

Intellectual Property Challenges

As the field of RNAi therapeutics is maturing, patent applications are being fully processed by national patent offices around the world. There is uncertainty about which patents will issue, and, if they do, as to when, to whom and with what claims. It is likely that there will be significant litigation and other proceedings, such as interference,

reexamination, inter partes review, post-grant review and opposition proceedings, in various patent offices relating to patent rights in the RNAi field. On September 16, 2012, the America Invents Act went into effect and provided for expanded patent challenge, i.e., inter partes review and post-grant review. These provide additional opportunities for third parties to challenge our patents. For example, as noted in the table above, various third parties have initiated oppositions to patents in our Kreutzer-Limmer and Tuschl II series in the EPO, as well as in other jurisdictions. We expect that additional oppositions will be filed in the EPO and elsewhere, and other challenges will be raised relating to other patents and patent applications in our portfolio. In many cases, the possibility of appeal exists for either us or our opponents, and it may be years before final, unappealable rulings are made with respect to these patents in certain jurisdictions. Given the importance of our intellectual property portfolio to our business operations, we intend to vigorously enforce our rights and defend against challenges that have arisen or may arise in this area. A description of ongoing legal matters relating to certain aspects of our intellectual property portfolio is set forth in Part I, Item 3, “Legal Proceedings,” of this annual report on Form 10-K.

Competition

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

Competition for Our Business in General

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

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

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

Companies working on chemically synthesized siRNAs include Takeda, Marina Biotech, Inc., Arrowhead Research Corporation, or Arrowhead, and its subsidiary, Calando Pharmaceuticals, Inc., or Calando, Quark Pharmaceuticals, Inc., or Quark, Silence Therapeutics plc, Arbutus, Sylentis, S.A.U., or Sylentis, Dicerna Pharmaceuticals, Inc., or Dicerna, WAVE Life Sciences Ltd., or WAVE, and Arcturus Therapeutics, Inc. Many of these companies have licensed our intellectual property. Benitec Biopharma Ltd., or Benitec, is working on gene therapy approaches to RNAi therapeutics. Companies working on microRNA therapeutics include Regulus Therapeutics, Inc., or Regulus, Rosetta Genomics Ltd., F. Hoffmann-La Roche Ltd, or Roche, through its acquisition in 2014 of Santaris Pharma A/S, miRagen Therapeutics, Inc., Mirna Therapeutics, Inc. and Asuragen, Inc.

Antisense technology uses short, single-stranded, DNA-like molecules to block mRNAs encoding specific proteins. While we believe that RNAi drugs may potentially have significant advantages over antisense oligonucleotides, or ASOs, including greater potency and specificity, others are developing ASO drugs that are currently at a more advanced stage of development than RNAi drugs. For example, Ionis has developed several ASO drugs that have received regulatory approval. Ionis is also developing antisense drugs using ligand-conjugated GalNAc technology licensed from us, and these drugs have been shown to have increased potency at lower doses in clinical and pre-clinical studies, compared with antisense drugs that do not use such licensed GalNAc technology. In addition, a number of other companies have ASO-based product candidates in various stages of pre-clinical and clinical development, including Roche, Celgene Corporation, Antisense Therapeutics, Ltd., WAVE and Sarepta Therapeutics, Inc.

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

Competing Drugs for Our Investigational RNAi Therapeutics in Advanced Clinical Development

Hereditary ATTR Amyloidosis. Until recently, organ transplantation was the only treatment option for patients with hATTR amyloidosis. Only a subset of patients with early stage disease qualify for this costly and invasive procedure, which carries significant morbidity and mortality. Even following liver transplantation, the disease continues to progress for many patients, presumably due to ongoing deposition of wild-type TTR protein. The only approved drug for ATTR amyloidosis is tafamidis, marketed by Pfizer Inc., for the treatment of early stage disease. Tafamidis is approved in Europe, certain countries in Latin America and Japan (where it is approved for all stages of disease). The only currently available treatments for cardiomyopathy due to hATTR amyloidosis are aimed at relief of symptoms, such as diuretics, or water pills, to treat the swelling of the ankles, one of the symptoms of the disease. For patients with advanced cardiomyopathy, heart transplant is a therapeutic option. Again, the scarcity of organs for transplantation, and the mortality, morbidity and cost associated with this procedure render it a realistic option for only a very small number of patients. Pfizer is currently evaluating tafamidis in a Phase 3 trial in patients with cardiomyopathy.

Several other drugs are in clinical development for the treatment of ATTR amyloidosis. Ionis, together with its partner GlaxoSmithKline plc, is developing IONIS-TTR_{Rx}, an ASO designed to treat hATTR amyloidosis. IONIS-TTR_{Rx} is administered as a subcutaneous injection, once-weekly. Ionis has reported that it has completed enrollment in a Phase 3 clinical trial of IONIS-TTR_{Rx} in ATTR amyloidosis patients with polyneuropathy and is expected to complete the study in 2017, likely in advance of the completion of our APOLLO Phase 3 study. In addition, diflunisal, a commercially available non-steroidal anti-inflammatory agent, has been found to stabilize TTR in vitro. A National Institute of Health-sponsored clinical trial concluded that the use of diflunisal compared with placebo for two years reduced the rate of progression of neurological impairment and preserved quality of life. As published, the discontinuation rate was high in this clinical trial in both treatment arms (approximately 50 percent overall) and the majority of patients continued to deteriorate, including patients on diflunisal. Furthermore, the safety profile of this drug and its known adverse effects, particularly on the kidney and heart, could likely limit the potential use of it in this disease.

Finally, several other companies have early stage programs evaluating monoclonal antibodies and small molecules for the treatment of ATTR amyloidosis. These companies are likely several years away from filing for marketing authorization for their investigational therapies.

Hemophilia. The global market for treatments of hemophilia and bleeding disorders is valued at more than $10.0 billion. Products on the market include: Factor VIII replacement products marketed by Shire plc (formerly marketed by Baxalta Incorporated), Bayer Healthcare Pharmaceuticals, Pfizer, CSL Behring, Biogen Inc. and others; Factor IX replacement products marketed by Pfizer, Shire, Biogen, CSL Behring and others. Several factor replacement products with extended half-lives (Eloctate/Elocta, Alprolix, Idelvion) have been recently approved and several more are in development. For the treatment of persons with inhibitors, a Factor VIIa replacement product marketed by Novo Nordisk and an activated prothrombin complex concentrate marketed by Shire are available.

New, innovative molecules are currently in development, which may offer new treatments for people with HA and HB, with and without inhibitors. Roche/Genentech, Inc. is developing a bi-specific antibody (emicizumab or ACE910) which binds to factors IXa and X and mimics the Factor VIII cofactor function in people with HA. This product has been shown to reduce the incidence of bleeding events in people with HA with and without inhibitors in a completed Phase 1 trial and a recently completed Phase 3 trial in people with HA with inhibitors. A Phase 3 study of emicizumab in people with HA without inhibitors has also been initiated. Several companies are developing monoclonal antibodies against tissue factor pathway inhibitor, or TFPI, for the treatment of HA and HB. Novo Nordisk (concizumab) and Bayer (BAY 1093884) have programs, which are currently in Phase 1 clinical trials, and Shire has a program in pre-clinical development.

A number of companies are actively developing gene therapy products that use a virus to deliver a functional segment of a particular gene into the cells of the person with hemophilia. Companies with development programs in gene therapy include Spark Therapeutics Inc. (SPK-9001 – Phase 1/2, HB), uniQure N.V., or uniQure, (AMT-060 – Phase 1/2, HB), Dimension Therapeutics, Inc. (DTX-101 – Phase 1/2, HB) and BioMarin Pharmaceutical Inc. (BMN 270 – Phase 1/2, HA). Recent data suggests that these agents may be effective in restoring and maintaining adequate factor levels to prevent bleeding in some patients.

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

of dyslipidemia, in the United States and the EU for use in patients with HoFH. In addition, mipomersen, a lipid-lowering weekly-injectable drug targeting apolipoprotein B-100, developed by Ionis, is approved in the United States for the treatment of patients with HoFH.

In 2015, two anti-PCSK9 antibodies were approved for the treatment of hypercholesterolemia in the United States and Europe, alirocumab, developed by Regeneron Pharmaceuticals, Inc., in collaboration with Sanofi, and evolocumab, developed by Amgen Inc. In 2017, the U.S. District Court in Delaware granted an injunction against Sanofi and Regeneron requiring the withdrawal of alirocumab from the market in the United States as a result of a patent infringement lawsuit brought by Amgen.

Other PCSK9-targeted approaches are in development at a number of companies, including Dicerna and Ionis.

Acute Hepatic Porphyrias. The only approved treatments for acute attacks are preparations of heme derived from human blood. The global market for AHP is made up of intravenous hemin in the United States and intravenous heme arginate in the EU. Both products are currently manufactured by Recordati S.p.A. Despite the lack of randomized studies demonstrating clinical

efficacy, heme has been shown in case studies to hasten recovery from attacks and has been marketed since 1999 in the EU for the treatment of acute attacks of AIP, hereditary coproporphyria and variegate porphyria.

In addition to heme, the AIPGENE consortium, a European collaboration that included industry sponsors UniQure and Digna Biotech, was developing AMT-021, a gene therapy product for the treatment of AIP, but this development program is currently on hold. We are aware of other companies that have pre-clinical development programs for the treatment of AHPs.

Other Competition

Finally, for many of the diseases that are the subject of our early stage clinical, pre-clinical development and discovery RNAi therapeutic programs, there are already drugs on the market or in development. For example, the global market for drugs that specifically target complement-mediated diseases is significant. The only product in this market is eculizumab, a monoclonal antibody developed by Alexion Pharmaceuticals, Inc. that inhibits the cleavage of the protein complement component 5 (C5) into its components C5a and C5b. Eculizumab has been approved by the FDA and the EC to treat PNH, as well as aHUS, a systemic disease cause by chronic uncontrolled activation of the complement system. Eculizumab is also currently being studied in a number of other diseases that are believed to be complement-mediated including: neuromyelitis optica, myasthenia gravis, antibody-mediated rejection and delayed graft function. A number of other products are also in development for the treatment of complement-mediated diseases. In addition, with respect to ALN-HBV, oral nucleoside/nucleotide analogues have demonstrated the ability to potently inhibit HBV replication and suppress levels of HBV DNA in patients with HBV and are approved for the treatment of these patients in the United States, Europe and other countries. In addition, a large number of novel agents, including agents using chemically synthesized siRNA, are currently in development for the treatment of patients with chronic HBV infection. However, notwithstanding the availability of existing drugs or drug candidates, we believe there currently exists sufficient unmet medical need to warrant the advancement of our investigational RNAi therapeutic programs.

Regulatory Matters

U.S. Regulatory Considerations

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

The steps ordinarily required before a new drug product may be marketed in the United States include nonclinical laboratory tests, animal tests and formulation studies, the submission to the FDA of an investigational new drug, or IND, application, which must become effective prior to commencement of clinical testing, approval by an institutional review board, or IRB, at each clinical site before each trial may be initiated, completion of adequate and well-controlled clinical trials to establish that the drug product is safe and effective for the indication for which FDA approval is sought, submission to the FDA of an NDA, review and recommendation by an advisory committee of independent experts (particularly for new chemical entities), satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with current good

manufacturing practice, or cGMP, requirements, satisfactory completion of an FDA inspection of the major investigational sites to ensure data integrity and assess compliance with good clinical practice, or GCP, requirements and FDA review and approval of the NDA. Satisfaction of FDA pre-market approval requirements typically takes several years, but may vary substantially depending upon the complexity of the product and the nature of the disease. Government regulation may delay or prevent marketing of potential products for a considerable period of time and impose costly procedures on a company's activities. Success in early stage clinical trials does not necessarily assure success in later stage clinical trials. Data obtained from clinical activities, including but not limited to the data derived from our clinical trials for patisiran, fitusiran, givosiran and inclisiran, is not always conclusive and may be subject to alternative interpretations that could delay, limit or even prevent regulatory approval. Even if a product receives regulatory approval, later discovery of previously unknown problems with a product, including new safety risks, may result in restrictions on the product or even complete withdrawal of the product from the market.

Clinical Trials.

Nonclinical tests include laboratory evaluation of product chemistry and formulation, as well as animal testing to assess the potential safety and efficacy of the product. The conduct of the nonclinical tests and formulation of compounds for testing must

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

A 30-day waiting period after the filing of an IND is required prior to such application becoming effective and the commencement of clinical testing in humans. If the FDA has not commented on, or questioned, the application during this 30-day waiting period, clinical trials may begin. If the FDA has comments or questions, these must be resolved to the satisfaction of the FDA prior to commencement of clinical trials. The IND review process can result in substantial delay and expense. We, an IRB, or the FDA may, at any time, suspend, terminate or impose a clinical hold on ongoing clinical trials. For example, in October 2016, we discontinued development of revusiran, an investigational RNAi therapeutic that was in development for the treatment of patients with cardiomyopathy due to hATTR amyloidosis, due to safety concerns. If the FDA imposes a clinical hold, clinical trials cannot commence or recommence without FDA authorization and then only under terms authorized by the FDA.

Clinical trials involve the administration of an investigational new drug to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted in compliance with federal regulations and requirements, including GCP, which are ethical and scientific quality standards and FDA requirements for conducting, recording and reporting clinical trials to assure data integrity and protect the rights, safety and well-being of trial participants and include the requirement that all research subjects provide their informed consent for their participation in any clinical study. Clinical studies are conducted under protocols detailing, among other things, the objectives of the trial and the safety and effectiveness criteria to be evaluated. Each protocol involving testing on human subjects in the United States must be submitted to the FDA as part of the IND. In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations.

Clinical trials to support NDAs for marketing approval are typically conducted in three sequential phases, which may overlap or be combined.

- In Phase 1, the initial introduction of the drug into healthy human subjects or patients, the drug is tested to primarily assess safety, tolerability, pharmacokinetics, pharmacological actions and metabolism associated with increasing doses.
- Phase 2 usually involves trials in a limited patient population, to assess the optimum dosage and dose regimen, identify possible adverse effects and safety risks, and provide preliminary support for the efficacy of the drug in the indication being studied.
- If Phase 2 clinical trials demonstrate that a drug may be effective and the risks are considered acceptable given the observed efficacy of the drug and the severity of the illness, Phase 3 clinical trials may be undertaken to further evaluate the drug's clinical efficacy, side effects, and safety in an expanded patient population, typically at geographically dispersed clinical trial sites, to establish the overall benefit-risk relationship of the drug and to provide adequate information for the labeling of the drug.

Phase 1, Phase 2 or Phase 3 testing of any drug candidates may not be completed successfully within any specified time period, if at all. The FDA closely monitors the progress of each of the three phases of clinical trials that are conducted in the United States. The FDA may, at its discretion, reevaluate, alter, suspend or terminate the testing based upon the data accumulated to that point and the FDA's assessment of the risk/benefit ratio to the subject. An IRB or a clinical trial sponsor also may suspend or terminate clinical trials at any time for various reasons, including a finding that the subjects or patients are being exposed to an unacceptable health risk. The FDA can also request that additional clinical trials be conducted as a condition to product approval. Finally, sponsors are required to publicly disseminate information about certain ongoing and completed clinical trials on a government website administered by

the National Institutes of Health, or NIH, and are subject to civil monetary penalties and other civil and criminal sanctions for failing to meet these obligations. After successful completion of the required clinical testing, as well as nonclinical testing and manufacturing requirements, generally an NDA is prepared and submitted to the FDA.

New Drug Applications.

We believe that any RNAi product candidate we develop, whether for the treatment of ATTR amyloidosis, hemophilia and RBD, AHPs, hypercholesterolemia or the various indications targeted in our development or nonclinical discovery programs, will be regulated as a new drug by the FDA. FDA approval of an NDA is required before marketing of a new drug may begin in the United States. The NDA must include the results of extensive nonclinical, clinical and other testing, as described above, a compilation of data relating to the product's pharmacology, chemistry, manufacture and controls, proposed labeling and other information. In addition, an NDA for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must contain data assessing the safety and effectiveness for the claimed indication in all relevant pediatric subpopulations, and support dosing and

administration for each pediatric subpopulation for which the drug is shown to be safe and effective. In some circumstances, the FDA may grant deferrals for the submission of some or all pediatric data, or full or partial waivers.

The cost of preparing and submitting an NDA is substantial. Under federal law, NDAs are subject to substantial application user fees and the sponsor of an approved NDA is also subject to annual product and establishment user fees. Under the Prescription Drug User Fee Act, or PDUFA, as amended, each NDA must be accompanied by a user fee. The FDA adjusts the PDUFA user fees on an annual basis. According to the FDA's fee schedule, effective through September 30, 2017, the user fee for each NDA application requiring clinical data is approximately $2.0 million. PDUFA also imposes an annual product fee for drugs, and an annual establishment fee on facilities used to manufacture prescription drugs. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. Additionally, no user fees are assessed on NDAs for products designated as orphan drugs, unless the product also includes a non-orphan indication.

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

If the FDA evaluation of the NDA and the inspections of manufacturing facilities and clinical trial sites are favorable, the FDA may issue an approval letter, which authorizes commercial marketing of the drug with specific prescribing information for a specific indication. As a condition of NDA approval, the FDA may require post-approval testing, sometimes referred to as Phase 4 trials and surveillance to monitor the drug's safety or effectiveness and may impose other conditions, including labeling restrictions, which can materially impact the potential market and profitability of the drug. In addition, the FDA may impose distribution and use restrictions and other limitations on labeling and communication activities with respect to an approved drug product through a Risk Evaluation and Mitigation Strategy, or REMS, plan. Once granted, product approvals may be further limited or withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

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

variations already allowed in the approval. Certain changes to the product, its labeling or its manufacturing require prior FDA approval and may require the conduct of further clinical investigations to support the change, which may require the payment of additional, substantial user fees. Such approvals may be expensive and time-consuming and, if not approved, the FDA will not allow the product to be marketed as modified.

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

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

Abbreviated Applications.

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

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

Additionally, in the event that the sponsor of the listed drug has properly informed the FDA of patents covering its listed drug, applicants submitting an ANDA or 505(b)(2) application referencing the listed drug are required to make one of four patent certifications for each listed patent, except for patents covering methods of use for which the ANDA or 505(b)(2) applicant is not seeking approval. If an applicant certifies its belief that one or more listed patents are invalid, unenforceable, or not infringed (and thereby indicates it is seeking approval prior to patent expiration), it is required to provide notice of its filing to the NDA sponsor and the patent holder within certain time limits. If the patent holder then initiates a suit for patent infringement against the ANDA or 505(b)(2) applicant within 45 days of

receipt of the notice, the FDA cannot grant effective approval of the ANDA or 505(b)(2) application until either 30 months have passed or there has been a court decision or settlement order holding or stating that the patents in question are invalid, unenforceable or not infringed. If the patent holder does not initiate a suit for patent infringement within the 45 days, the ANDA or 505(b)(2) application may be approved immediately upon successful completion of FDA review, unless blocked by another listed patent or regulatory exclusivity period. If the ANDA or 505(b)(2) applicant certifies that it does not intend to market its generic product before some or all listed patents on the listed drug expire, then the FDA cannot grant effective approval of the ANDA or 505(b)(2) application until those patents expire. The first of the ANDA applicants submitting substantially complete applications certifying that one or more listed patents for a particular product are invalid, unenforceable, or not infringed may qualify for an exclusivity period of 180 days running from when the generic product is first marketed, during which subsequently submitted ANDAs containing similar certifications cannot be granted effective approval. The 180-day generic exclusivity can be forfeited in various ways, including if the first applicant does not market its product within specified statutory timelines. If more than one applicant files a substantially complete ANDA on the same day, each such first applicant will be entitled to share the 180-day exclusivity period, but there will only be one such period, beginning on the date of first marketing by any of the first applicants.

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, also collectively referred to as the PPACA or the Affordable Care Act, signed into law on March 23, 2010, includes a subtitle called the

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

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

Orphan Drug Designation (ODD).

Under the Orphan Drug Act, the FDA may grant ODD to a drug intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for this type of disease or condition will be recovered from sales in the United States for that drug. ODD must be requested before submitting an NDA. After the FDA grants ODD, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. We intend to request ODD designation for our product candidates, if applicable. For example, the FDA has granted ODD for patisiran as a therapeutic approach for the treatment of ATTR amyloidosis, fitusiran as a therapeutic approach for hemophilia and givosiran as a therapeutic approach for AHPs.

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

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

Pediatric Study Plans.

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

Fast Track Program.

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new drugs and biological products that meet certain criteria. Specifically, new drugs and biological products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug or biological product may request the FDA to designate the drug or biologic as a Fast Track product at any time during the clinical development of the product, but ideally no later than the pre-NDA or –biologics license application, or BLA, meeting. Notable to a Fast Track product, the FDA may consider for review sections of the marketing application on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the application, the FDA agrees to accept sections of the application and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the application. We intend to request Fast Track designation for our product candidates, if applicable. For example, the FDA granted Fast Track designation to patisiran for the treatment of hATTR amyloidosis.

Any product submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. Any product is eligible for priority review if it treats a serious condition and, if approved, would provide a significant improvement in the safety or effectiveness of treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biological product designated for priority review in an effort to facilitate the review, and the FDA's goal for taking action on an application with a Priority Review designation is six months instead of ten months. Additionally, a product may be eligible for accelerated approval. Drug or biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical studies establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than irreversible morbidity or mortality that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefits. As a condition of approval, the FDA may require that a sponsor of a drug or biological product receiving accelerated approval perform adequate and well-controlled post-marketing clinical studies to verify the predicted clinical benefit. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product. Fast Track designation, priority review and accelerated approval do not change the standards for approval but may expedite the development or approval process.

Breakthrough Therapy Designation.

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

ensure that the design of the clinical trials is as efficient as practicable, and allowing a rolling review. We intend to request “breakthrough therapy” designation for our product candidates, if applicable.

Pharmaceutical Coverage, Pricing and Reimbursement.

Significant uncertainty exists as to the coverage and reimbursement status of any drug products for which we obtain regulatory approval. In the United States and markets in other countries, sales of any products for which we may receive regulatory approval for commercial sale will depend in part on the availability of reimbursement from third-party payors. Third-party payors include government healthcare programs, managed care providers, private health insurers and other organizations. The process for determining whether a payor will provide coverage for a drug product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the drug product. Third-party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drugs for a particular indication. Third-party payors may provide coverage, but place stringent limitations on such coverage, such as requiring alternative treatments to be tried first. These third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. In addition, significant uncertainty exists as to the reimbursement status of newly approved healthcare products. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the

medical necessity and cost-effectiveness of our products, in addition to incurring the costs required to obtain FDA approvals. Our product candidates may not be considered medically reasonable or necessary or cost-effective. Even if a drug product is covered, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

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

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

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, the emphasis on managed care in the United States has increased and we expect will continue to exert downward pressure on pharmaceutical pricing. Coverage policies, third-party reimbursement rates and pharmaceutical pricing regulations may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

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

- The Medicaid Drug Rebate Program requires pharmaceutical manufacturers to enter into and have in effect a national rebate agreement with the Secretary of the Department of Health and Human Services a condition for states to receive federal matching funds for the manufacturer's outpatient drugs furnished to Medicaid patients. Effective in 2010, the PPACA made several changes to the Medicaid Drug Rebate Program, including increasing pharmaceutical manufacturers' rebate liability by raising the minimum basic Medicaid rebate on most branded prescription drugs and biologic products from 15.1 percent of average manufacturer price, or AMP, to 23.1 percent of AMP and adding a new rebate calculation for "line extensions" (i.e., new formulations, such as extended release formulations) of solid oral dosage forms of branded products, as well as potentially impacting their rebate liability by modifying the statutory definition of AMP. In addition, the PPACA provides for the public availability of retail survey prices and certain weighted average AMPs under the Medicaid program. The implementation of this requirement by the Centers for Medicare and Medicaid Services, or CMS, may also provide for the public availability of pharmacy acquisition of cost data, which could negatively impact our sales.
- In order for a drug product to receive federal reimbursement under the Medicare Part B and Medicaid programs or to be sold directly to U.S. government agencies, the manufacturer must extend discounts to entities eligible to participate in the 340B drug pricing program. The required 340B discount on a given product is calculated based on the AMP and Medicaid rebate amounts reported by the manufacturer. Effective in 2010, the PPACA expanded the

types of entities eligible to receive discounted 340B pricing, although, under the current state of the law, with the exception of children's hospitals, these entities will not be eligible to receive discounted 340B pricing on orphan drugs. In addition, as 340B drug pricing is determined based on AMP and Medicaid rebate data, the revisions to the Medicaid rebate formula and AMP definition described above could cause the required 340B discount to increase.

- Effective in 2011, the PPACA imposed a requirement on manufacturers of branded drugs and biologic products to provide a 50 percent discount off the negotiated price of branded drugs dispensed to Medicare Part D patients in the coverage gap (i.e., "donut hole").
- Effective in 2011, the PPACA imposed an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic products, apportioned among these entities according to their market share in certain government healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications.

- Effective in 2012, the PPACA required certain manufacturers to track certain financial arrangements with physicians and teaching hospitals, including any "transfer of value" made or distributed to such entities, as well as any investment interests held by physicians and their immediate family members. Manufacturers annually report this information to CMS, which posts this information on its website.
- As of 2010, a new Patient-Centered Outcomes Research Institute was established pursuant to the PPACA to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research. The research conducted by the Patient-Centered Outcomes Research Institute may affect the market for certain drug products.
- The PPACA created the Independent Payment Advisory Board which, beginning in 2014, has authority to recommend certain changes to the Medicare program to reduce expenditures by the program that could result in reduced payments for prescription drugs. Under certain circumstances, these recommendations will become law unless Congress enacts legislation that will achieve the same or greater Medicare cost savings.
    - The PPACA established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending. Funding has been allocated to support the mission of the Center for Medicare and Medicaid Innovation from 2011 to 2019.

Possible Change in Laws or Policies.

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

EU Regulatory Considerations

In the EU medicinal products are subject to extensive pre- and post-market regulation by regulatory authorities at both the EU and national levels.

Clinical Trials.

Clinical trials of medicinal products in the EU must be conducted in accordance with EU and national regulations and the International Conference on Harmonization, or ICH, guidelines on GCP. If the sponsor of the clinical trial is not established within the EU, it must appoint an entity within the EU to act as its legal representative. The sponsor must take out a clinical trial insurance policy, and in most EU countries the sponsor is liable to provide 'no fault' compensation to any study subject injured in the clinical trial.

Prior to commencing a clinical trial, the sponsor must obtain a clinical trial authorization, or CTA, from the competent authority, and a positive opinion from an independent ethics committee. The application for a CTA must include, among other things, a copy of the trial protocol and an investigational medicinal product dossier containing information about the manufacture and quality of the medicinal product under investigation. Currently, CTAs must be submitted to the competent authority in each EU member state in which the trial will be conducted. Under the new Regulation on Clinical Trials, which is currently expected to take effect in October 2018, there will be a centralized application procedure where one national authority takes the lead in reviewing the application and the other national authorities have only a limited involvement. Any substantial changes to the trial protocol or other information submitted with the clinical trial applications must be notified to or approved by the relevant competent authorities and

ethics committees.

The sponsor of a clinical trial must register the clinical trial in advance, and information related to the product, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial will be made public as part of the registration. The results of the clinical trial must be submitted to the competent authorities and, with the exception of non-pediatric Phase 1 trials, will be made public at the latest within 12 months after the end of the trial.

During the development of a medicinal product, the EMA and national medicines regulators within the EU provide the opportunity for dialogue and guidance on the development program. At the EMA level, this is usually done in the form of scientific advice, which is given by the Scientific Advice Working Party of the Committee for Medicinal Products for Human Use, or CHMP. A fee is incurred with each scientific advice procedure. Advice from the EMA is typically provided based on questions concerning, for

example, quality (chemistry, manufacturing and controls testing), nonclinical testing and clinical studies, and pharmacovigilance plans and risk-management programs. Advice is not legally binding with regard to any future marketing authorization application of the product concerned.

Marketing Authorizations.

After completion of the required clinical testing, we must obtain a marketing authorization before we may place a medicinal product on the market in the EU. There are various application procedures available, depending on the type of product involved. All application procedures require an application in the common technical document, or CTD, format, which includes the submission of detailed information about the manufacturing and quality of the product, and nonclinical study and clinical trial information. There is an increasing trend in the EU towards greater transparency and, while the manufacturing or quality information is currently generally protected as confidential information, the EMA and national regulatory authorities are now liable to disclose much of the nonclinical and clinical information in marketing authorization dossiers, including the full clinical study reports, in response to freedom of information requests after the marketing authorization has been granted. In October 2014, the EMA adopted a policy under which clinical study reports would be posted on the agency's website following the grant, denial or withdrawal of a marketing authorization application, subject to procedures for limited redactions and protection against unfair commercial use. A similar requirement is contained in the new Regulation on Clinical Trials that is currently expected to take effect in October 2018.

The centralized procedure gives rise to marketing authorizations that are valid throughout the EU and, by extension (after national implementing decisions), in Norway, Iceland and Liechtenstein, which, together with the EU member states, comprise the European Economic Area, or EEA. Applicants file MAAs with the EMA, where they are reviewed by a relevant scientific committee, in most cases the CHMP. The EMA forwards CHMP opinions to the European Commission, or EC, which uses them as the basis for deciding whether to grant a marketing authorization. The centralized procedure is compulsory for medicinal products that (1) are derived from biotechnology processes, (2) contain a new active substance (not yet approved on November 20, 2005) indicated for the treatment of certain diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative disorders, viral diseases or autoimmune diseases and other immune dysfunctions, (3) are orphan medicinal products or (4) are advanced therapy medicinal products, such as gene or cell therapy medicines. For medicines that do not fall within these categories, an applicant may voluntarily submit an application for a centralized marketing authorization to the EMA, as long as the CHMP agrees that (i) the medicine concerned contains a new active substance (not yet approved on November 20, 2005), (ii) the medicine is a significant therapeutic, scientific, or technical innovation, or (iii) if its authorization under the centralized procedure would be in the interest of public health.

For those medicinal products for which the centralized procedure is not available, the applicant must submit MAAs to the national medicines regulators through one of three procedures: (1) a national procedure, which results in a marketing authorization in a single EU member state; (2) the decentralized procedure, in which applications are submitted simultaneously in two or more EU member states; and (3) the mutual recognition procedure, which must be used if the product has already been authorized in at least one other EU member state, and in which the EU member states are required to grant an authorization recognizing the existing authorization in the other EU member state, unless they identify a serious risk to public health. A national procedure is only possible for one member state; as soon as an application is submitted in a second member state the mutual recognition or decentralized procedure will be triggered.

Under the centralized procedure in the EU, the maximum timeframe for the evaluation of an MAA is 210 days. However, this timeline excludes clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the CHMP, so the overall process typically takes a year or more. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is expected to

be of a major public health interest, defined by three cumulative criteria: the seriousness of the disease (e.g., heavy disabling or life-threatening diseases) to be treated; the absence or insufficiency of an appropriate alternative therapeutic approach; and anticipation of high therapeutic benefit. In this circumstance, EMA ensures that the opinion of the CHMP is given within 150 days.

Data Exclusivity.

MAAs for generic medicinal products do not need to include the results of pre-clinical studies and clinical trials, but instead can refer to the data included in the marketing authorization of a reference product for which regulatory data exclusivity has expired. If a marketing authorization is granted for a medicinal product containing a new active substance, that product benefits from eight years of data exclusivity, during which generic MAAs referring to the data of that product may not be accepted by the regulatory authorities, and a further two years of market exclusivity, during which such generic products may not be placed on the market. The two-year period may be extended to three years if during the first eight years a new therapeutic indication with significant clinical benefit over existing therapies is approved.

There is a special regime for biosimilars, or biological medicinal products that are similar to a reference medicinal product but that do not meet the definition of a generic medicinal product, for example, because of differences in raw materials or manufacturing processes. For such products, the results of appropriate pre-clinical studies or clinical trials must be provided, and guidelines from the EMA detail the type of quantity of supplementary data to be provided for different types of biological product. There are no such guidelines for complex biological products, such as gene or cell therapy medicinal products, and so it is unlikely that biosimilars of those products will currently be approved in the EU. However, guidance from the EMA states that they will be considered in the future in light of the scientific knowledge and regulatory experience gained at the time.

Orphan Medicinal Products.

The EMA's COMP may recommend orphan medicinal product designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the EU. Additionally, designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the product in the EU would be sufficient to justify the necessary investment in developing the medicinal product. The COMP may only recommend orphan medicinal product designation when the product in question offers a significant clinical benefit over existing approved products for the relevant indication. Following a positive opinion by the COMP, the EC adopts a decision granting orphan status. The COMP will reassess orphan status in parallel with EMA review of an MAA and orphan status may be withdrawn at that stage if it no longer fulfills the orphan criteria (for instance because in the meantime a new product was approved for the indication and no convincing data are available to demonstrate a significant benefit over that product). Orphan medicinal product designation entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity is granted following marketing authorization. During this period, the competent authorities may not accept or approve any similar medicinal product, unless it offers a significant clinical benefit. This period may be reduced to six years if the orphan medicinal product designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

Post-Approval Controls.

The holder of a marketing authorization must establish and maintain a pharmacovigilance system and appoint an individual qualified person for pharmacovigilance, or QPPV, who is responsible for oversight of that system. Key obligations include expedited reporting of suspected serious adverse reactions and submission of periodic safety update reports, or PSURs.

All new MAAs must include a risk management plan, or RMP, describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. The regulatory authorities may also impose specific obligations as a condition of the marketing authorization. Such risk-minimization measures or post-authorization obligations may include additional safety monitoring, more frequent submission of PSURs, or the conduct of additional clinical trials or post-authorization safety studies. RMPs and PSURs are routinely available to third parties requesting access, subject to limited redactions.

All advertising and promotional activities for the product must be consistent with the approved summary of product characteristics, and therefore all off-label promotion is prohibited. Direct-to-consumer advertising of prescription medicines is also prohibited in the EU. Although general requirements for advertising and promotion of medicinal products are established under EU directives, the details are governed by regulations in each member state and can differ from one country to another.

Manufacturing.

Medicinal products may only be manufactured in the EU, or imported into the EU from another country, by the holder of a manufacturing authorization from the competent national authority. The manufacturer or importer must have a qualified person, or QP, who is responsible for certifying that each batch of product has been manufactured in accordance with EU standards of cGMP before releasing the product for commercial distribution in the EU or for use in a clinical trial. Manufacturing facilities are subject to periodic inspections by the competent authorities for compliance with cGMP.

Pricing and Reimbursement.

Governments influence the price of medicinal products in the EU through their pricing and reimbursement rules and control of national healthcare systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other member states allow companies to fix their own

prices for medicines, but monitor and control company profits. The downward pressure on healthcare costs in general, particularly prescription medicines, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

Foreign Regulation of New Drug Compounds

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

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

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

The approval procedure also varies among countries and can involve requirements for additional testing. The time required may differ from that required for FDA approval and may be longer than that required to obtain FDA approval. Thus, there can be substantial delays in obtaining required approvals from foreign regulatory authorities after the relevant applications are filed.

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

Hazardous Materials

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

Manufacturing

To date, we have manufactured only limited supplies of drug substance for use in IND-enabling toxicology studies in animals at our own facility, as well as patisiran formulated bulk drug product for use in clinical trials. We have contracted with several third-party contract manufacturing organizations, or CMOs, for the supply of drug substance and finished product, other than patisiran, to meet our testing needs for pre-clinical toxicology and clinical testing. We expect to continue to rely on third-party CMOs for the supply of drug substance and certain drug product, including siRNAs and siRNA conjugates, for our product candidates for at least the next several years, including to support the launch of our first several products. During 2015, we amended our manufacturing agreement with Agilent Technologies, Inc., or Agilent, to provide for Agilent to supply, subject to any conflicting obligations under our third-party agreements, a specified percentage of the active pharmaceutical ingredients required for certain of our

products in clinical development, as well as other products the parties may agree upon in the future, over an initial term of four years. We are required to provide rolling forecasts for products on a quarterly basis, a portion of which will be considered a binding, firm order. Agilent is required to reserve sufficient capacity to ensure that it can supply products in the amounts specified under such firm orders, as well as up to a certain percentage of the remaining, non-binding portions of each forecast. Subject to any conflicting obligations under our third-party agreements, we have also agreed to negotiate in good faith to enter into a separate commercial manufacturing supply agreement with Agilent for certain products, consistent with certain specified terms, including a specified minimum purchase commitment. In April 2016, we completed our purchase of a parcel of land in Norton, Massachusetts. We have commenced construction of a cGMP manufacturing facility at this site for drug substance, including siRNAs and siRNA conjugates, for clinical and commercial use, which we currently expect to be commercially operational in 2020.

During 2012, we established a manufacturing facility and have developed cGMP capabilities and processes for the manufacture of patisiran formulated bulk drug product for late stage clinical trials and commercial use. During 2013, we manufactured our first cGMP batches of patisiran for use in our Phase 2 OLE and Phase 3 clinical trials. We expect to manufacture late stage clinical and commercial supply for patisiran formulated bulk drug product in our facility. Commercial quantities of any

drugs that we may seek to develop will have to be manufactured in facilities, and by processes, that comply with FDA regulations and other federal, state and local regulations, as well as comparable foreign regulations.

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

Commercial Operations

After years of work, successfully discovering a new product platform technology, developing a potential new class of innovative medicines and retaining broad commercial rights, our next objective is to introduce our RNAi therapeutics to as many patients in need as possible. To meet that new challenge, we intend to build a global commercial operation which will be fully integrated and ready to sequentially manage the potential of multiple product launches across multiple geographies. As a commercial-stage biopharmaceutical company, we intend to have the ability to market and sell our products ourselves in many countries. The conduct of these commercial activities will be dependent upon if, and when, regulatory approval is obtained for our product candidates and on agreements that we have made or may make in the future with strategic collaborators, currently as follows:

- For patisiran, if APOLLO is positive, we have rights to commercialize in the United States, Canada and Western Europe while Sanofi Genzyme has rights to commercialize in the rest of the world;
- For fitusiran, if ATLAS is positive, we have rights to co-commercialize with Sanofi Genzyme in the United States, Canada and Western Europe, and Sanofi Genzyme has rights to commercialize in the rest of the world;
- For givosiran, we retain global rights to commercialize; and
- For inclisiran, we have granted MDCO global rights to commercialize.

Throughout the development of our product candidates, we have remained focused on keeping patients at the center of everything we do. This patient focus will continue as we move towards commercialization. Moreover, our late stage programs are focused on orphan diseases, and these patients and their families are often in need of more than just a product. It is our goal to identify information, education solutions and services that benefit these patients and their families, and to have a rich patient services approach in these orphan diseases. In addition, we are focused early in the product development cycle on establishing evidence that we can bring to payors about the pharmacoeconomic opportunities that our product candidates represent to ensure access for patients.

During 2016, we started to assemble key components of a commercial organization with a focus on preparation for the potential commercial launch of patisiran in 2018, if APOLLO is positive and regulatory approval is obtained. We are beginning to assemble a focused commercial team with broad experience in marketing, sales, patient access, distribution and product reimbursement, in particular for orphan diseases. As we continue to prepare for a potential patisiran commercial launch in the United States, Canada and Western Europe, we plan to expand our commercial organization over the next twelve to eighteen months. This expansion will include incorporation of appropriate quality systems, compliance policies and procedures, implementation of internal systems and infrastructure in order to support commercial sales, and establishment of patient-focused programs. We have also begun to establish a presence in major European markets with the hiring of country general managers, market access professionals and medical experts. In each country where our product candidates are approved by health authorities (if, when and where), we plan to build a full commercial team composed of marketing, field sales and patient services on time to execute

successful launches. For some territories/countries, we may also elect in to utilize strategic partners, distributors or contract sales forces to assist in the commercialization of our products.

Scientific Advisors

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

- our research and development programs;
- the design and implementation of our clinical programs;
- our patent and publication strategies;

- new technologies relevant to our research and development programs; and
- specific scientific and technical issues relevant to our business.

The current members of our scientific advisory board are:

Name	Position/Institutional Affiliation
Dennis A. Ausiello, M.D.	Director/Center for Assessment Technology and Continuous Health (CATCH); Jackson Distinguished Professor of Clinical Medicine/Harvard Medical School; Physician-in-Chief Emeritus/Massachusetts General Hospital
David P. Bartel, Ph.D.	Member/Whitehead Institute for Biomedical Research; Professor/Massachusetts Institute of Technology; Investigator/Howard Hughes Medical Institute
Nancy J. Brown, M.D.	Professor of Medicine and Pharmacology, Hugh J. Morgan Chair of the Department of Medicine/Vanderbilt University School of Medicine
Robert S. Langer, Ph.D.	Institute Professor/Massachusetts Institute of Technology
Judy Lieberman, M.D., Ph.D.	Senior Investigator/Immune Disease Institute — Harvard Medical School; Professor/Harvard Medical School; Chair in Cellular and Molecular Medicine/Boston Children's Hospital
Muthiah Manoharan, Ph.D.	Senior Vice President, Innovation Chemistry and Distinguished Scientist/Alnylam Pharmaceuticals, Inc.
Rachel Meyers, Ph.D.	Industry Consultant; Former Senior Vice President, Research/Alnylam Pharmaceuticals, Inc.
Daniel J. Rader, M.D.	Associate Director, Institute for Translational Medicine and Therapeutics, Chief, Division of Translational Medicine and Human Genetics and Professor of Molecular Medicine/Perelman Center for Advanced Medicine, University of Pennsylvania
Paul R. Schimmel, Ph.D.	Ernest and Jean Hahn Professor/Skaggs Institute for Chemical Biology, The Scripps Research Institute
Phillip A. Sharp, Ph.D.	Institute Professor/The Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology
Markus Stoffel, M.D., Ph.D.	Professor/Institute of Molecular Health Sciences, Swiss Federal Institute of Technology (ETH) Zurich
Thomas H. Tuschl, Ph.D.	Professor/Rockefeller University; Investigator/Howard Hughes Medical Institute
Phillip D. Zamore, Ph.D.	Gretchen Stone Cook Professor/University of Massachusetts Medical School; Chair/RNA Therapeutics Institute, University of Massachusetts Medical School; Investigator/Howard Hughes Medical Institute

Employees

At January 31, 2017, we had 514 employees, 407 of whom were engaged in research and development. None of our employees are represented by a labor union or covered by a collective bargaining agreement, nor have we experienced work stoppages. We believe that relations with our employees are good.

Financial Information About Geographic Areas

See the section entitled "Segment Information" appearing in Note 2 to our consolidated financial statements for financial information about geographic areas. The Notes to our consolidated financial statements are contained in Part II,

Item 8, “Financial Statements and Supplementary Data,” of this annual report on Form 10-K.

Corporate Information

Alnylam Pharmaceuticals, Inc. is a Delaware corporation that was formed in May 2003. Alnylam U.S., Inc., one of our wholly owned subsidiaries, is also a Delaware corporation that was formed in June 2002 as our initial corporate entity. Our principal executive office is located at 300 Third Street, Cambridge, Massachusetts 02142, and our telephone number is (617) 551-8200.

Investor Information

We maintain an internet website at http://www.alnylam.com. The information on our website is not incorporated by reference into this annual report on Form 10-K and should not be considered to be a part of this annual report on Form 10-K. Our website address is included in this annual report on Form 10-K as an inactive technical reference only. Our reports filed or furnished pursuant

to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, including our annual reports on Form 10-K, our quarterly reports on Form 10-Q and our current reports on Form 8-K, and amendments to those reports, are accessible through our website, free of charge, as soon as reasonably practicable after these reports are filed electronically with, or otherwise furnished to, the United States Securities and Exchange Commission, or SEC. We also make available on our website the charters of our audit committee, compensation committee, nominating and corporate governance committee, and science and technology committee, as well as our corporate governance guidelines and our code of business conduct and ethics. In addition, we intend to disclose on our web site any amendments to, or waivers from, our code of business conduct and ethics that are required to be disclosed pursuant to the SEC rules.

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

Executive Officers of the Registrant

Set forth below is information about our executive officers, as of January 31, 2017.

Name	Age	Position
John M. Maraganore, Ph.D.	54	Chief Executive Officer and Director
Barry E. Greene	53	President
Akshay K. Vaishnaw, M.D., Ph.D.	54	Executive Vice President, Research and Development
Yvonne L. Greenstreet, MBChB	54	Executive Vice President and Chief Operating Officer
Laurie B. Keating	62	Senior Vice President, General Counsel and Secretary
Michael P. Mason	42	Vice President of Finance and Treasurer

John M. Maraganore, Ph.D. has served as our Chief Executive Officer and as a member of our board of directors since December 2002. Dr. Maraganore also served as our President from December 2002 to December 2007. From April 2000 to December 2002, Dr. Maraganore served as Senior Vice President, Strategic Product Development at Millennium Pharmaceuticals, Inc., a biopharmaceutical company (now Millennium: The Takeda Oncology Company). Dr. Maraganore serves as the chairman of the board of directors of Agios Pharmaceuticals, Inc., a biotechnology company and as a member of the board of directors of bluebird bio, Inc., a biotechnology company.

Barry E. Greene has served as our President since December 2007, as our Chief Operating Officer from the time he joined us in October 2003 through September 2016, and from February 2004 through December 2005, as our Treasurer. From February 2001 to September 2003, Mr. Greene served as General Manager of Oncology at Millennium Pharmaceuticals, Inc., a biopharmaceutical company (now Millennium: The Takeda Oncology Company). Mr. Greene serves as a member of the board of directors of Acorda Therapeutics, Inc., a biotechnology company and as the lead director of Karyopharm Therapeutics Inc., a clinical-stage pharmaceutical company.

Akshay K. Vaishnaw, M.D., Ph.D. has served as our Executive Vice President of Research and Development since December 2014 and served as our Chief Medical Officer from June 2011 to December 2016. He served as our Executive Vice President from June 2012 to December 2014 and prior to that as our Senior Vice President from June 2011 to June 2012. He served as our Senior Vice President, Clinical Research from December 2008 to June 2011, and

prior to that served as our Vice President, Clinical Research from the time he joined us in January 2006. From December 1998 through December 2005, Dr. Vaishnaw held various positions at Biogen Inc., a biopharmaceutical company. Dr. Vaishnaw serves as a member of the board of directors of Editas Medicine, Inc., a biotechnology company. Dr. Vaishnaw is a Member of the Royal College of Physicians, United Kingdom.

Yvonne L. Greenstreet, MBChB has served as our Executive Vice President and Chief Operating Officer since September 2016. Prior to joining Alnylam, Dr. Greenstreet most recently served as the founder and Managing Director of Highgate LLC, from January 2014 to August 2016. Prior to that time, Dr. Greenstreet served as the Senior Vice President and Head of Medicines Development at Pfizer Inc., a multinational pharmaceutical company, from December 2010 to November 2013. Prior to joining Pfizer, Dr. Greenstreet worked for 18 years at GlaxoSmithKline plc, or GSK, a multinational pharmaceutical, biologics, vaccines and consumer healthcare company, where she served in various positions, most recently as Senior Vice President and Chief of Strategy for Research and Development and as a member of GSK’s Product Management Board. Dr. Greenstreet serves as a member of the board of directors of Pacira Pharmaceuticals, Inc., a specialty pharmaceutical company, Indivior PLC, a global specialty pharmaceutical business, and Advanced Accelerator Applications S.A., a radiopharmaceutical company. Dr. Greenstreet also serves on the Scientific Advisory Committee of the Bill and Melinda Gates Foundation.

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

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

ITEM 1A. RISK FACTORS

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

Risks Related to Our Business

Risks Related to Being a Clinical Stage Company

Although we have product candidates in late stage clinical development, there is limited information about our ability to successfully overcome many of the risks and uncertainties encountered by companies in the biopharmaceutical industry.

Although we have product candidates in late stage 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:

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- 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 and development on RNAi technology and our future success depends on the successful development of this technology and products based on it. Neither we nor any other company has received regulatory approval to market therapeutics utilizing siRNAs, the class of molecule we are trying to develop into drugs. The scientific

discoveries that form the basis for our efforts to discover and develop new drugs are relatively new. The scientific evidence to support the feasibility of developing drugs based on these discoveries is both early stage 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, or the ability to enter cells within relevant tissues in order to exert their effects. We currently have limited data to suggest that we can introduce these properties into siRNAs. We have spent and expect to continue to spend large amounts of money trying to develop siRNAs that possess the properties typically required of drugs, and we 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. For example, in October 2016, we discontinued development of revusiran, an investigational RNAi therapeutic that was in development for the treatment of patients with cardiomyopathy due to hATTR amyloidosis, due to safety concerns, and are conducting a comprehensive evaluation of the revusiran data. We may never succeed in developing a marketable product, we may not become profitable and the value of our common stock will decline.

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

Risks Related to Our Financial Results and Need for Financing

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

We have experienced significant operating losses since our inception. At December 31, 2016, we had an accumulated deficit of $1.66 billion. To date, we have not received regulatory approval to market or sell any products nor generated any revenues from the sale of products. Further, we do not expect to generate any product revenues until at the earliest 2018, assuming we receive marketing approval for patisiran. 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 maintain our existing alliances or secure and maintain new 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 and reimbursement for these novel drugs and manufacturing, marketing and selling them. We may never succeed in these activities, and may never generate revenues that are significant enough to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. If we cannot become and remain consistently profitable, the market price of our common stock could decline. In addition, we may be unable to raise capital, expand our business, develop additional product candidates or continue

our operations.

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

We have used substantial funds to develop our RNAi technologies and will require substantial funds to conduct further research and development, including pre-clinical testing and clinical trials of our product candidates, and to manufacture, market and sell 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;
- 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, prepare for the commercialization of our product candidates, and obtain and maintain licenses to third-party intellectual property;
- our ability to establish, maintain and operate our own manufacturing facilities in a timely and cost effective manner;
- 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; 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. For example, our decision in October 2016 to discontinue development of revusiran and the subsequent decline in our stock price may make it more difficult for us to obtain additional funding on acceptable terms.

In April 2016, our subsidiary, Alnylam U.S., Inc., entered into an aggregate of $150.0 million in term loan agreements with Bank of America N.A., or BOA, and Wells Fargo Bank, National Association, or Wells, for which we are the guarantor, related to the build out of our new drug substance manufacturing facility, that mature in April 2021. Interest on the borrowings is calculated based on LIBOR plus 0.45 percent. During an event of default under either agreement, the obligations under such agreement will bear interest at a rate per annum equal to the interest rate then in effect plus two percent. The obligations under the term loan agreements are secured by cash collateral in an amount equal to, at any given time, at least 100 percent of the principal amount of all term loans outstanding under the credit agreements at such time. The agreements include restrictive covenants that could limit our flexibility in conducting future business activities and further limit our ability to change the nature of our business and, in the event of insolvency, the lenders would be paid before holders of equity securities received any distribution of corporate assets. If an event of default occurs, the interest rate would increase and the lenders would be entitled to take various actions, including the acceleration of amounts due under the loan. Our ability to satisfy our obligations under these agreements and meet our debt service obligations will depend upon our future performance, which will be subject to financial, business and other factors affecting our operations, many of which are beyond our control.

In addition, the terms of any financing may adversely affect the holdings or the rights of our stockholders. For example, if we raise additional funds by issuing equity securities, further dilution to our existing stockholders will result. In addition, as a condition to providing additional funding to us, future investors may demand, and may be granted, rights superior to those of existing stockholders. Moreover, our investor agreement with Sanofi Genzyme provides Sanofi Genzyme with the right, subject to certain exceptions, generally to maintain its ownership position in

us until Sanofi Genzyme owns less than 7.5 percent of our outstanding common stock, subject to certain additional limited rights of Sanofi 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, Sanofi Genzyme exercised its right to purchase an additional 344,448 shares of our common stock. In January 2015, Sanofi Genzyme also exercised its right to purchase 196,251 shares based on its 2014 compensation-related right and its right to purchase 744,566 shares in connection with our public offering. In February 2016, Sanofi Genzyme purchased an additional 205,030 shares based on its 2015 compensation-related right. These purchases allowed Sanofi Genzyme to maintain its ownership level of

approximately 12 percent of our outstanding common stock. While the exercise of these rights by Sanofi Genzyme has provided us with an additional $126.3 million in cash to date, and while any exercise of these rights by Sanofi Genzyme in the future will provide us with further additional cash, these exercises have caused, and any future exercise of these rights by Sanofi Genzyme will also cause further, dilution to our stockholders. In January 2017, Sanofi Genzyme elected not to exercise its compensation-related right for 2016. In November 2016, Sanofi Genzyme elected to expand its regional rights for fitusiran and opt-in to co-develop and co-commercialize fitusiran in the United States, Canada and Western Europe, in addition to developing and commercializing the product in the Sanofi Genzyme Territory. In connection with the exercise of this right, Sanofi Genzyme paid us in January 2017 for its incremental share of co-development costs incurred from January 2016 to September 2016, in accordance with the 2014 Sanofi Genzyme collaboration. Going forward, Sanofi Genzyme will share in 50 percent of certain development and sales and marketing costs for fitusiran, which will result in increased expense reimbursement to us.

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, and our ability to achieve our strategy for 2020 may be delayed or diminished. We also could be required to seek funds through arrangements with collaborators or others that may require us to relinquish rights to some of our technologies, product candidates or products that we would otherwise pursue on our own.

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

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

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

At December 31, 2016, we had $942.6 million in cash, cash equivalents and fixed income marketable securities, excluding our investment in equity securities of Regulus and the $150.0 million of restricted investments related to the term loan agreements with BOA and Wells. We historically have invested these amounts in high–grade corporate notes, commercial paper, securities issued or sponsored by the U.S. government and money market funds meeting the criteria of our investment policy, which is focused on the preservation of our capital. Corporate notes also include foreign bonds denominated in U.S. dollars. 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

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, as well as 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 in certain territories, and we intend to enter into additional such alliances in the future. Our collaboration strategy is to form alliances that create significant value for us 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 Sanofi Genzyme in 2014 pursuant to which we retain development and commercial rights for our current and future Genetic Medicine products in the United States, Canada and Western Europe, and Sanofi Genzyme has the right to develop and commercialize our current and future Genetic Medicine products principally in the rest of the world, 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 development and commercialization rights. We currently have a global alliance with MDCO to advance inclisiran.

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) Sanofi Genzyme for the development and commercialization of patisiran, fitusiran and potentially other of our Genetic Medicine programs in territories outside of the United States, Canada and Western Europe, and (ii) MDCO for all future development and commercialization of inclisiran worldwide. If Sanofi Genzyme and/or MDCO are not successful in their commercialization efforts, our future revenues from RNAi therapeutics for these indications may be adversely affected. In addition, Sanofi Genzyme may elect not to opt into one or more of our Genetic Medicine programs. For example, during 2016, Sanofi Genzyme elected not to take a regional license for our givosiran and ALN-CC5 programs. While we intend to advance these programs independently, retaining global development and commercial rights, our ability to advance these programs and successfully develop and commercialize these product candidates may be adversely affected as a result of Sanofi Genzyme's decision.

We may not be successful in entering into future 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. For example, our decision in October 2016 to discontinue development of revusiran could make it more difficult for us to attract collaborators due to concerns around the safety and/or efficacy of our technology platform or product candidates. Even if we do succeed in securing any such alliances, we may not be able to maintain them if, for example, development or approval of a product candidate is delayed, challenges are raised as to the validity or scope of our intellectual property, we are unable to secure adequate reimbursement from payors or sales of an approved drug are lower than we expected.

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

For certain product candidates that we may develop, we have formed collaborations to fund all or part of the costs of drug development and commercialization, such as our collaborations with Sanofi Genzyme and 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 with respect to the collaboration or a particular program under the collaboration, under certain circumstances. Moreover, our agreement with MDCO relating to the development and commercialization of inclisiran 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 expanded sales, distribution and marketing capabilities internally, 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, development and/or commercialization 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 expanded sales and marketing capabilities outside of the United States and EU, make it more difficult for us to attract new collaborators and could adversely affect how we are perceived in the business and financial communities. For example, in March 2011, Arbutus (formerly 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 Arbutus regarding the achievement by Arbutus 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. The Arbutus arbitration hearing was held in May 2015. In March 2016, the arbitration panel ruled in our favor and as a result, no milestone payment is due to Arbutus at this time. The grounds on which Arbutus could appeal this ruling were limited and Arbutus did not appeal by the deadline.

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 control only certain aspects of their activity and therefore, we cannot be assured that these third parties will adequately perform all of their contractual obligations to us. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on third parties does not relieve us of our regulatory responsibilities. We and our contract research organizations are required to comply with GCPs, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities for all of our product candidates in clinical development. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our contract research organizations fail to comply with applicable GCP requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, the EMA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP regulations.

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 and/or regulatory reviews for marketing approvals may be delayed or terminated. As a result, our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to

generate revenues could be delayed.

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

We have limited manufacturing experience. In order to develop our product candidates, apply for regulatory approvals and commercialize our products, if approved, we will need to develop, contract for, or otherwise arrange for the necessary manufacturing capabilities. Historically, our internal manufacturing capabilities were limited to small-scale production of material for use in in vitro and in vivo experiments that is not required to be produced under cGMP standards. During 2012, we developed cGMP capabilities and processes for the manufacture of patisiran formulated bulk drug product for late stage clinical trial use and commercial supply. In addition, in April 2016, we completed our purchase of a parcel of land in Norton, Massachusetts, where we have commenced construction of a cGMP manufacturing facility for drug substance, including siRNAs and siRNA conjugates, for clinical and commercial use.

We may manufacture limited quantities of clinical trial materials ourselves, but otherwise we currently rely on third parties to manufacture the drug substance and, with the exception of patisiran, the finished product we will require for any clinical trials that we initiate and to support the commercial launch of our first several products. There are a limited number of manufacturers that supply synthetic siRNAs. We currently rely on a limited number of CMOs for our supply of synthetic siRNAs. For example, in July 2015, we amended our manufacturing agreement with Agilent, to provide for Agilent to supply, subject to any conflicting obligations under our third-party agreements, a specified percentage of the active pharmaceutical ingredients required for certain of our products in clinical development, as well as other products the parties may agree upon in the future. There are risks inherent in pharmaceutical manufacturing that could affect the ability of our CMOs, including Agilent, 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/or contamination during the manufacturing process, as well as other issues with the CMO's facility and ability to comply with the applicable manufacturing requirements, which could result in unusable product and cause delays in our manufacturing timelines and ultimately delay our clinical trials, as well as result in additional expense to us. To fulfill our siRNA requirements, we will likely need to secure alternative suppliers of synthetic siRNAs and such alternative suppliers are limited and may not be readily available, or we may be unable to enter into agreements with them on reasonable terms and in a timely manner. As noted above, in order to ensure long-term supply capabilities for our RNAi therapeutics, we are developing our own capabilities to manufacture drug substance, including siRNAs and siRNA conjugates, for clinical and commercial use.

In addition to the manufacture of the synthetic siRNAs, we may have additional manufacturing requirements related to the technology required to deliver the siRNA to the relevant cell or tissue type, such as LNPs or conjugates. In some cases, the delivery technology we utilize is highly specialized or proprietary, and for technical and/or 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 and/or take significant time. 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 manufacture our delivery technology and/or formulate our siRNAs for delivery could result in unusable product. Furthermore, competition for supply from our manufacturers from other companies, 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 drug substance, we have developed cGMP capabilities and processes for the manufacture of patisiran formulated bulk drug product for late stage clinical use and commercial supply. During 2015, we scaled our cGMP manufacturing capacity for patisiran and believe we should have adequate resources to supply our commercial needs. In addition, as noted above, we are developing our own capabilities to manufacture drug substance, including siRNAs and siRNA conjugates, for clinical and commercial use. In developing these manufacturing capabilities by building our own manufacturing facilities, we have incurred substantial expenditures, and expect to incur significant additional expenditures in the future. In addition, the construction and qualification of our drug substance facility is expected to take several years to complete and there are many risks inherent in the construction of a new facility that could result in delays and additional costs, including the need to obtain access to necessary equipment and third-party technology, if any. Also, we have had to, and will likely need to continue to, hire and train qualified employees to staff our facilities. 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 facilities in the future, we may also need to secure alternative suppliers of patisiran formulated bulk drug product and drug substance, and such alternative suppliers may not be available, or we may be unable to enter into agreements with them on reasonable terms and in a timely manner.

The manufacturing process for any products that we may develop is subject to the FDA and foreign regulatory authority approval process and we will need to meet, and will need to contract with manufacturers who can meet, all

applicable FDA and foreign regulatory authority requirements on an ongoing basis. In addition, if we receive the necessary regulatory approval for any product candidate, we also expect to rely on third parties, including potentially our commercial collaborators, to produce materials required for commercial supply. We may experience difficulty in obtaining adequate manufacturing capacity for our needs and the needs of our collaborators, who we have, in some instances, the obligation to supply. If we are unable to obtain or maintain CMOs 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, including Agilent, 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 Agilent or any other 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, including Agilent, fails to perform its obligations, we may be forced to manufacture the materials ourselves, for which we may not have the capabilities or resources, or enter into an agreement with a different third-party manufacturer, which we may not be able to do on reasonable terms, if at all. In either scenario, our clinical trials or commercial distribution could be delayed significantly as we establish alternative supply sources. In some cases, the technical skills required to manufacture our products or product candidates may be unique or proprietary to the original manufacturer and we may have difficulty, or there may be contractual restrictions prohibiting us from, transferring such skills to a back-up or alternate supplier, or we may be unable to transfer such skills at all. In addition, if we are required to change manufacturers for any reason, we will be required to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. We will also need to verify, such as through a manufacturing comparability study, that any new manufacturing process will produce our product according to the specifications previously submitted to or approved by the FDA or another regulatory authority. The delays associated with the verification of a new manufacturer could negatively affect our ability to develop product candidates in a timely manner or within budget. Furthermore, a manufacturer may possess technology related to the manufacture of our product candidate that such manufacturer owns independently. This would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have another third party manufacture our products or product candidates.

We have no sales or distribution experience and only early capabilities for marketing, sales and market access, and expect to invest significant financial and management resources to establish these capabilities and to establish infrastructure in the EU.

We have no sales or distribution experience and only early capabilities for marketing, sales and market access. We currently expect to rely heavily on third parties to launch and market certain of our product candidates in certain geographies, if approved. However, we intend to commercialize the majority of our products on our own in the United States and EU, as well as globally in the case of givosiran. Accordingly, we will need to develop internal sales, distribution and marketing capabilities as part of our core product strategy initially in the United States and the EU, and longer-term on a global basis, which will require significant financial and management resources. For the majority of our Genetic Medicine programs where we will perform sales, marketing and distribution functions ourselves in the United States, Canada and Western Europe, and for future Cardio-Metabolic and Hepatic Infectious Disease products we successfully develop where we intend to retain significant product development and commercialization rights, we could face a number of additional risks, including:

- we may not be able to attract and build a significant marketing or sales force;
- we may not be able to establish our capabilities and infrastructure in the EU or in other territories in a timely manner;
- 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 in the United States and the EU, as well as globally for certain products, we will not be able to successfully commercialize our products 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.

Our ability to secure additional financing in addition to the term loan agreements with BOA and Wells and to satisfy our financial obligations under indebtedness outstanding from time to time will depend upon our future operating performance, which is subject to then prevailing general economic and credit market conditions, including interest rate levels and the availability of credit generally, and financial, business and other factors, many of which are beyond our control. In light of periodic uncertainty in the capital and credit markets, there can be no assurance that sufficient financing will be available on desirable or even any terms to fund investments, acquisitions, stock repurchases, dividends, debt refinancing or extraordinary actions.

Risks Related to Managing Our Operations

If we are unable to attract and retain qualified key management and scientists, development and commercial 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 arrangements 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 anticipate continuing to add a significant number of additional employees as we focus on achieving our Alnylam 2020 strategy. We face intense competition for qualified individuals from numerous pharmaceutical and biotechnology companies, universities, governmental entities and other research institutions, many of which have substantially greater resources with which to reward qualified individuals than we do. In addition, due to our recent decision to discontinue our revusiran program, and the related decline in our stock price, we may face additional challenges in attracting and retaining employees. Accordingly, 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 U.S.-based company primarily involved in discovery, pre-clinical testing and clinical development into a global company 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 in the United States and continue to build operations in the EU and eventually other territories. As noted above, we have grown our workforce significantly over the past year and anticipate continuing to hire additional employees, including employees in the EU, as we focus on achieving our Alnylam 2020 strategy. This expected growth is placing a strain on our administrative and operational infrastructure, and we will need to develop additional and/or new infrastructure and capabilities to support our growth and obtain additional space to conduct our operations in the United States and the EU. 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, quality, compliance, and marketing and sales capabilities in the United States and the EU 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, as well as delays in the commercialization of our products, 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 and potential commercialization of our product candidates could be delayed.

The results of the United Kingdom's referendum on withdrawal from the EU may have a negative effect on global economic conditions, financial markets and our business.

In June 2016, the United Kingdom, or UK, held a referendum in which voters approved an exit from the EU, commonly referred to as "Brexit." This referendum has created political and economic uncertainty, particularly in the UK and the EU, and this uncertainty may persist for years. A withdrawal could, among other outcomes, disrupt the free movement of goods, services and people between the UK and the EU, and result in increased legal and regulatory complexities, as well as potential higher costs of conducting business in Europe. The UK's vote to exit the EU could also result in similar referendums or votes in other European countries in which we do business. Given the lack of comparable precedent, it is unclear what financial, trade and legal implications the withdrawal of the UK from the EU would have and how such withdrawal would affect us.

For example, Brexit could result in the UK or the EU significantly altering its regulations affecting the clearance or approval of our product candidates that are developed in the UK. Any new regulations could add time and expense to the conduct of our business, as well as the process by which our products receive regulatory approval in the UK, the EU and elsewhere. In addition, the announcement of Brexit and the withdrawal of the UK from the EU have had and may continue to have a material adverse effect on global economic conditions and the stability of global financial markets, and may significantly reduce global market liquidity and restrict the ability of key market participants to operate in certain financial markets. Any of these effects of Brexit, among others, could adversely affect our business, our results of operations, liquidity and financial condition.

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 nonclinical tests and clinical trials to demonstrate the safety and efficacy in humans of our product candidates. Nonclinical and clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome, and the historical failure rate for product candidates is high. In October 2016, we discontinued development of one of our product candidates, which included a Phase 3 clinical trial. We currently have multiple other programs in clinical development, including one program in a Phase 3 clinical trial, as well as several earlier stage clinical programs. However, we may not be able to further advance these or any other product candidate through clinical trials and regulatory approval.

If we enter into clinical trials, the results from nonclinical 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 July 2016, we announced updated results from our Phase 1 clinical trial of fitusiran, including initial clinical data on a small number of people with hemophilia with inhibitors. Although the initial clinical data from this trial are encouraging, the data are preliminary in nature, based on a limited number of people with hemophilia with inhibitors, and the fitusiran Phase 1 study is not complete. These data, or other positive data, may not continue for these people with hemophilia or occur for any future patients 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. In addition, in June 2016, we reported initial data from PNH patients in our ALN-CC5 Phase 1/2 clinical trial, and we reiterated that we now plan to pursue a more focused development path in PNH where ALN-CC5 would be evaluated in eculizumab poor responders and for eculizumab sparing, as well as potentially in other indications. 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, fitusiran and our other product candidates each employ novel delivery technologies that have yet to be extensively evaluated in human clinical trials and proven safe and effective.

In addition, we, the FDA or other applicable regulatory authorities, or an IRB or similar foreign review board or committee, may delay initiation of or 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 or related product on healthy volunteer subjects or patients in a clinical trial could result in our decision, or a decision by the FDA or foreign regulatory authorities, to suspend or terminate the trial, or, in the case of regulatory agencies, a refusal to approve a particular product candidate for any or all indications of use. For example, in October 2016, we announced our decision to discontinue development of revusiran, an investigational RNAi therapeutic that was being developed for the treatment of patients with cardiomyopathy due to hATTR amyloidosis. Our decision followed the recommendation of the revusiran ENDEAVOUR Phase 3 study DMC to suspend dosing and the observation of an imbalance in mortality in revusiran-treated patients as compared to those on placebo. Separately, the patisiran APOLLO DMC met at our request following our decision to

discontinue development of revusiran, and recommended continuation of the APOLLO Phase 3 trial of patisiran, without modification. We are conducting a comprehensive evaluation of the revusiran data. While we believe that the decision to discontinue development of revusiran does not affect patisiran, which is in development for the treatment of hATTR amyloidosis, or any of our other investigational RNAi therapeutic programs in development, our comprehensive evaluation of the revusiran data is preliminary and ongoing. We expect this evaluation will take some time to complete and there remains uncertainty regarding the cause of the findings that led to the discontinuation of the revusiran program.

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 availability of clinical trials for other investigational drugs for the same disease or condition, 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 fitusiran, due to the availability of existing approved treatments, as well as other investigational treatments in development. Delays or difficulties in patient enrollment or difficulties retaining trial participants, including as a result of the availability of existing or other investigational treatments, can result in increased costs, longer development times or termination of a clinical trial.

Although our investigational RNAi therapeutics have been generally well tolerated in our clinical trials to date, new safety findings may emerge. For example, as noted above, in October 2016, we made the decision to discontinue our revusiran program. Following reports in the revusiran Phase 2 OLE study of new onset or worsening peripheral neuropathy, the revusiran ENDEAVOUR Phase 3 study DMC assembled in early October 2016 at our request to review these reports and ENDEAVOUR safety data on an unblinded basis. The DMC did not find conclusive evidence for a drug-related neuropathy signal in the ENDEAVOUR trial, but informed us that the benefit-risk profile for revusiran no longer supported continued dosing. We subsequently reviewed unblinded ENDEAVOUR data which revealed an imbalance of mortality in the revusiran arm as compared to placebo. We had previously reported, in July 2016, preliminary data from our revusiran Phase 2 OLE study for 12 patients who had reached the 12-month endpoint as of the data transfer date of May 26, 2016. SAEs were observed in 14 patients, one of which, a case of lactic acidosis, was deemed possibly related to the study drug and the patient discontinued treatment. There were a total of seven deaths reported at that time in the revusiran OLE study, all of which were unrelated to study drug. The majority of the AEs were mild or moderate in severity; ISRs were reported in 12 patients. In August 2015, we reported that three patients had discontinued from the revusiran Phase 2 OLE study due to recurrent localized reactions at the injection site or a diffuse rash; no further discontinuations due to ISRs had occurred as of May 26, 2016. In our patisiran Phase 2 OLE study in patients with polyneuropathy due to hATTR amyloidosis, based on preliminary 24-month data reported from 27 patients as of the data cutoff on May 12, 2016, the most common drug-related or possibly drug-related AEs were flushing and infusion-related reactions, all of which were all mild in severity and did not result in any discontinuations. There were nine reports of SAEs in six patients, all of which were unrelated to study drug, including one discontinuation for gastroesophageal cancer at approximately 20 months in a patient who subsequently died and one death due to myocardial infarction in a 79 year-old patient who died after having completed the full 24 months of treatment. As noted above, the patisiran APOLLO Phase 3 study DMC met at our request following our decision to discontinue development of revusiran, and recommended continuation of the APOLLO Phase 3 trial without modification. In addition, 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. As demonstrated by the recent discontinuation of our revusiran program, the occurrence of AEs 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 or, outside of the United States, an independent ethics committee, which continually review clinical investigations and protect the rights and welfare of human subjects. Inability to obtain or delay in obtaining IRB or ethics committee 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 or ethics committee review and approval, as the case may be, in support of a marketing application.

Our product candidates that we develop may encounter problems during clinical trials that will cause us, an IRB, ethics committee 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, nonclinical testing and the clinical trial process that could delay or prevent regulatory approval or our ability to commercialize our product candidates, including:

- our nonclinical tests or clinical trials may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional nonclinical testing or clinical trials, or we may abandon projects that we expect to be promising;
- delays in filing IND applications or comparable foreign applications or delays or failure in obtaining the necessary approvals from regulators or IRBs/ethics committees 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 ethics committee, or the FDA or comparable foreign authorities regarding the scope or design of our clinical trials;
- problems in engaging IRBs or ethics committees to oversee clinical trials or problems in obtaining or maintaining IRB or ethics committee 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 nonclinical 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 nonclinical testing and clinical trials and an extensive regulatory approval process are required to be successfully completed in the United States and in many foreign jurisdictions before a new drug can be marketed. Satisfaction of these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. It is possible that none of the product candidates we may develop will obtain the regulatory approvals necessary for us or our collaborators to begin selling them.

We have limited experience in conducting and managing the clinical trials necessary to obtain regulatory approvals, including approval by the FDA. The time required to obtain FDA and other regulatory 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 nonclinical and clinical activities is subject to confirmation and interpretation by regulatory authorities, which could delay, limit or prevent regulatory approval. We may also encounter unexpected delays or increased costs due to new government regulations, for example, from future legislation or administrative action, or from changes in FDA policy during the period of product development, clinical trials and FDA regulatory review. It is impossible to predict whether legislative changes will be enacted, or whether FDA or foreign regulations, guidance or interpretations will be changed, or what the impact of such changes, if any, may be.

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

Any delay or failure in obtaining required approvals could have a material adverse effect on our ability to generate revenues from the particular product candidate for which we are seeking approval. Furthermore, any regulatory approval to market a product may be subject to limitations on the approved uses for which we may market the product or the labeling or other restrictions. In addition, the FDA has the authority to require a REMS plan as part of an 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. In the EU, we could be required to adopt a similar plan, known as a RMP, and our products could be subject to specific risk minimization measures, such as restrictions on prescription and supply, the conduct of post-marketing safety or efficacy studies, or the distribution of patient and/or prescriber educational materials. In either instance, these limitations and restrictions may limit the size of the market for the product and affect reimbursement by third-party payors.

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

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

Following any initial regulatory approval of any drugs we may develop, we will also be subject to continuing regulatory oversight, including the review of adverse drug experiences and clinical results that are reported after our drug products are made commercially available. This would include results from any post-marketing tests or surveillance to monitor the safety and efficacy of the drug product required as a condition of approval or agreed to by us. Any regulatory approvals that we receive for our product candidates may also be subject to limitations on the approved uses for which the product may be marketed. Other ongoing regulatory requirements include, among other things, submissions of safety and other post-marketing information and reports, registration and listing, as well as

continued compliance with cGMP requirements and GCP requirements 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, our future Norton facility, and Agilent and other third-party manufacturers, will also be subject to periodic review and inspection by the FDA and other regulatory agencies. To date, our Cambridge manufacturing facility has not been subject to an inspection by any regulatory authority. The discovery of any new or previously unknown problems with us or our third-party manufacturers, or our or their manufacturing processes or facilities, may result in restrictions on the drug or manufacturer or facility, including withdrawal of

the drug from the market. We have developed cGMP capabilities and processes for the manufacture of patisiran formulated bulk drug product for Phase 3 clinical and commercial use. In addition, in April 2016, we completed our purchase of a parcel of land in Norton, Massachusetts, where we have commenced construction of a cGMP manufacturing facility for drug substance, including siRNAs and siRNA conjugates, for clinical and 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.

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 or new or different therapeutic approaches and mechanisms of action;
- 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 those treatments.

For example, patisiran utilizes an intravenous mode of administration that physicians and/or patients may not readily adopt or which may not compete with other potentially available options. In addition, fitusiran represents a new approach to treating hemophilia which may not be readily accepted by patients and their caregivers.

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 Anti-Kickback statute, which prohibits, among other things, persons from soliciting, receiving, offering or paying 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 laws, which prohibit, among other things, individuals or entities from knowingly presenting or causing to be presented, claims for payment by government-funded programs such as Medicare or Medicaid that are false or fraudulent, and which may apply to us by virtue of statements and representations made to customers or third parties;
- the U.S. federal Health Insurance Portability and Accountability Act and Health Information Technology for Economic and Clinical Health Act, which impose requirements relating to the privacy, security, and transmission of individually identifiable health information; and require notification to affected individuals and regulatory authorities of certain breaches of security of individually identifiable health information;
- the U.S. federal Open Payments requirements were implemented by CMS pursuant to the PPACA, also referred to as the Affordable Care Act. Under the Open Payments Program, manufacturers of medical devices, medical supplies, biological products and drugs covered by Medicare, Medicaid and the 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, including in the EU laws prohibiting giving healthcare professionals any gift or benefit in kind as an inducement to prescribe our products, national transparency laws requiring the public disclosure of payments made to healthcare professionals and institutions, and data privacy laws, in addition to anti-kickback and false claims laws applicable to commercial insurers and other non-federal payors, requirements for mandatory corporate regulatory compliance programs, and laws relating to government reimbursement programs, patient data privacy and security.

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

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

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

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

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

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

The regulations that govern marketing approvals, pricing and reimbursement for new drugs vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In 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 actively monitoring these regulations as several of our programs move into late stages of development, however, a number of our programs are currently in the earlier stages of development and we will not be able to assess the impact of price regulations for a number of years. As a result, we might obtain regulatory approval for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product and negatively impact the revenues we are able to generate from the sale of the product in that country and potentially in other countries due to reference pricing.

Our ability to commercialize any products successfully also will depend in part on the extent to which reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. Even if we succeed in bringing one or more products to the market, these products may not be considered cost-effective, and the amount reimbursed for any products may be insufficient to allow us to sell our products on a competitive basis. Increasingly, the third-party payors who reimburse patients or healthcare providers, such as government and private insurance plans, are requiring that drug companies provide them with predetermined discounts from list prices, and are seeking to reduce the prices charged or the amounts reimbursed for drug 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, or if reimbursement is denied, our return on investment could be adversely affected.

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

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

There may be significant delays in obtaining coverage for newly-approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA or foreign regulatory authorities. Moreover, eligibility for coverage does not imply that any drug will be reimbursed in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution or that covers a particular provider’s cost of acquiring the drug. 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 legislation changed the system of healthcare insurance and benefits intended to broaden coverage and control costs. The law also contains provisions that 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 were increased, and the rebate requirement was extended to drugs used in risk-based Medicaid managed care plans.
- The 340B Drug Pricing Program under the Public Health Service Act was extended to require mandatory discounts for drug products sold to certain critical access hospitals, cancer hospitals and other covered entities.
- Pharmaceutical companies are required to offer discounts on brand-name drugs to patients who fall within the Medicare Part D coverage gap, commonly referred to as the “donut hole.”
- Pharmaceutical companies are required to pay an annual non-tax deductible fee to the federal government based on each company’s market share of prior year total sales of branded products to certain federal healthcare programs, such as Medicare, Medicaid, Department of Veterans Affairs and Department of Defense. Since we expect our branded pharmaceutical sales to constitute a small portion of the total federal healthcare program pharmaceutical market, we do not expect this annual assessment to have a material impact on our financial condition.
- The 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 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. This 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.

As a result of the 2016 election in the United States, there is great political uncertainty concerning the fate of the PPACA and other healthcare laws. The United States Congress is expected to draft legislation to repeal parts of the PPACA, but it is uncertain when such legislation would be passed and whether Congress would replace the law and what any replacement law would encompass.

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 percent per fiscal year, starting in 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.

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. Following the decision to discontinue clinical development of revusiran, we have undertaken a comprehensive evaluation of available revusiran data, which is ongoing. Notwithstanding the risks undertaken by all persons who participate in clinical trials, and the information on risks provided to study investigators and patients participating in revusiran studies, it is possible that product liability claims will be asserted against us relating to the worsening of a patient's condition alleged to have been caused by revusiran. Such claims might not be fully covered by product liability insurance. If we succeed in marketing products, product liability 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 involve 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.

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 manufacture and 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 may 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 may be adversely affected. Despite our efforts and the efforts of our collaborators to protect our proprietary rights, unauthorized parties may

be able to obtain and use information that we regard as proprietary. While issued patents are presumed valid, this does not guarantee that the patent will survive a validity challenge or be held enforceable. Any patents we have obtained, or obtain in the future, may be challenged, invalidated, adjudged unenforceable or circumvented by parties attempting to design around our intellectual property. Moreover, third parties or the USPTO may commence interference proceedings involving our patents or patent applications. Any challenge to, finding of unenforceability or invalidation or circumvention of, our patents or patent applications, would be costly, would require significant time and attention of our management and could have a material adverse effect on our business.

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

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

We are a party to a number of licenses that give us rights to third-party intellectual property that is necessary or useful for our business. In particular, we have obtained licenses from, among others, CRT, Ionis (formerly Isis), MIT, Whitehead, Max Planck Innovation and Arbutus. 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 use as therapeutics, and RNAi-related mechanisms; chemical modifications to siRNAs that improve their suitability for therapeutic and other uses; siRNAs directed to specific targets as treatments for particular diseases; delivery technologies, such as in the fields of carbohydrate conjugates and cationic liposomes; and all aspects of our specific development candidates.

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, as well as inter partes and post-grant review proceedings introduced by provisions of the America Invents Act, which became available to third party challengers on September 16, 2012, in various patent offices relating to patent rights in the RNAi field. For example, various third parties have initiated oppositions to patents in our McSwiggen, Kreutzer-Limmer and Tuschl II series in the EPO and in other jurisdictions. We expect that additional oppositions will be filed in the EPO and elsewhere, and other challenges will be raised relating to other patents and patent applications in our portfolio. In many cases, the possibility of appeal exists for either us or our opponents, and it may be years before final, unappealable rulings are made with respect to these patents in certain jurisdictions. The timing and outcome of these and other proceedings is uncertain and may adversely affect our business if we are not successful in defending the patentability and scope of our pending and issued patent claims. In addition, third parties may attempt to invalidate our intellectual property rights. Even if our rights are not directly challenged, disputes could lead to the weakening of our intellectual property rights. Our defense against any attempt by third parties to circumvent or invalidate our intellectual property rights could be costly to us, could require significant 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 or protect our proprietary information and trade secrets. For example, during the second quarter of 2015, we filed a trade secret misappropriation lawsuit against Dicerna to protect our rights in the RNAi assets we purchased from Merck. A third party may also claim that we have improperly obtained or used its confidential or proprietary information. For example, in March 2011, Arbutus (formerly Tekmira) filed a civil complaint against us alleging, among other things, misappropriation of its confidential and proprietary information and trade secrets. In November 2012, we settled this litigation and restructured our contractual relationship with Arbutus. 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, The University of Utah, or Utah, filed a complaint in the United States District Court for the District of Massachusetts, or the MA District Court, against us, Max Planck Gesellschaft Zur Foerderung Der Wissenschaften e.V. and Max Planck Innovation, together, Max Planck, Whitehead, MIT and UMass, claiming that a professor of Utah is the sole inventor, or in the alternative, a joint inventor of certain of our in-licensed patents. Utah was seeking correction of inventorship of the Tuschl patents, unspecified damages and other relief. After several years of court proceedings and discovery, in September 2015, the MA District Court granted our motions for summary judgment, finding that there was no collaboration between Dr. Bass and Dr. Tuschl, which is a pre-requisite for co-inventorship,

and dismissing Utah's state law damages claims as well. On October 28, 2015, Utah filed a notice of appeal from this ruling to the United States Court of Appeals for the Federal Circuit, or CAFC. On December 18, 2015, the CAFC entered an order dismissing Utah's appeal following a joint motion filed by us and Utah seeking dismissal of the appeal with prejudice. This disposed of Utah's inventorship claims and its state law claims for damages. On October 14, 2015, we filed a motion with the MA District Court seeking reimbursement of costs and fees associated with defending this action in the amount of approximately $8.0 million. On November 30, 2015, the MA District Court denied our motion and on December 15, 2015 we filed a notice of appeal of this ruling with the CAFC. Oral arguments were heard on January 12, 2017 and we anticipate a ruling on our appeal during the second quarter of 2017, however, the timing will be determined by the CAFC. While we believe a fee award is merited in this case, such awards are not customary and are made at the discretion of the court.

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

initiation and continuation of any litigation could delay our research and development efforts and limit our ability to continue our operations.

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

If we fail to comply with our obligations under any licenses or related agreements, we may be required to pay damages and could lose license or other rights that are necessary for developing and protecting our RNAi technology and any related product candidates that we develop, or we could lose certain 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, market and sell products that are covered by the licensed technology or enable a competitor to gain access to the licensed technology. For example, in 2013, Arbutus (formerly Tekmira) notified us that it believed it had 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 notified Arbutus that we did 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 Arbutus had not yet met the conditions of the milestone and was not entitled to payment at the time. The Arbutus arbitration hearing was held in May 2015. On March 9, 2016, the arbitration panel ruled in our favor and as a result, no milestone payment is due to Arbutus at this time. The grounds on which Arbutus could appeal this ruling were limited and Arbutus did not appeal by the deadline.

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

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

In order to protect our proprietary technology and processes, we rely in part on confidentiality agreements with our collaborators, employees, consultants, outside scientific collaborators and sponsored researchers, and other advisors.

These agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. In addition, others may independently discover trade secrets and proprietary information, and in such cases we could not assert any trade secret rights against such party. Costly and time-consuming litigation could be necessary to enforce and determine the scope of our proprietary rights, and failure to obtain or maintain trade secret protection could adversely affect our competitive business position.

Risks Related to Competition

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

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

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

We will face intense competition from drugs that have already been approved and accepted by the medical community for the treatment of the conditions for which we may develop drugs. We also expect to face competition from new drugs that enter the market. We believe a number of drugs are currently under development, and may become commercially available in the future, for the treatment of conditions for which we may try to develop drugs. These drugs may be more effective, safer, less expensive, or marketed and sold more effectively, than any products we develop. For example, we are developing patisiran for the treatment of hATTR amyloidosis. We have completed enrollment in our ongoing Phase 3 clinical trial and expect to report top-line data from our Phase 3 clinical trial in mid-2017. We are aware of other approved products used to treat this disease, including tafamidis, marketed by Pfizer, as well as product candidates in various stages of clinical development, including an investigational drug being developed for which Ionis has completed enrollment in an ongoing Phase 3 clinical trial. Patisiran may not compete favorably with these products and product candidates, and even if approved, it may not achieve commercial success.

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

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

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

methods for the diseases we are targeting could make our product candidates noncompetitive, obsolete or uneconomical.

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

In addition to the competition we face from competing drugs in general, we also face competition from other companies working to develop novel drugs using technology that competes more directly with our own. We are aware of multiple companies that

are working in the field of RNAi. In addition, we granted licenses or options for licenses to Ionis (formerly Isis), Benitec, Arrowhead and its subsidiary, Calando, Arbutus, Quark, Sylentis and others under which these companies may independently develop RNAi therapeutics against a limited number of targets. Any one of these companies may develop its RNAi technology more rapidly and more effectively than us.

In addition, as a result of agreements that we have entered into, Arrowhead, as the assignee of Roche, and Takeda have obtained non-exclusive licenses, and Arrowhead, as the assignee of Novartis Pharma AG, has obtained specific exclusive licenses for 30 gene targets, to certain aspects of our technology that give them the right to compete with us in certain circumstances. We also compete with companies working to develop antisense-based drugs. Like RNAi therapeutics, antisense drugs target mRNAs in order to suppress the activity of specific genes. Ionis (formerly Isis) is currently marketing an antisense drug and has several antisense product candidates in clinical trials, including one for the treatment of hATTR amyloidosis. Ionis is also developing antisense drugs using ligand-conjugated GalNAc technology licensed from us, and these drugs have been shown to have increased potency at lower doses in clinical and pre-clinical studies, compared with antisense drugs that do not use such licensed GalNAc technology. The development of antisense drugs is more advanced than that of RNAi therapeutics, and antisense technology may become the preferred technology for drugs that target mRNAs to silence specific genes.

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

Risks Related to Our Common Stock

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

The market price of our common stock has fluctuated significantly and may continue to fluctuate significantly in response to factors that are beyond our control. The stock market in general has from time to time experienced extreme price and volume fluctuations, and the biotechnology in particular has very recently experienced extreme price and volume fluctuations. The market prices of securities of pharmaceutical and biotechnology companies have been extremely volatile, and have experienced fluctuations that often have been unrelated or disproportionate to the clinical development progress or operating performance of these companies, including as a result of adverse development events. These broad market and sector fluctuations have resulted and could in the future result in extreme fluctuations in the price of our common stock, which could cause purchasers of our common stock to incur substantial losses.

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

Our stock price may fluctuate for many reasons, including as a result of public announcements regarding the progress of our development efforts or the development efforts of our collaborators and/or competitors, the addition or departure of our key personnel, variations in our quarterly operating results and changes in market valuations of pharmaceutical and biotechnology companies. For example, in October 2016, we announced that we were discontinuing the development of revusiran and our stock price declined significantly as a result. When the market price of a stock has been volatile as our stock price has been, holders of that stock have occasionally brought securities

class action litigation against the company that issued the stock. If any of our stockholders were to bring a lawsuit of this type against us, even if the lawsuit is without merit, we could incur substantial costs defending the lawsuit. The lawsuit could also divert the time and attention of our management.

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

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

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

Sanofi Genzyme currently holds approximately 12 percent of our outstanding common stock and has the right to increase its ownership up to 30 percent, as well as the right to maintain its ownership percentage through the term of our collaboration, subject to certain limitations. This concentration of ownership may harm the market price of our common stock by:

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

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

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

- a classified board of directors;
- a prohibition on actions by our stockholders by written consent;
- limitations on the removal of directors; and
- advance notice requirements for election to our board of directors and for proposing matters that can be acted upon at stockholder meetings.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15 percent of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15 percent of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. These provisions would apply even if the proposed merger or acquisition could be considered beneficial by some stockholders.

ITEM 1B. UNRESOLVED STAFF COMMENTS

Not applicable.

ITEM 2. PROPERTIES

Our operations are based primarily in Cambridge, Massachusetts; Zug, Switzerland; and Maidenhead, United Kingdom. A description of certain of the facilities we lease as of January 31, 2017 is included in the table below.

Location	Primary Use	Approximate Square Footage	Lease Expiration Date	Renewal Option
300 Third Street Cambridge, Massachusetts	Corporate headquarters and primary research facility	129,000	September 2021	One five-year term
101 Main Street Cambridge, Massachusetts	Additional office space	72,000	March 2019 and June 2021	One five-year term on each lease
675 West Kendall Street Cambridge, Massachusetts	Future corporate headquarters and research facility*	295,000	On or around February 2034	Two five-year terms
665 Concord Avenue Cambridge, Massachusetts	cGMP manufacturing	15,000	August 2022	One five-year term
Braywick Gate Braywick Road, Maidenhead Berkshire, United Kingdom	Office space	21,500	May 2026	None

* We intend to move our corporate headquarters and research facility to this location in early 2019. The term will commence on May 1, 2018 and rent payments will become due commencing upon substantial completion of the building improvements, which is currently expected to be on or around February 2019, and will continue for 15 years from the rent commencement date.

In addition to the locations above, we also maintain small offices in several locations in and outside of the United States to support our operations and growth.

In April 2016, we completed the purchase of 12 acres of undeveloped land in Norton, Massachusetts. We have commenced construction of a manufacturing facility at this site for drug substance, including siRNAs and siRNA conjugates, for clinical and commercial use.

In the future, we may lease, operate, purchase or construct additional facilities in which to conduct expanded research, development and manufacturing activities and support future commercial operations. We believe that the total space available to us under our current leases will meet our needs for the foreseeable future and that additional space would be available to us on commercially reasonable terms if required.

ITEM 3. LEGAL PROCEEDINGS

For a discussion of material pending legal proceedings, please read Note 7, Commitments and Contingencies – Litigation, to our consolidated financial statements included in Part II, Item 8, “Financial Statements and Supplementary Data,” of this annual report on Form 10-K, which is incorporated into this item by reference.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

PART II

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

Market Information

Our common stock trades on The NASDAQ Global Select Market under the symbol "ALNY." The following table sets forth the high and low sale prices per share for our common stock on The NASDAQ Global Select Market for the periods indicated:

Year Ended December 31, 2015:	High	Low
First Quarter	$121.93	$82.06
Second Quarter	$140.00	$98.63
Third Quarter	$137.89	$76.46
Fourth Quarter	$110.75	$71.14

Year Ended December 31, 2016:	High	Low
First Quarter	$98.00	$51.51
Second Quarter	$75.08	$49.96
Third Quarter	$80.11	$53.56
Fourth Quarter	$71.67	$31.38

Holders of record

At January 31, 2017, there were 35 holders of record of our common stock. Because many of our shares are held by brokers and other institutions on behalf of stockholders, we are unable to estimate the total number of beneficial holders represented by these record holders.

Dividends

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

Securities Authorized for Issuance Under Equity Compensation Plans

We intend to file with the SEC a definitive Proxy Statement, which we refer to herein as the Proxy Statement, not later than 120 days after the close of the fiscal year ended December 31, 2016. The information required by this item relating to our equity compensation plans is incorporated herein by reference to the information contained under the section captioned "Equity Compensation Plan Information" of the Proxy Statement.

Stock Performance Graph

The following performance graph and r