

ALNYLAM PHARMACEUTICALS, INC.  
Form 10-K  
February 14, 2019

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, 2018

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 (I.R.S. Employer

Incorporation or Organization) 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:

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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 every Interactive Data File required to be submitted 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 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, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	Accelerated filer
Non-accelerated filer	Smaller reporting company
	Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

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 29, 2018, was \$9,819,826,967. 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, 2019, the registrant had 106,258,250 shares of Common Stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2019 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, 2018, are incorporated by reference into Part II, Item 5 and Part III of this Form 10-K.

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ALNYLAM PHARMACEUTICALS, INC.

ANNUAL REPORT ON FORM 10-K

For the Year Ended December 31, 2018

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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 global commercial-stage biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. RNAi is a naturally occurring biological pathway within cells for sequence-specific silencing and regulation of gene expression. By harnessing the RNAi pathway, we have developed a new class of innovative medicines, known as RNAi therapeutics. RNAi therapeutics are comprised of small interfering RNA, or siRNA, and function upstream of conventional medicines by potently silencing messenger RNA, or mRNA, that encode for disease-causing proteins, thus preventing them from being made. We believe this is a revolutionary approach with the potential to transform the care of patients with genetic and other diseases. Our efforts to advance this revolutionary approach culminated with the approval in 2018 of the first ever RNAi therapeutic, ONPATPRO® (patisiran), for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis, or hATTR amyloidosis, in adults in the U.S. and for the treatment of hATTR amyloidosis in adult patients with Stage 1 or Stage 2 polyneuropathy in the European Union, or EU.

Our research and development strategy is to target genetically validated genes that have been implicated in the cause or pathway of human disease. We utilize a lipid nanoparticle (LNP) or N-acetylgalactosamine (GalNAc) conjugate approach to enable hepatic delivery of siRNAs. For delivery to the central nervous system, or CNS, and the eye (ocular delivery), we intend to utilize an alternative conjugate approach. Our focus is on clinical indications where there is a high unmet need, 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.

We are committed to the advancement of our Alnylam 2020 strategy of building a multi-product, commercial biopharmaceutical company with a sustainable pipeline of RNAi therapeutics to address the needs of patients who have limited or inadequate treatment options. Specifically, our broad pipeline of investigational RNAi therapeutics is focused in four Strategic Therapeutic Areas, or “STArS:” Genetic Medicines; Cardio-Metabolic Diseases; Hepatic Infectious Diseases; and CNS/Ocular Diseases. In August 2018, we received regulatory approval for ONPATPRO from the United States Food and Drug Administration, or FDA, for the treatment of the polyneuropathy of hATTR amyloidosis in adults. Also, in August 2018, the European Commission, or EC, granted marketing authorisation for ONPATPRO for the treatment of hATTR amyloidosis in adults with Stage 1 or Stage 2 polyneuropathy. We began

selling ONPATTRO in the U.S. in August 2018 and in Germany in October 2018, and are now marketing ONPATTRO in several additional countries in Europe. During 2018, we also submitted regulatory applications for the approval of ONPATTRO in Japan, Canada and Switzerland. Regulatory filings in additional markets in Europe and elsewhere are planned throughout 2019.

In addition to our first marketed product, we have five late-stage investigational programs advancing toward potential commercialization. These programs include our wholly owned programs: givosiran for the treatment of acute hepatic porphyria, or AHP, lumasiran for the treatment of primary hyperoxaluria type 1, or PH1, and vutrisiran for the treatment of ATTR amyloidosis. Inclisiran for the treatment of hypercholesterolemia and atherosclerotic cardiovascular disease, or ASCVD is being advanced by our partner, The Medicines Company, or MDCO, and fitusiran for the treatment of hemophilia is being advanced by our partner Sanofi Genzyme, the specialty care global business unit of Sanofi.

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, MDCO, Vir Biotechnology, Inc., or Vir, and Regeneron Pharmaceuticals, Inc., or Regeneron.

## Key 2018 and Recent Highlights

### Commercial/Late Stage Pipeline

#### ◆ ONPATTRO (patisiran) – hATTR Amyloidosis

##### Commercial Highlights

- o Launched ONPATTRO in the U.S. in August 2018 and in several countries in Europe during the fourth quarter of 2018
- o Recognized ONPATTRO net revenue of \$12.5 million for the year ended December 31, 2018

##### R&D Highlights

- o Received FDA approval of ONPATTRO for the treatment of the polyneuropathy of hATTR amyloidosis in adults
- o Received marketing authorisation from the EC for ONPATTRO for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy
- o Submitted a new drug application, or NDA, to Japan's Pharmaceuticals and Medical Devices Agency, or PMDA
- o Received a Priority Review designation in Canada
  - o Submitted a marketing authorisation application, or MAA, to The Swiss Agency for Therapeutic Products
    - Vutrisiran (ALN-TTRsc02) – ATTR Amyloidosis
- o Initiated the HELIOS-A Phase 3 study
- o Received Orphan Drug Designations, or ODDs, from U.S. and EU regulatory agencies
- ◆ Givosiran – Acute Hepatic Porphyria
- o Completed enrollment in the ENVISION Phase 3 study, with 94 patients across 36 sites in 18 countries
- o Reported positive topline results from the ENVISION interim efficacy analysis
- o Initiated a rolling submission of an NDA to the FDA
- ◆ Lumasiran – Primary Hyperoxaluria Type 1
- o Received Breakthrough Therapy and Priority Medicines Designations from the U.S. and EU regulatory authorities, respectively
- o Initiated the ILLUMINATE-A Phase 3 study of lumasiran in children and adults with PH1
- o Aligned with the FDA on trial design for ILLUMINATE-B, a Phase 3 pediatric study in PH1 patients less than six years of age
- ◆ Fitusiran - Hemophilia (in collaboration with Sanofi Genzyme)
- o Initiated enrollment into the ATLAS Phase 3 studies
- ◆ Inclisiran – Hypercholesterolemia (in collaboration with MDCO)
- o Advanced ORION Phase 3 program; received recommendation from the Independent Data Monitoring Committee, or DMC, to continue the ongoing Phase 3 ORION trials as designed and to be conducted without modification, following the fifth review of unblinded safety and efficacy data
- o Accumulated more than 2,450 years of patient safety data as of January 7, 2019



## Early to Mid-Stage Pipeline

• Cemdisiran for the treatment of complement-mediated diseases; discontinued Phase 2 study in atypical hemolytic uremic syndrome, or aHUS, due to recruitment challenges and obtained regulatory approval to initiate a Phase 2 study in IgA nephropathy

• ALN-AAT02 for the treatment of alpha-1 liver disease, which is based on our Enhanced Stabilization Chemistry-Plus, or ESC+, GalNAc conjugate technology; obtained approval of a clinical trial application, or CTA, and initiated a Phase 1/2 study

• ALN-HBV02 (VIR-2218) for the treatment of chronic hepatitis B virus, or HBV, infection; initiated dosing in a Phase 1/2 study in collaboration with our partners at Vir

## Corporate Highlights

### • Finance

o Ended 2018 with \$1.13 billion in cash, cash equivalents, and marketable debt securities and restricted investments, excluding equity securities

### • Business

o Completed a strategic restructuring of our rare disease alliance with Sanofi Genzyme, originally formed in 2014, with us obtaining global rights to our ATTR amyloidosis programs – ONPATPRO and vutrisiran – and Sanofi Genzyme obtaining global rights to fitusiran

o Formed a strategic collaboration with Regeneron to identify and advance RNAi therapeutics for the treatment of nonalcoholic steatohepatitis, or NASH, a chronic liver disease

### • Public Offering

o In January 2019, sold 5,000,000 shares of our common stock through an underwritten public offering at a price to the public of \$77.50 per share, receiving aggregate net proceeds of approximately \$382 million

## RNAi Therapeutics – A New Class of Innovative Medicines

RNAi is a natural cellular process that was discovered in 1998 and was recognized with the award of the 2006 Nobel Prize for Physiology and Medicine to Dr. Andrew Fire and Dr. Craig Mello.

RNAi therapeutics harness the natural RNAi pathway to silence disease-associated genes and knock down production of proteins implicated in disease, representing the opportunity to create a new class of innovative medicines. RNAi therapeutics exert 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 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
- Sustained 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 be administered via subcutaneous injection when using 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 therapeutics, even in competitive markets, and in August 2018, we received the first ever regulatory approval of an RNAi therapeutic from the FDA and the European Medicines Agency, or EMA. 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, Circulation, The New England Journal of Medicine and The Lancet.

## Our Product Platform

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

1	Genetically validated, target gene	<ul style="list-style-type: none"> <li>• High unmet need population</li> <li>• Opportunity for highly competitive profile</li> </ul>
2	Biomarker for human proof-of-concept, or POC, in Phase 1	<ul style="list-style-type: none"> <li>• Delivery with GalNAc- or alternate conjugate platform</li> <li>• Blood- or urine-based</li> </ul>
3	Definable path to potential approval and market	<ul style="list-style-type: none"> <li>• Informative disease correlation</li> <li>• Establish dose/regimen for late stage development</li> <li>• Clinical development plans with established endpoints</li> </ul>
		<ul style="list-style-type: none"> <li>• Demonstrable value for payors</li> </ul>

#### Overview 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 Alnylam 2020 strategy.

Early efforts focused on delivery of RNAi therapeutics utilizing 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 demonstrated 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 recently approved product, ONPATPRO, is formulated utilizing LNPs.

In parallel, we have advanced 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 directed to liver expressed target genes, a key aspect of our platform. Results from our Enhanced Stabilization Chemistry, or ESC-GalNAc-conjugate delivery platform demonstrated a durability of effect that we believe, based on our clinical results, 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. During 2018, we continued to invest in the enhancement of this platform and reported pre-clinical results from our ESC+ GalNAc-conjugates. ESC+ GalNAc-conjugates utilize advanced design features to further improve specificity, including a glycol nucleic acid modification in the antisense seed region of the siRNA, while maintaining potency and durability, further improving our already wide therapeutic index by up to six-fold. Our first two investigational RNAi therapeutics based on this ESC+ design, ALN-AAT02 and ALN-HBV02, entered the clinic in

late 2018.

Our platform enhancements have also provided a strong foundation for pursuing a conjugate-based approach to extra-hepatic delivery. To this end, in 2018, for the very first time, we reported on our progress with delivery to the brain and spinal cord, as well as ocular delivery, with POC demonstrated in rodent and non-human primates.

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

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## Our Product Pipeline

Our broad pipeline including one approved and multiple investigational RNAi therapeutics is focused in four STArS: Genetic Medicines; Cardio-Metabolic Diseases; and Hepatic Infectious Diseases; and CNS/Ocular Diseases. The chart below is a summary of our product development programs as of January 31, 2019. It identifies those programs in which we have achieved human POC by demonstrating target gene knockdown and/or additional evidence of activity in clinical studies, those programs for which we have received Breakthrough Therapy Designation from the FDA, the stage of our programs, and our commercial rights to such programs:

As indicated in the chart above, to date we have received marketing approval for our first product, ONPATTRO. We also have multiple product candidates in late stage development. 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 these investigational therapeutics have been approved by the FDA, EMA or any other health authority and no conclusions can or should be drawn regarding the safety or efficacy of these investigational therapeutics.

## Our Newly Marketed Medicine

### ONPATTRO (patisiran)

ONPATTRO (patisiran) is the first ever FDA-approved RNAi therapeutic and our first product to receive marketing approval. In the U.S., ONPATTRO is indicated for the treatment of the polyneuropathy of hATTR amyloidosis in adults. In the EU, ONPATTRO is indicated for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy.

Hereditary ATTR amyloidosis is an inherited, progressively debilitating, and often fatal disease caused by mutations in the transthyretin, or TTR, gene. TTR protein is primarily produced in the liver and is normally a carrier of vitamin A. Mutations in the TTR gene cause abnormal amyloid proteins to accumulate and damage body organs and tissue, such as the peripheral nerves and heart, resulting in intractable peripheral sensory-motor neuropathy, autonomic neuropathy, and/or cardiomyopathy, as well as other disease manifestations. hATTR amyloidosis represents a major unmet medical need with significant morbidity and mortality, affecting approximately 50,000 people worldwide. The median survival is 4.7 years following diagnosis, with a reduced survival (3.4 years) for patients presenting with cardiomyopathy. In Europe, treatment options that can modify the course of the disease are limited and there remains a pressing need for novel medicines to help treat patients with hATTR amyloidosis.

The approval of ONPATTRO in the U.S. and EU was based on positive results from the randomized, double-blind, placebo-controlled, global APOLLO Phase 3 study, the largest-ever study in hATTR amyloidosis patients with polyneuropathy. Results from the APOLLO study were published in the July 5, 2018 issue of The New England Journal of Medicine and in the journal Circulation on September 14, 2018 (online) and January 22, 2019 (print). We launched ONPATTRO in the U.S. in August 2018 and in several countries in Europe thereafter. Applications for regulatory approval are pending in Japan, Canada and Switzerland and additional applications in other territories are expected in 2019.

#### APOLLO-B Phase 3 Study

In early 2019, we announced our intention to initiate the APOLLO-B study following alignment with the FDA on trial design. APOLLO-B is a randomized, double-blind, placebo-controlled study in ATTR amyloidosis patients with cardiomyopathy. The study will enroll patients with confirmed cardiomyopathy and medical history of symptomatic heart failure due to ATTR amyloidosis (either wild-type (wt) or hereditary (h)). Patients will be randomized 1:1 to patisiran or placebo and concomitant use of local standard care will be allowed during study. After 12-months of treatment, the primary endpoint of six-minute walk distance, or 6-MWD, will be evaluated, as well as other key secondary and exploratory endpoints. We anticipate initiating this study in mid-2019.

In January 2018, we and Sanofi Genzyme entered into an amendment to our 2014 collaboration, as well as an Exclusive License Agreement, referred to as the Exclusive TTR License, pursuant to which we have global rights for the development and commercialization of ONPATTRO, together with vutrisiran, discussed below, and all back-up products. The 2014 Sanofi Genzyme collaboration, as amended in January 2018, as well as the Exclusive TTR License, are described below under the heading “Strategic Alliances.”

#### Our Phase 3 Programs

##### Vutrisiran – ATTR amyloidosis

Vutrisiran (formerly ALN-TTRsc02) is an investigational, subcutaneously administered RNAi therapeutic targeting TTR in development for the treatment of ATTR amyloidosis. It is designed to target and silence specific mRNA, blocking the production of wild-type and mutant TTR protein. This may help to reduce the deposition and facilitate the clearance of TTR amyloid deposits in tissues like the nerves, heart and gastrointestinal tract which may potentially restore function.

ATTR amyloidosis is a rare, progressively debilitating, and often fatal disease caused by misfolded TTR proteins that accumulate as amyloid deposits in multiple tissues including the nerves, heart, and GI tract. TTR protein is primarily produced in the liver and is normally a carrier of vitamin A. hATTR amyloidosis is an inherited, progressive disease that occurs when mutations in the TTR gene cause abnormal amyloid proteins to accumulate and damage body organs and tissues, such as the peripheral nerves and heart, resulting in intractable peripheral sensory neuropathy, autonomic neuropathy, and/or cardiomyopathy, as well as other disease manifestations. hATTR amyloidosis represents a major unmet medical need with significant morbidity and mortality, affecting approximately 50,000 people worldwide. The median survival is 4.7 years following diagnosis, with a reduced survival (3.4 years) for patients presenting with cardiomyopathy. Wild-type ATTR, or wtATTR, amyloidosis is a nonhereditary, progressive disease of undefined etiology that occurs when misfolded TTR proteins accumulate as amyloid deposits in multiple organs, including the heart, resulting predominantly in cardiomyopathy, leading to heart failure and mortality within two to six years. The

prevalence of wtATTR amyloidosis is uncertain, however estimates suggest fewer than 200,000 patients across the U.S. and Europe.

#### HELIOS-A Phase 3 Study

Vutrisiran is currently being evaluated in the HELIOS-A randomized, open-label Phase 3 study in hereditary ATTR amyloidosis patients, which we initiated in late 2018. The study will enroll approximately 160 patients with a 3:1 randomization where 120 patients will receive a 25 mg subcutaneous injection of vutrisiran once every three months and 40 patients will receive a 0.3 mg/kg intravenous infusion of ONPATTRO once every three weeks as a reference comparator. The study co-primary endpoints are the mean change from baseline in the modified Neuropathy Impairment Score +7, or mNIS+7, and the Norfolk Quality of Life Diabetic Neuropathy score, or Norfolk QoL-DN, at nine months as compared to the mean change observed in the placebo arm of the APOLLO Phase 3 study of patisiran.

#### HELIOS-B Phase 3 Study

Vutrisiran is expected to also be evaluated in HELIOS-B, a Phase 3 study in ATTR amyloidosis patients with cardiomyopathy. We anticipate initiating this study in late 2019.

## Phase 1 Study

A Phase 1, randomized, single blind, ascending fixed-dose study of vutrisiran was conducted in 80 healthy volunteers. The study included cohorts of eight participants randomized 6:2 to receive a single dose of subcutaneously administered vutrisiran (5 mg to 300 mg) or placebo. The primary objective of the study was to evaluate the safety and tolerability of single doses of vutrisiran. Vutrisiran was generally well-tolerated at all dose levels and no serious adverse events, or SAEs, were observed. No discontinuations due to adverse events, or AEs, were reported and all AEs were mild or moderate in severity. Vutrisiran demonstrated a mean maximum TTR reduction of 83 percent after a single 25 mg dose. Both sustained TTR reduction at clinically relevant doses observed on study and pharmacodynamic modeling data suggest that quarterly dosing with vutrisiran will be supported. With repeat dosing, peak TTR knockdown of approximately 90 percent is predicted.

## Regulatory Designations

- ◆ Orphan Drug Designation (FDA) for the treatment of ATTR amyloidosis
  - ◆ Orphan Medicinal Product Designation (EMA) for the treatment of ATTR amyloidosis
- Givosiran — Acute Hepatic Porphyria

Givosiran is an investigational, subcutaneously administered RNAi therapeutic in development for the treatment of AHP. AHP refers to a family of rare, genetic diseases characterized by potentially life-threatening attacks, and for some patients, chronic debilitating symptoms that negatively impact daily functioning and quality of life. In the U.S. and Europe, it is estimated that approximately 1,000 people suffer recurrent attacks and approximately 5,000 people experience sporadic attacks. AHP is comprised of four subtypes, each resulting from a genetic defect leading to deficiency in one of the enzymes of the heme biosynthesis pathway in the liver: acute intermittent porphyria, or AIP, hereditary coproporphyria, or HCP, variegate porphyria, or VP, and ALAD-deficiency porphyria, or ADP. These defects cause the accumulation of neurotoxic heme intermediates aminolevulinic acid, or ALA, and porphobilinogen, or PBG, with ALA believed to be the primary neurotoxic intermediate responsible for disease manifestations. Common symptoms of AHP include severe, diffuse abdominal pain, weakness, nausea, and fatigue. The nonspecific nature of AHP signs and symptoms can often lead to misdiagnoses of other more common conditions such as irritable bowel syndrome, appendicitis, fibromyalgia, and endometriosis, and consequently, patients afflicted by AHP often remain without a proper diagnosis for up to 15 years. In addition, long-term complications of AHP and its treatment can include chronic neuropathic pain, hypertension, chronic kidney disease and liver disease, including iron overload, fibrosis, cirrhosis and hepatocellular carcinoma. Currently, there are no treatments approved to prevent debilitating attacks or to treat the chronic manifestations of the disease. Intravenous, or IV, hemin is currently approved for the treatment of acute AHP attacks, and is sometimes used prophylactically off-label by some porphyria specialists to prevent attacks, despite its unclear efficacy, short duration of action and association with significant side effects.

Givosiran specifically targets aminolevulinic acid synthase 1, or ALAS1, the key regulator of the heme biosynthesis pathway in the liver. Monthly administration of givosiran has the potential to significantly lower induced liver ALAS1 levels in a sustained manner and thereby decrease neurotoxic heme intermediates, ALA and PBG, to near normal levels. By reducing accumulation of these intermediates, givosiran has the potential to prevent or reduce the occurrence of severe and life-threatening attacks, control chronic symptoms and decrease the burden of the disease. Givosiran is currently being evaluated in the ENVISION Phase 3 pivotal study, which we initiated in November 2017.



ENVISION Phase 3 Clinical Trial

The ENVISION Phase 3 trial is a randomized, double-blind, placebo-controlled, global, multicenter study to evaluate the efficacy and safety of givosiran in patients with a documented diagnosis of AHP. Enrollment was completed in August 2018 with 94 patients enrolled across 36 sites in 18 countries. Patients were randomized on a 1:1 basis to receive 2.5 mg/kg of givosiran or placebo subcutaneously administered monthly, over a six-month treatment period. The primary endpoint is the annualized rate of porphyria attacks requiring hospitalization, urgent healthcare visit or IV hemin administration at home over the six-month treatment period. All patients completing the six-month treatment period will be eligible to continue on the open-label extension, or OLE, portion of the ENVISION study in which they will receive treatment with givosiran for up to 30 months.

In September 2018, we reported on the results of the interim efficacy analysis from the ENVISION Phase 3 study. The analysis showed that givosiran treatment was associated with a statistically significant reduction in urinary ALA levels in AIP patients, relative to placebo (p less than 0.001). The interim analysis had a data cut-off date of August 22, 2018 and included 43 patients with AHP (41 patients with AIP, one with VP and one with HCP) who were on study for at least three months. As of the data cut-off date, there were no deaths, and SAEs were reported in 22 percent (5/23) of givosiran patients and ten percent (2/20) of placebo patients. One patient (4 percent) on givosiran discontinued treatment due to an increase in liver transaminase – which resolved – that was greater than eight times the upper limit of normal, a protocol-defined stopping rule. There were no treatment discontinuations in the placebo group. We expect to report topline full study results from ENVISION in March 2019.

Following the interim analysis, we determined, in consultation with the FDA, to pursue a full approval based on the complete results of the ENVISION Phase 3 study of givosiran, rather than filing based on the interim Phase 3 results. The FDA agreed to a rolling NDA submission, which was initiated in late 2018 with full clinical sections expected to be submitted in mid-2019, assuming positive study results.

#### Phase 1 Clinical Trial and Phase 1/2 OLE Study

During 2018, we reported complete data from the Phase 1 clinical trial of givosiran and interim data from the ongoing Phase 1/2 OLE study of givosiran.

A randomized, double-blind, placebo-controlled Phase 1 study has been completed. Parts A (single ascending dose) and B (multi-ascending dose) of the study enrolled subjects with AIP not experiencing attacks (N=23), and Part C (multi-dose) of the study enrolled AIP patients (N=17) experiencing attacks. SAEs were noted in six patients, with none assessed as related to study drug. As previously reported, one patient experiencing recurrent attacks died due to hemorrhagic pancreatitis complicated by a pulmonary embolism and following a recent hospitalization for bacteremia. All eligible patients from Part C (N=16) enrolled into a Phase 1/2 OLE study.

As of the data cut-off date of June 7, 2018, a robust treatment effect was maintained in givosiran-treated patients with extended dosing in the Phase 1/2 OLE study, with mean time in the OLE study of 13.6 months and with up to 25 months of total treatment across the Phase 1 and OLE studies. In patients who received givosiran during the Phase 1 study and continued with givosiran dosing in the OLE study (N=12), mean reductions in annualized attack rate, or AAR, of 93 percent and annualized hemin use of 94 percent were observed, relative to the Phase 1 run-in period. Similarly, patients in the placebo arm of the Phase 1 study crossing over to givosiran treatment in the OLE study (N=4) experienced mean reductions in AAR of 95 percent and annualized hemin use of 98 percent. As of the data cut-off date, one patient had discontinued from the OLE due to an SAE of anaphylaxis. Four patients have reported SAEs in the OLE; with the exception of the case of anaphylaxis in the discontinued patient, all remaining SAEs have been assessed as unlikely related to study drug.

#### Regulatory Designations

Givosiran has been granted the following regulatory designations for the treatment of AHP:

- Orphan Drug Designation (FDA)
- Orphan Medicinal Product Designation (EMA)
- PRIME Designation (EMA)
- Breakthrough Therapy Designation (FDA)

In 2016, Sanofi Genzyme elected not to opt into the development and commercialization of givosiran in the Sanofi Genzyme Territory, as defined below, providing us with full global control of the program for further development and commercialization, if approved. The 2014 Sanofi Genzyme collaboration, as amended in January 2018, is

described below under the heading “Strategic Alliances.”

Lumasiran — PH1

Lumasiran is an investigational, subcutaneously administered RNAi therapeutic targeting glycolate oxidase, or GO, for the treatment of PH1. Lumasiran is designed to reduce hepatic levels of the GO enzyme, thereby depleting the substrate necessary for the production of oxalate – the metabolite that directly contributes to the pathophysiology of PH1.

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PH1 is an ultra-orphan disease in which excessive oxalate production results in the deposition of calcium oxalate crystals in the kidneys and urinary tract and can lead to the formation of painful and recurrent kidney stones and nephrocalcinosis. Renal damage is caused by a combination of tubular toxicity from oxalate, calcium oxalate deposition in the kidneys, and urinary tract obstruction by calcium oxalate stones. Compromised kidney function exacerbates the disease as the excess oxalate can no longer be effectively excreted, resulting in subsequent accumulation in bones, eyes, skin, and heart, leading to severe illness and potentially death. Current treatment options are very limited and include frequent renal dialysis or combined organ transplantation of liver and kidney, a procedure with high morbidity that is limited due to organ availability. Although a small minority of patients respond to vitamin B6 therapy, there are no approved pharmaceutical therapies for PH1. PH1 affects one to three individuals per million, with a higher prevalence in some regions, such as the Middle East and North Africa. In the U.S. and Europe, there may be approximately 2,500 to 5,000 cases.

In September 2018, we initiated the ILLUMINATE-A Phase 3 study of lumasiran. We expect to complete enrollment in ILLUMINATE-A in mid-2019 and report topline results in late 2019. We also plan on initiating ILLUMINATE-B and ILLUMINATE-C clinical trials for patients with PH1 in 2019.

#### ILLUMINATE- A, -B and -C Phase 3 Clinical Trials

ILLUMINATE-A is a randomized, double-blind, placebo-controlled, global, multicenter Phase 3 study to evaluate the efficacy and safety of lumasiran in approximately 30 patients who are six years or older with relatively preserved renal function and documented diagnosis of PH1. Patients will be randomized 2:1 to receive three monthly doses of lumasiran or placebo at 3 mg/kg followed by quarterly maintenance doses. The primary endpoint is the reduction of urinary oxalate at six months relative to baseline in the patients treated with lumasiran as compared to placebo. At month six, the placebo patients will cross over to the lumasiran arm for long-term follow up out to 60 months.

ILLUMINATE-B and ILLUMINATE-C are Phase 3 studies that will evaluate the efficacy and safety of lumasiran in patients less than six of age with relatively preserved renal function, and in pediatric and adult patients with renal insufficiency, respectively.

#### Phase 1/2 and Phase 2 OLE Results

In 2018, we reported new results from the Phase 1/2 and Phase 2 OLE studies of lumasiran. New results from the Phase 1/2 study were as of a data cut-off date of August 15, 2018. Lumasiran demonstrated a mean maximal reduction in urinary oxalate of 75 percent (range: 43-87 percent) relative to baseline across cohorts dosed at 1 mg/kg monthly or 3 mg/kg monthly or quarterly (N=20). The mean reduction relative to baseline was 66 percent when measured 28 days post last dose. All patients (100 percent) achieved oxalate lowering to less than 1.5 times the upper limit of normal (less than 0.69 mmol/24hr/1.73m<sup>2</sup>). Among patients receiving 3 mg/kg monthly or quarterly doses of lumasiran (N=12), 83 percent achieved urinary oxalate levels within the normal range (less than 0.46 mmol/24hr/1.73m<sup>2</sup>).

The Phase 1/2 safety results in patients with PH1 were based on a median study duration of seven months (range: 5 to 14 months) since first dose. As of the data cut-off date, there were no discontinuations from study treatment. SAEs were reported for one patient (33 percent) receiving placebo and five patients (25 percent) receiving lumasiran; none were related to study drug. AEs were reported in three (100 percent) patients during placebo dosing and 19 (95 percent) patients after lumasiran dosing. The majority of AEs were mild or moderate in severity and were assessed as unrelated to study drug. ISRs were reported in three (15 percent) patients receiving lumasiran. ISRs were mild or moderate in severity and were self-limiting.

For those patients who have transitioned to the Phase 2 OLE study, which is designed to evaluate long-term safety and efficacy, the tolerability profile of lumasiran remained generally consistent with data from the Phase 1/2 study. Phase

2 OLE safety results (N=8) were based on a median study duration of 2.7 months (range: 0.03 to 3.02 months) since first dose. As of the data cut-off date of October 3, 2018, there were no discontinuations from study treatment. SAEs were reported for two patients (25 percent); none were assessed as related to study drug. AEs were reported in five patients (63 percent); all were mild or moderate in severity and majority were assessed as unrelated to study drug. There were no reports of ISRs or clinically significant laboratory changes.

## Regulatory Designations

Lumasiran has been granted the following regulatory designations for the treatment of PH1:

- ◆ Orphan Drug Designation (FDA)
- ◆ Orphan Medicinal Product Designation (EMA)
- ◆ PRIME Designation (EMA)
- ◆ Breakthrough Therapy Designation (FDA)

In 2018, Sanofi Genzyme elected not to opt into the development and commercialization of lumasiran 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, as amended in January 2018, is described below under the heading “Strategic Alliances.”

## Inclisiran — Hypercholesterolemia

Inclisiran is an investigational, subcutaneously administered RNAi therapeutic targeting proprotein convertase subtilisin/kexin type 9, or PCSK9, for the treatment of hypercholesterolemia. PCSK9 is a protein involved in the regulation of low-density lipoprotein, or LDL, receptor levels on hepatocytes and the metabolism of LDL cholesterol, or LDL-C, which is commonly referred to as “bad” cholesterol.

Approximately 100 million people worldwide are treated with lipid lowering therapies, predominantly statins, to reduce LDL-C and the associated risk of death, nonfatal myocardial infarction and nonfatal stroke or associated events. However, residual risk for cardiovascular events remains and statins are associated with well-known limitations. First, not all subjects reach LDL-C levels associated with optimal protection against clinical events. Second, not all subjects tolerate statins or are able to take statins at sufficiently-intensive doses. Third, observational studies have demonstrated that >50 percent of patients do not adhere to statin therapy for more than six months. Despite statins alone or in combination with other lipid lowering medications, current therapies for the management of elevated LDL-C remain insufficient in some subjects. This is particularly true in patients with pre-existing coronary heart disease and/or diabetes or a history of familial hypercholesterolemia, or FH, who are at the highest risk and require the most intensive management. There is an unmet need for additional treatment options beyond currently-available treatments for lowering of the LDL-C level to reduce cardiovascular risk.

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, MDCO assumed responsibility for the development and commercialization of inclisiran from Phase 2 forward. A description of our agreement with MDCO is included below under the heading “Strategic Alliances.”

In 2017, MDCO initiated the ORION Phase 3 program for inclisiran, a comprehensive set of clinical trials to assess LDL-C lowering and safety in a wide range of patients. In 2018, MDCO completed enrollment into the ORION-9, -10 and -11 trials, with topline results expected in the second half of 2019 and a potential NDA filing anticipated at or around year-end 2019, assuming positive Phase 3 results.

## Orion Phase 3 Clinical Program

The Phase 3 program includes the five Phase 3 clinical trials described below and represents the largest clinical experience for an investigational RNAi therapeutic to date, with more than 2,450 years of patient exposure to an

RNAi therapeutic:

- ORION-11 – a placebo-controlled, double-blind, randomized Phase 3 study of inclisiran versus placebo (1:1) in patients (N=1,500) with ASCVD, or ASCVD-risk equivalents, and elevated LDL-C despite maximum tolerated doses of LDL-C lowering therapies, including statins.
- ORION-10 – a placebo-controlled, double-blind, randomized Phase 3 study of inclisiran versus placebo (1:1) in ASCVD patients (N=1,500).
- ORION-9 – a placebo-controlled, double-blind, randomized Phase 3 study of inclisiran versus placebo (1:1) in patients (N=400) with heterozygous FH.
- ORION-5 – a placebo-controlled, double-blind, randomized Phase 3 study of inclisiran versus placebo (1:1) in patients (N=60) with homozygous FH, or HoFH.
- ORION-4 – a placebo-controlled, double-blind, randomized Phase 3 study of inclisiran versus placebo (1:1) in patients (N=15,000) with ASCVD.

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## Regulatory Designations

Inclisiran has been granted the following regulatory designation for the treatment of HoFH:

### Orphan Drug Designation (FDA)

Fitusiran — Hemophilia

Fitusiran is an investigational, subcutaneously administered RNAi therapeutic targeting antithrombin, or AT, for the treatment of people with hemophilia A and B, with and without inhibitors. Fitusiran is designed to lower levels of AT with the goal of promoting sufficient thrombin generation to prevent bleeding. AT acts by inactivating thrombin and other coagulation factors, and plays a key role in normal hemostasis by helping to limit the process of fibrin clot formation.

Hemophilia is a hereditary bleeding disorder characterized by an underlying defect in the ability to generate adequate levels of thrombin needed for effective fibrin clot formation, thereby resulting in recurrent bleeds into joints, muscles, and major internal organs. 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.

There are approximately 200,000 people living with hemophilia A and hemophilia B worldwide. Standard treatment for people with hemophilia currently involves replacement of the deficient clotting factor either as prophylaxis or on-demand therapy, which can lead to a temporary restoration of thrombin generation capacity. However, with current factor replacement treatments people with hemophilia are at risk of developing neutralizing antibodies, or inhibitors, to their replacement factor, a very serious complication affecting as many as one third of people with severe hemophilia A and a smaller fraction of people with hemophilia B. People who develop inhibitors become refractory to replacement factor therapy and are twice as likely to be hospitalized for a bleeding episode.

Fitusiran is currently being evaluated in the ATLAS Phase 3 program, with dosing initiated in early 2018.

## ATLAS Phase 3 Clinical Program

**Trial Design:** ATLAS is a global, multicenter program designed to evaluate the safety and efficacy of fitusiran in three separate trials, including patients with hemophilia A and B with or without inhibitors.

- **ATLAS-INH**, a nine-month, open-label, randomized, controlled trial designed to enroll approximately 50 patients with hemophilia A or B with inhibitors receiving prior on-demand therapy with bypassing agents.
- **ATLAS-A/B**, a nine-month, open-label, randomized, controlled trial designed to enroll approximately 120 patients with hemophilia A or B without inhibitors receiving prior on-demand therapy with factor or bypassing agents.



ATLAS-PPX, an open-label, one-way crossover study designed to enroll approximately 30 patients with hemophilia A or B with inhibitors receiving prior prophylaxis therapy with factor or bypassing agents. In this study, patients will receive standard of care factor or bypassing agent prophylaxis therapy for six months and then transition to fitusiran treatment for seven months. The annualized bleeding rate will be prospectively measured in both periods.

#### Regulatory Designations

Fitusiran has been granted the following regulatory designations for the treatment of hemophilia A and B:

- ◆ ODD (FDA)
- ◆ Orphan Medicinal Product Designation (EMA)

In January 2018, we and Sanofi Genzyme entered into an amendment to our 2014 collaboration, as well as the ALN-AT3 Global License Terms, referred to as the AT3 License Terms, pursuant to which Sanofi Genzyme has global rights to develop and commercialize fitusiran and any back-up products. In mid-2018, we completed the transition period relating to the transition of the fitusiran program to Sanofi Genzyme. The 2014 Sanofi Genzyme collaboration, as amended in January 2018, as well as the AT3 License Terms, are described below under the heading “Strategic Alliances.”

## Early Stage Clinical Development Programs

### Cemdisiran (ALN-CC5) — Complement-Mediated Diseases

Cemdisiran is an investigational, subcutaneously administered RNAi therapeutic targeting the C5 component of the complement pathway in development 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 and aHUS, amongst others. Complement component C5, which is predominantly expressed in liver cells, is a genetically and clinically validated target; loss-of-function human mutations are associated with an attenuated immune response against certain infections and intravenous anti-C5 monoclonal antibody, or mAb, therapy has demonstrated clinical activity and tolerability in a number of complement-mediated diseases. A subcutaneously administered RNAi therapeutic that silences C5 represents a novel approach for the potential treatment of complement-mediated diseases.

In mid-2018, we discontinued our Phase 2 study in aHUS due to recruitment challenges. In February 2019, we announced that we received regulatory approval to initiate a Phase 2 study of cemdisiran in IgA nephropathy.

During 2016, Sanofi Genzyme elected not to opt into the development and commercialization of cemdisiran 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, as amended in January 2018, is described below under the heading “Strategic Alliances.”

### ALN-AAT02 — Alpha-1 Anti-Trypsin Deficiency-Associated Liver Disease

ALN-AAT02 is an investigational, subcutaneously administered RNAi therapeutic targeting alpha-1 antitrypsin, or AAT, in development for the treatment of AAT deficiency-associated liver disease, or alpha-1 liver disease. ALN-AAT02 is one of the first two RNAi therapeutics to utilize our ESC+ GalNAc-conjugate technology.

AAT deficiency is an autosomal disorder that results in disease of the lungs and liver. AAT is a liver-produced serine proteinase inhibitor with the primary function of protecting the lungs from neutrophil elastase and other irritants that cause inflammation. About 95 percent of people with AAT deficiency are homozygous and carry two copies of the abnormal Z allele, or PiZZ, which expresses the Z-AAT protein. In the liver, misfolding of the mutant Z-AAT protein hinders its normal release into the blood thereby causing it to aggregate in hepatocytes, leading to liver injury, fibrosis, cirrhosis, and hepatocellular carcinoma. There are estimated to be approximately 120,000 individuals with the PiZZ mutation in the U.S. and major European countries, and of these, about ten percent have an associated liver pathology (alpha-1 liver disease) caused by the aggregates of the misfolded Z-AAT protein. The only treatment options presently available for alpha-1 liver disease patients are supportive care and, in the case of advanced cirrhosis, liver transplantation. RNAi-mediated inhibition of AAT in people with alpha-1 liver disease may represent a promising new way to treat this rare disease.

In December 2018, we initiated a Phase 1/2 study of ALN-AAT02 in alpha-1 liver disease and expect to report initial results in 2019.

ALN-HBV02 (VIR-2218) – Chronic Hepatitis B Virus Infection

ALN-HBV02 (VIR-2218) is a subcutaneously administered, investigational RNAi therapeutic targeting the HBV genome for the treatment of chronic HBV infection being advanced by our collaborators at Vir. ALN-HBV02 is designed to inhibit expression of all HBV proteins, including hepatitis B surface antigen. ALN-HBV02 is the second RNAi therapeutic to utilize our ESC+ GalNAc delivery platform.

Almost one-third of the world's population have previous or current HBV infection. Worldwide, more than 250 million people are chronically infected with HBV, and an estimated 1 million people die each year from complications of chronic HBV such as cirrhosis and hepatocellular carcinoma. Current treatment options include life-long suppressive antiviral therapies. There is a significant need for safe and convenient novel therapeutics that restore the host immune response, leading to control of the virus after a finite duration of therapy, which is the definition of a functional cure.

In November 2018, Vir initiated a Phase 1/2 study of ALN-HBV02 in chronic HBV infection, with initial results expected in 2019.

### Additional Early Stage and Pre-clinical Programs

In addition to the programs listed above, we are also advancing other earlier-stage pipeline programs and plan to file one or more new CTAs in 2019. We also intend to continue to build on our progress with extra-hepatic delivery during 2019, advancing our CNS and ocular programs.

### Our Collaboration and Licensing Strategy

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

Our collaboration strategy is to form alliances that create significant value for ourselves and our collaborators in the advancement of RNAi therapeutics as a new class of innovative medicines. Specifically, with respect to our Genetic Medicine pipeline, we formed a broad strategic alliance with Sanofi Genzyme in 2014 pursuant to which we retain development and commercial rights for our current and future Genetic Medicine products in the U.S., 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, referred to as the Sanofi Genzyme Territory, subject to certain broader rights. As referenced above, in January 2018, we and Sanofi Genzyme amended our 2014 Sanofi Genzyme collaboration and entered into the Exclusive TTR License with respect to all TTR products, including ONPATTRO, vutrisiran and any back-up products, and the AT3 License Terms with respect to fitusiran and any back-up products. The 2018 amendment, together with the Exclusive TTR License and the AT3 License Terms, revised the terms and conditions of the 2014 collaboration to (i) provide us with the exclusive right to pursue the further global development and commercialization of all TTR products, including ONPATTRO, vutrisiran and any back-up products, (ii) provide Sanofi Genzyme the exclusive right to pursue the further global development and commercialization of fitusiran and any back-up products and (iii) terminate the previous co-development and co-commercialization rights related to revusiran, vutrisiran and fitusiran under the 2014 Sanofi Genzyme collaboration. Sanofi Genzyme continues to have the right to opt into our other rare genetic disease programs for development and commercialization in territories outside of the Alnylam Territory, as defined below, as contemplated in the 2014 Sanofi Genzyme collaboration, as well as one right to a global license.

With respect to our Cardio-Metabolic pipeline, we intend to seek future strategic alliances for these programs, under which we may retain certain product development and commercialization rights, or we may structure as global alliances, as we did in our collaboration with MDCO to advance inclisiran. In March 2018, we entered into a discovery collaboration with Regeneron to identify RNAi therapeutics for NASH and potentially other related diseases, and in November 2018, we and Regeneron entered into a separate, fifty-fifty collaboration to further research, co-develop and commercialize any therapeutic product candidates that emerge from these discovery efforts.

With respect to our Hepatic Infectious Disease pipeline, in October 2017, we announced an exclusive licensing agreement with Vir for the development and commercialization of RNAi therapeutics for infectious diseases, including chronic HBV infection.

We may also seek future collaborations, including potentially global licenses, for one or more programs in our early stage CNS/ocular pipeline.

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, referred to as the 2014 Sanofi Genzyme collaboration. The 2014 Sanofi Genzyme collaboration superseded and replaced the previous collaboration between us and Sanofi Genzyme entered into in October 2012 to develop and commercialize RNAi therapeutics targeting TTR for the treatment of hATTR amyloidosis, including patisiran and revusiran, in Japan and the Asia-Pacific region.

In January 2018, we and Sanofi Genzyme entered into an amendment to our 2014 Sanofi Genzyme collaboration. In connection and simultaneously with entering into the 2018 amendment to the 2014 Sanofi Genzyme collaboration, we and Sanofi Genzyme also entered into the Exclusive TTR License and the AT3 License Terms. As a result, we have the exclusive right to pursue the further global development and commercialization of all TTR products, including ONPATTRO, vutrisiran and any back-up products, and Sanofi Genzyme has the exclusive right to pursue the further global development and commercialization of fitusiran and any back-up products.

Under the 2014 Sanofi Genzyme collaboration, Sanofi Genzyme has certain rights to our current and future Genetic Medicine programs that reach Human Proof-of-Principle Study Completion, as defined in the Sanofi Genzyme master agreement, by the end of 2019, subject to extension to the end of 2021 in various circumstances. Under the 2014 Sanofi Genzyme collaboration, we were leading development and commercialization of ONPATTRO in the Alnylam Territory, while Sanofi Genzyme had rights to develop and commercialize the product in the Sanofi Genzyme Territory. Sanofi Genzyme also had a right to opt in to co-develop and co-promote vutrisiran in the Alnylam Territory along with its regional opt-in rights. In addition, Sanofi Genzyme had opted in to co-develop and co-promote fitusiran in the Alnylam Territory, as well as develop and commercialize fitusiran in the Sanofi Genzyme Territory.

The 2018 amendment, together with the Exclusive TTR License and the AT3 License Terms, revised the terms and conditions of the 2014 Sanofi Genzyme collaboration to (i) provide us with the exclusive right to pursue the further global development and commercialization of all TTR products, including ONPATTRO, vutrisiran and any back-up products, (ii) provide Sanofi Genzyme the exclusive right to pursue the further global development and commercialization of fitusiran and any back-up products and (iii) terminate the previous co-development and co-commercialization rights related to revusiran, vutrisiran and fitusiran under the 2014 Sanofi Genzyme collaboration.

Sanofi Genzyme continues to have the right to opt into our other rare genetic disease programs for development and commercialization in territories outside of the Alnylam Territory as contemplated in the 2014 Sanofi Genzyme collaboration, as well as one right to a global license.

For more information regarding the 2014 Sanofi Genzyme collaboration, as amended in January 2018, as well as the Exclusive TTR License and the AT3 License Terms, including the ongoing or expected financial and accounting impact on our business, please read Note 4, 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 in a comprehensive Phase 3 development program. For more information regarding the MDCO agreement, including its ongoing financial and accounting

impact on our business, please read Note 4, 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. 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 4, 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, now known as Alnylam Europe 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 are required to pay Max Planck Innovation single-digit royalties on net sales of ONPATPRO and will be required to pay such royalties for future 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 U.S. 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., or Protiva, 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 ONPATPRO, 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. We also have the right to manufacture and have manufactured our LNP-based RNAi therapeutics, which right may be sublicensed to our collaborators. Pursuant to the 2012 cross-license agreement, we are obligated to pay a low, single-digit royalty for certain LNP-based products,



including ONPATTRO.

Under the 2012 cross-license agreement, Arbutus has one exclusive and five non-exclusive licenses to research, develop and commercialize RNAi therapeutics directed to up to six gene targets. Arbutus may sublicense its 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 each of four 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 six 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.

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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 U.S. 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 U.S. 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 ONPATTRO. 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 ONPATTRO sales, as well as other product sales, if any.

Concurrent with the execution of the research agreement, we also entered into a supplemental agreement with Arbutus, 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. 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 U.S. 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.

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

Patent	First	Priority	Inventors	Status	Expiration Date*	Alnylam Rights
Licenser/Owner	Subject Matter	Date				
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	1/9/2001	R. Kreutzer,	U.S. 7,868,160 & U.S.	1/9/2022	Owned

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gene and medicament for treating a tumor disease

S. Limmer, 8,143,390

H-P. Vornlocher,

P. Hadwiger, EP 1799270 & EP 1349927

A. Geick, (opposed and maintained in amended form)

M. Ocker,

C. Herold,

D. Schuppan

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. 9,587,240	1/9/2022	Owned
Alnylam	Composition and methods for inhibiting a target nucleic acid with double-stranded RNA	4/21/1999	C. Pachuk, C. Sathishchandran	EP 1171586, AU 781598 (Australia)  Additional applications pending in the U.S. and several foreign jurisdictions	4/19/2020	Owned

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Patent		First				
Licensors/Owner	Subject Matter	Priority Date	Inventors	Status	Expiration Date*	Alnylam Rights
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	3/30/2021	Exclusive rights for therapeutic purposes**
				EP 1309726 (opposed and maintained in amended form/under appeal), EP 2028278 (opposed), EP 2345742, EP 2360253 (opposed) & EP 2361981 (opposed), AU 2001249622 (Australia), NZ 522045 (New Zealand), KR 08724437 & KR 10-0909681 (Korea)		
				Additional applications pending in the U.S. and several foreign jurisdictions		

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Massachusetts Institute of Technology, Whitehead Institute, University of Massachusetts, Max Planck Gesellschaft (U.S.)***	Synthetic and chemically modified siRNAs as therapeutic products including patents with claims including those directed to double-stranded RNA of between 19 to 23 or 19 to 25 nucleotides, with and without a 3' overhang; claims directed to double-stranded RNA of between 19 to 52 nucleotides with a 3' overhang; claims directed to double-stranded RNA of 14 to 24 base pairs or up to 25 base pairs with at least one nucleotide analogue, along with methods of using and making such double-stranded RNA	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 & U.S. 9,567,582	11/29/2021	Exclusive rights for therapeutic purposes***
European Molecular Biology Laboratory (ex-U.S.)****				EP 1407044 (opposed and maintained in amended form/under appeal), EP 1873259, EP 2348133, EP 2348134, EP 2351852 (opposed) & EP 2813582, AU 2002235744 (Australia), ZA 2003/3929 (South Africa), SG 96891 (Singapore), NZ 52588 (New Zealand), JP 4 095 895 (opposed and maintained) & JP 4 494 392 (Japan), RU 2322500 (Russia), CN 1568373 (China)		

				Additional applications pending in the U.S. and several foreign jurisdictions		
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)	1/31/2021	Owned
				Additional applications pending in the U.S., Australia and Canada		
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)	7/23/2021	Exclusive rights for therapeutic purposes
				Additional applications pending in the U.S. and several foreign jurisdictions		



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Patent		First				
Licensors/Owner	Subject Matter	Priority Date	Inventors	Status	Expiration Date*	Alnylam Rights
Alnylam	Claims directed to carbohydrate conjugates linked to siRNA	4/17/2003	M. Manoharan	U.S. 7,723,509, U.S. 7,745,608, U.S. 7,851,615, U.S. 8,017,762, U.S. 8,507,661, U.S. 8,344,125, U.S. 8,796,436, U.S. 8,865,677 & U.S. 8,426,377	9/21/2024	Owned
				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	12/4/2028	Owned
				Additional applications pending in the U.S. and several foreign jurisdictions		
Sirna*****	Claims directed to highly chemically modified oligonucleotides with granted claims directed to double-stranded RNA of between 18 and 24 nucleotides with various combinations of chemical modifications	2/20/2002	J. McSwiggen	U.S. 7,923,547, U.S. 7,956,176, U.S. 7,989,612, U.S. 8,232,383, U.S. 8,268,986, U.S. 8,236,944, U.S. 8,272,979, U.S. 8,273,866, U.S. 8,242,257, U.S. 8,618,277, U.S. 8,846,894,	2/20/2023-2028	Owned

U.S. 8,648,185,  
U.S. 9,181,551,  
U.S. 9,732,344  
& U.S.  
9,771,588

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  
(Australia), CA  
2526831  
(Canada), JP  
49481631  
(Japan)

Additional cases  
pending in the  
U.S. 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 exclusive rights to the interest owned by Massachusetts Institute of Technology, or MIT, Whitehead Institute for Biomedical Research, or Whitehead, Max Planck Gesellschaft zur Foerderung der Wissenschaften e.V., or Max Planck. The University of Massachusetts, or UMass, licensed its interest separately to Sirna Therapeutics, Inc., or Sirna. In March 2014, we acquired Sirna from Merck Sharp & Dohme Corp, or Merck, thus

we hold the exclusive rights of all four co-owners until March 20, 2019, the effective date of the termination of the license held by Sirna, leaving unaffected our exclusive rights to the interest owned by the other three co-owners.

\*\*\* 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.

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

The Tuschl patent applications owned by Whitehead, MIT, UMass and Max Planck 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, 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 between 19-52 nucleotides in length, 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 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. With this acquisition, we obtained patents and patent applications with early priority dates 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 U.S. 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. Several patents have been granted in the U.S. with claims directed to various combinations of chemical modifications to double-stranded RNA of between 18 and 24 nucleotides. Notably, U.S. Patent No. 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, additional European 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. Patent No. 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-acetylgalactosamine (wherein the GalNAc 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. In addition, in August 2017 the United States Patent and Trademark Office, or USPTO, granted U.S. Patent No. 9,732,344 with claims directed to single-stranded antisense polynucleotide molecules of 18-20 nucleotides, comprising 10 or more phosphorothioates and 10 or more modified pyrimidine molecules.

#### 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 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 and GalNAc-single stranded polynucleotide 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.

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 but not limited to ONPATTRO, 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 Certain 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 European Patent Office, or 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. 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 U.S. and many foreign countries. Granted U.S. Patent No. 8,618,277 obtained in the Sirna acquisition and set to expire on February 20, 2023, contains claims directed to a highly chemically modified double-stranded siRNA of between 18-24 nucleotides specifically targeting the HBV 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 biantennary 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.

In August 2017, we were granted U.S. Patent No. 9,738,899 with claims directed to single-stranded antisense polynucleotide molecules, capable of inhibiting expression of the human TTR gene, of 18-20 nucleotides, comprising 10 or more phosphorothioates and 10 or more modified pyrimidine molecules, 2'-deoxy-, -O-Methyl, -Fluoro, -methoxyethoxy (MOE), pyrimidines, LNA-pyrimidines or a combination, with or without conjugation to a galactosamine or cholesterol.

#### 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 composition of matter, 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 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., or Marina, Arrowhead Pharmaceuticals, Inc., or Arrowhead, and its subsidiary, Calando Pharmaceuticals, Inc., or Calando, Quark Pharmaceuticals, Inc., or Quark, Silence Therapeutics plc, or Silence, Arbutus, Sylentis, S.A.U., or Sylentis, Dicerna Pharmaceuticals, Inc., or Dicerna, and its collaborators, Boehringer Ingelheim, Alexion Pharmaceuticals, Inc. and Eli Lilly and Company, WAVE Life Sciences Ltd., or WAVE, Silenseed Ltd., Ascleptis Pharma Inc., Biomics Biopharma, Sirnaomics Inc., Olix Pharmaceuticals Inc., Phio Pharmaceuticals, Amgen Pharmaceuticals Inc., or Amgen, BioPath Holding Inc. and Arcturus Therapeutics, Inc., or Arcturus. 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., 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 oligonucleotide, or ASO, drugs, 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 to Ionis and its collaborator Biogen Inc., a number of other companies have ASO-based product candidates in various stages of pre-clinical and clinical development, including Roche, Celgene Corporation, Akcea Therapeutics, Inc., or Akcea, 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 Marketed Product and Late Stage Investigational RNAi Therapeutics

ATTR Amyloidosis. Until recently, organ transplantation was the only treatment option for patients with hATTR amyloidosis in the U.S. Only a subset of patients with early-stage disease qualify for this costly and invasive procedure, which carries significant morbidity and risk of mortality. Even following liver transplantation, the disease continues to progress for many patients, presumably due to ongoing deposition of wtTTR protein. Liver transplant is also a treatment option for hATTR amyloidosis patients in other countries.

In addition to ONPATTRO, approved treatments for hATTR amyloidosis now include inotersen (approved in the U.S., EU and Canada) and tafamidis (approved in several countries outside of the U.S.). Indications vary by region for each product.

There are no approved therapies or treatments for patients with wtATTR amyloidosis.

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Several investigational drugs exist, in varying stages of clinical development, for ATTR amyloidosis. We believe that the following approved drugs and if approved, drug candidates, could compete with ONPATTRO and, if approved, vutrisiran:

Drug	Company	Drug Description	Phase	Administration/Dosing
Tafamidis	Pfizer	Small molecule drug to stabilize TTR protein	Approved in the EU, Japan and certain countries in Latin America (hATTR polyneuropathy indication varies by region)	Daily oral capsule
Tafamidis	Pfizer	Small molecule drug to stabilize TTR protein	Two NDAs accepted for review by FDA for approval to treat ATTR cardiomyopathy; JNDA accepted for review by PMDA in Japan	Daily oral capsule
Inotersen	Ionis/Akcea	ASO to reduce production of TTR Protein	Approved in U.S., EU and Canada	Weekly Subcutaneous injection (SC)
AKCEA-TTR-L <sub>Rx</sub> or ION-TTR-L <sub>Rx</sub>	Ionis/Akcea	ASO to reduce production of TTR Protein	Phase 1/2	SC
PRX004	Prothena Corporation plc	mAb to clear amyloid deposits	Phase 1	Unknown
GSK 2398852 + 2315698	GlaxoSmith Kline	Antibody combination to clear amyloid deposits	Phase 2; study suspended in 2018	Intravenous infusion (IV)
Diflunisal	N/A (generic)	Non-steroid anti-inflammatory agent	Approved	Twice-daily oral capsule/dose
Tolcapone	SOM Biotech	Small molecule repurposed generic drug	Phase 1/2	Daily oral dose
AG10	Eidos Therapeutics	Small molecule drug to stabilize TTR protein	Phase 2	Twice daily oral dose

We are also aware of other companies that have pre-clinical development programs for the potential treatment of ATTR amyloidosis.

Acute Hepatic Porphyria. There are two approved hemin products, Panhematin (U.S.) and Normosang (EU), for the treatment of acute porphyria attacks. Both are administered by intravenous infusion and are blood products currently manufactured by Recordati S.p.A. There are currently no products approved for prophylactic use; however, there is off-label prophylactic use of hemin by some physicians. We are aware of other companies that have pre-clinical development programs for the potential treatment of AHP.

Primary Hyperoxaluria. Currently used treatments for PH include hyper hydration, oral citrate or dual liver/kidney transplantation. Transplantation is costly and is an invasive procedure, which carries significant morbidity and mortality. This leaves a high unmet medical need for a severe and primarily pediatric disorder. Presently, there are several investigational drugs in varying stages of clinical development for the treatment of PH. We believe that the following drug candidates, if approved, could compete with lumasiran:

Drug	Company	Drug Description	Phase	Administration/Dosing
DCR-PHXC	Dicerna	siRNA to reduce production of LDHA enzyme	Phase 1	SC with monthly dosing expected
Reloxaliase	Allena Pharmaceuticals, Inc.	Oxalate-degrading enzyme for enteric hyperoxaluria	Phase 3	Up to five daily oral doses
Oxabact OC5	Oxthera Pharmaceuticals, Inc.	Anaerobic bacteria that metabolize oxalate in the gut	Phase 3	Twice daily oral dose

We are aware of other companies that have pre-clinical development programs for the potential treatment of PH.

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; Factor IX replacement products; factor replacement products with extended half-lives, and most recently a bispecific antibody mimicking Factor VIII. For the treatment of persons with inhibitors, there is an approved Factor VIIa replacement product and an activated prothrombin complex concentrate, as well as a bispecific antibody mimicking Factor VIII. In addition, new, innovative molecules are currently in development which may offer new treatments for people with hemophilia A and B, with and without inhibitors. A number of companies are also actively developing gene therapy products that use virus-like particles to deliver a functional section of a particular gene into the liver cells of a person with hemophilia.

We believe that the following approved drugs and, if approved, drug candidates, could compete with fitusiran, along with additional approved drugs and drug candidates:

Drug (Company)	Drug Description	Phase	Administration
<b>Hemophilia A</b>			
Advate (Shire), Adynovate (Shire), Kogenate (Bayer), Kovaltry (Bayer), Novoeight (Novo Nordisk), Xyntha (Pfizer), Nuwiq (Octapharma), Eloctate (Bioverativ)	Recombinant FVIII factor products	Approved	IV
Valoctocogene roxaparvovec (BioMarin)	Gene therapy	Phase 3	IV - Single Administration
Emicizumab HemLibra, ACE-910 (Roche)	Bispecific antibody mimetic of FVIII	Approved	SC
<b>Hemophilia B</b>			
Rixubis (Shire), Rebinyn (Novo Nordisk), BeneFIX (Pfizer), Alprolix (Bioverativ), Idelvion (CSL Behring)	Recombinant FIX factor products	Approved	IV
AMT-061, FIX (uniQure)	rAAV5 FIX gene therapy	Phase 3	IV - Single Administration
SPK-9001 (Spark Therapeutics)	Spark200 AAV FIX gene therapy	Phase 3	IV - Single Administration
<b>Inhibitor Patients</b>			
Emicizumab HemLibra, ACE-910 (Roche)	Bispecific antibody mimetic of FVIII	Approved	SC
Feiba (Shire)	Bypassing agent	Approved	IV
NovoSeven (Novo Nordisk)	Bypassing agent	Approved	IV
<b>Hemophilia A and B</b>			
Concizumab, anti-TFPI (Novo Nordisk)	anti-TFPI antibody	Phase 2	IV - Single Administration

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. Several anti-PCSK9 antibodies have also been approved for the treatment of hypercholesterolemia in the U.S. and Europe. Other PCSK9-targeted approaches are in development at a number of companies.

We believe that the following approved drugs and if approved, drug candidates, could compete with inclisiran:

Drug	Company	Drug Description	Phase	Administration/Dosing
Repatha	Amgen	Anti-PSCK9 mAb	Marketed	SC
Praluent	Sanofi	Anti-PSCK9 mAb	Marketed	SC
Bempedoic Acid (ETC-1002)	Esperion	Oral fatty acid and cholesterol synthesis dual inhibitor	Phase 3	Oral
REGN1500 (evinacumab)	Regeneron	Anti-ANGPTL3 mAb for hypercholesterolemia	Phase 2	SC
Arrowhead- ARO-ANG3	Arrowhead	siRNA targeting ANGPTL3	Phase 1	SC
Akcea-ANGPTL3-Lrx	Akcea	ASO therapy to reduce levels of ANGPTL3	Phase 2	SC

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## 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. 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 U.S. and the rest of the world. In the U.S., 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, labeling, 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 U.S. 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 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 fitusiran, givosiran and inclisiran, are not always conclusive and may be subject to alternative interpretations that could delay, limit or even prevent regulatory approval. Even if a product receives regulatory approval, later discovery of previously unknown problems with a product, including new safety risks, may result in restrictions on the product or even complete withdrawal of the product from the market.

### Nonclinical Tests and 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. Clinical testing in humans may not commence until an IND is in effect.

An IND becomes effective 30 days after receipt by the FDA unless the FDA notifies the sponsor that the proposed investigation(s) are subject to a clinical hold. If the FDA imposes a clinical hold, the FDA's concerns must be resolved prior to the 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 decided to discontinue 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 the clinical trials can commence or recommence only under the terms authorized by the FDA. For example, in September 2017, we temporarily suspended dosing in all ongoing fitusiran studies pending further review of a fatal thrombotic SAE and agreement with regulatory authorities on a risk mitigation strategy. We reached alignment with study investigators and the FDA on safety measures and a risk mitigation strategy to enable resumption of dosing in clinical studies with fitusiran, including the Phase 2 OLE study and the ATLAS Phase 3 program, for which dosing was initiated in early 2018.

Clinical trials involve the administration of an investigational new drug to healthy volunteers or patients under the supervision of a qualified investigator. 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 U.S. must be submitted to the FDA as part of the IND. In addition, clinical trials must be conducted in compliance with federal regulations and requirements, commonly referred to as good clinical practice, or GCP, to assure data integrity and protect the rights, safety and well-being of trial participants. Among other things, GCP requires that all research subjects provide their informed consent prior to participating in any clinical study, and that an IRB at each institution participating in the clinical trial review and approve the plan for any clinical trial before it commences at that institution and conduct continuing review throughout the trial. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects.

Clinical trials to support NDAs 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.

Phase 3 clinical trials 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 U.S. The FDA may, at its discretion, re-evaluate, 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.

#### New Drug Applications.

We believe that any RNAi product candidate we develop, whether for the treatment of ATTR amyloidosis, AHP, hemophilia, hypercholesterolemia or the various indications targeted in our development or nonclinical discovery programs, will be regulated by the FDA as a new drug that is not considered to be a biologic, thus requiring an NDA. FDA approval of an NDA is required before commercial distribution of a non-biological new drug may begin in the U.S. An 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, CMC, 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 typically must contain data assessing the safety and effectiveness for the claimed indication in all relevant pediatric subpopulations, although deferrals or full or partial waivers may be available in some circumstances.

The cost of preparing and submitting an NDA is substantial. Under the Prescription Drug User Fee Act, or PDUFA, as amended, each NDA must be accompanied by a user fee. For fiscal year 2019, the user fee for each NDA requiring clinical data was approximately \$2.6 million. The PDUFA also imposes an annual program fee for each approved prescription drug, which was set at approximately \$300,000 for fiscal year 2019. The FDA adjusts the PDUFA user

fees on an annual basis. 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 or whether instead the FDA will issue a refuse to file determination. 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 the completion of its review of NDAs, although the goals are not binding and 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 often 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 current good manufacturing practice, or cGMP, requirements. 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, and could also conduct GCP inspections of the sponsor.

If the FDA evaluation of the NDA and the various inspections 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, or other surveillance to monitor the drug's safety or effectiveness and may impose other conditions, including labeling restrictions, such as a Boxed Warning, and/or distribution and use restrictions through a Risk Evaluation and Mitigation Strategy, or REMS, all of which can materially affect the potential market and profitability of the drug. Once granted, product approvals may be further limited or withdrawn if compliance with regulatory standards is not maintained or safety or other problems are identified following initial marketing.

Once an NDA is approved, a product will be subject to certain post-approval requirements, including requirements for manufacturing establishment registration and product listing, AE reporting, submission of other 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 adequate and well-controlled head-to-head clinical trials. To the extent that market acceptance of our products depends 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. Such approvals may be expensive and time-consuming and, if not approved, the FDA will not allow the product to be commercially distributed as modified.

If the FDA's evaluation of the NDA submission or GCP inspections or inspection of manufacturing facilities is not favorable, the FDA may refuse to approve the NDA and 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 allow FDA to approve the application. Such actions may include, among other things, conducting additional safety or efficacy studies. 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 that are considered to be medical 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 our product candidate when used with a specialized drug delivery system as a combination product, which could permit the combination to be approved through a single application, such as an NDA. Alternatively, the FDA could require separate, 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 NDA, or ANDA, or 505(b)(2) application. An ANDA generally provides an abbreviated approval pathway for 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. Drugs approved in this way are commonly referred to as generic equivalents to the listed drug 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.

The approval of ANDAs and 505(b)(2) applications can be delayed by patents and non-patent exclusivity covering the listed drug. Federal law provides for a period of three years of exclusivity following approval of a listed drug that contains a previously approved active ingredient if the FDA determines that new clinical investigations, other than bioavailability studies, were conducted or sponsored by the applicant and are essential to the approval of the application. This three-year exclusivity covers only the conditions of approval for which the new clinical investigations were essential, such as a new dosage form or indication. Accordingly, three-year exclusivity generally protects changes to a previously approved drug product that require clinical testing for approval 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 five-year period of new chemical entity, or NCE, exclusivity following approval of a drug that contains a NCE. An NCE is a drug that contains an active moiety (the molecule or ion responsible for the action of the drug substance) that has never previously been approved by the FDA. If a listed drug has NCE exclusivity, ANDAs and 505(b)(2) applications referencing the listed drug cannot be submitted to the FDA for five years unless the application contains a certification challenging a listed patent, i.e., a paragraph IV certification (discussed further below), in which case the ANDA or 505(b)(2) application may be submitted four years following approval of the listed drug. 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 clinical trials necessary to demonstrate safety and effectiveness.

Additionally, applicants submitting an ANDA or 505(b)(2) application referencing a listed drug generally are required to make a certification with respect to each patent listed in the FDA's publication Approved Drug Products with Therapeutic Equivalence Evaluations, commonly referred to as the Orange Book, for the listed drug. The only exception is if the applicant is not seeking approval of a use claimed by a method-of-use patent, in which case the applicant can submit a statement to that effect. These certifications (and statements) determine when the FDA can approve the ANDA or 505(b)(2) application. If the ANDA or 505(b)(2) applicant certifies that it does not intend to market its generic product before a listed patent expires (i.e., a paragraph III certification), then the FDA cannot grant effective approval of the ANDA or 505(b)(2) application until the relevant patent expires. If the ANDA or 505(b)(2) applicant certifies that a listed patent is invalid, unenforceable, or will not be infringed by its proposed product, and thus that it is seeking approval prior to patent expiration (i.e., a paragraph IV certification), the statute provides a process for litigating the patent infringement issues during the FDA's review of the ANDA or 505(b)(2) application. In particular, the applicant is required to provide notice of its patent challenge to the NDA sponsor and the patent holder within certain time limits. If the patent holder then initiates a suit for patent infringement 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 (which may be extended or shortened in certain cases) 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.

#### Orphan Drug Designation.

Under the Orphan Drug Act, as amended, the FDA may grant ODD to a drug intended to treat a rare disease or condition, which is a disease or condition that affects fewer than 200,000 individuals in the U.S. or for which there is no reasonable expectation of recovering drug development costs in the U.S. from sales in the U.S. 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 granted ODD for patisiran and vutrisiran as therapeutic approaches for the treatment of ATTR amyloidosis, givosiran as a therapeutic approach for AHP, lumasiran as a therapeutic

approach for PH1, fitusiran as a therapeutic approach for hemophilia A and B, and inclisiran as a therapeutic approach for HoFH.

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 drug exclusivity, which means that the FDA may not approve for seven years any other applications, including a full NDA, to market the same orphan drug for the same indication, except in limited circumstances. 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, as such designation may have been amended by the FDA. In addition, orphan drug exclusive marketing rights in the U.S. 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 FDCA, as amended by the Food and Drug Administration Safety and Innovation Act, or 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. Drugs with ODD are exempt from these requirements. 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 PSP 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 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 meeting. Fast Track designation provides opportunities for frequent interactions with FDA to expedite drug development and review as well as the opportunity for priority and/or rolling review of the NDA. 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, which was approved in August 2018.

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. A 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 available therapies. The FDA's goal for taking action on an application with a Priority Review designation is six months instead of ten months, except that two months are added to these time periods for drugs that contain a new molecular entity. 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 that can be measured earlier 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 requires as a condition for accelerated approval pre-approval of promotional materials, which could delay 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 create the “breakthrough therapy” designation. 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. The FDA granted Breakthrough Therapy Designation for patisiran, approved in August 2018, as well as givosiran and lumasiran. We intend to request “breakthrough therapy” designation for our other 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 U.S. 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 health care economic 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. Lack of adequate third-party reimbursement may mean we are not able to maintain price levels sufficient to realize an appropriate return on our investment in product development.

Federal, state and local governments in the U.S. and foreign governments continue to consider legislation to limit the growth of healthcare costs, including the cost of prescription drugs. Specifically, there have been several recent U.S. Congressional inquiries and proposed federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers. 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 U.S. 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.

The Patient Protection and Affordable Care Act, also referred to as the Affordable Care Act or the ACA, enacted in 2010, 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 ACA 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 as a condition for states to receive federal matching funds for the manufacturer's outpatient drugs furnished to Medicaid patients. The ACA increased pharmaceutical manufacturers' rebate liability by raising the minimum basic Medicaid rebate on most branded prescription drugs and biologic products to 23.1 percent of average manufacturer price, or AMP, and added a new rebate calculation for "line extensions" (i.e., new formulations, such as extended release formulations) of solid oral dosage forms of branded products, and modified the statutory definition of AMP. In addition, the ACA 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.

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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. The ACA 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, because 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.

The ACA 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"). Under the Bipartisan Budget Act of 2018, or the BBA, effective in 2019, the mandated manufacturer coverage gap discount increased to 70 percent.

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

The ACA created the Sunshine Act, which requires 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. Legislation passed in 2018 expands the scope of covered recipients to physician assistants and advanced practice nurses, effective in 2022.

The ACA established a new Patient-Centered Outcomes Research Institute 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 ACA created the Independent Payment Advisory Board, which 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 ACA 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.

The law expands eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133 percent of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability.

In December 2017, portions of the ACA dealing with the individual mandate insurance requirement were effectively repealed by the Tax Cuts and Jobs Act of 2017, or TCJA, and Congress and/or the President of the United States may seek to repeal other aspects of the ACA. In December 2018, a federal district court judge in Texas found the ACA to be unconstitutional, although the ruling was stayed while the case is appealed.

#### Health Care Fraud and Abuse.

Federal and state laws generally prohibit the payment or receipt of kickbacks, bribes or other remuneration in exchange for the referral of patients or other health-related business. For example, the Federal Anti-Kickback Statute prohibits anyone from, among other things, knowingly and willfully offering, paying, soliciting or receiving any bribe, kickback or other remuneration intended to induce the referral of patients for, or the purchase, order or recommendation of, health care products and services reimbursed by a federal health care program, including Medicare and Medicaid. Violations of this federal law can result in significant penalties, including imprisonment, monetary fines and assessments, and exclusion from Medicare, Medicaid and other federal health care programs. Exclusion of a manufacturer would preclude any federal health care program from paying for its products. In addition to the federal anti-kickback law, many states have their own laws that are analogous to the federal anti-kickback law,

but may apply regardless of whether any federal or state health care program business is involved.

In addition, federal and state false claims laws prohibit anyone from presenting, or causing to be presented, claims for payment to third-party payers that are false or fraudulent. For example, the federal False Claims Act, or FCA, imposes liability on any person or entity who, among other things, knowingly and willfully presents, or causes to be presented, a false or fraudulent claim for payment by a federal health care program, including Medicaid and Medicare. Some suits filed under the FCA, known as “qui tam” actions, can be brought by a “whistleblower” or “relator” on behalf of the government, and such individuals may share in any amounts paid by the entity to the government in fines or settlement. Manufacturers can be held liable under false claims laws, even if they do not submit

claims to the government, where they are found to have caused submission of false claims by, among other things, providing incorrect coding or billing advice about their products to customers that file claims, or by engaging in kickback arrangements or off-label promotion with customers that file claims. A number of states also have false claims laws, and some of these laws may apply to claims for items or services reimbursed under Medicaid and/or commercial insurance. Sanctions under these federal and state fraud and abuse laws may include civil monetary penalties and criminal fines, exclusion from government health care programs and imprisonment.

The Foreign Corrupt Practices Act of 1977 and similar worldwide anti-bribery laws in non-U.S. jurisdictions generally prohibit companies and their intermediaries from making improper payments to non-U.S. officials for the purpose of obtaining or retaining business.

Under the federal Sunshine Act, certain manufacturers must 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. Legislation passed in 2018 expands the scope of covered recipients to physician assistants and advance practice nurses, effective in 2022. Many state laws require drug manufacturers to report similar information related to payments and other transfers of value provided to other healthcare providers. Some states prohibit these expenditures altogether. Laws in a number of states also require companies to adopt marketing codes of conduct, companies to disclose pricing information about their products, or pharmaceutical sales representatives to be licensed.

#### 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 approval of the 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. Any substantial changes to the trial protocol or

other information submitted with the CTAs must be notified to or approved by the relevant competent authorities and ethics committees.

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 come into application in the second half of 2020, there will be a centralized application procedure where one national authority leads the scientific review of the application leading to increased information-sharing and decision-making between member states. Each concerned member state will continue to complete an ethical review of any CTA.

Information related to the product, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial is made public by the competent authority once the CTA is approved. The results of the clinical trial must be submitted by the sponsor to the competent authorities and, with the exception of non-pediatric Phase 1 trials, will be made public at the latest within six months of the end of a pediatric clinical trial, or otherwise 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 (CMC testing), nonclinical testing and clinical studies, and pharmacovigilance plans and risk-management programs. Advice is not legally binding with regard to any future MAA of the product concerned.

#### Marketing Authorisations.

After completion of the required clinical testing, we must obtain a marketing authorisation 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 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 authorisation dossiers, including the full clinical study reports, in response to freedom of information requests after the marketing authorisation 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 an MAA, 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 the second half of 2020.

The centralized procedure gives rise to marketing authorisations 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 relevant scientific committees, including the CHMP. The EMA forwards CHMP opinions to the EC, which uses them as the basis for deciding whether to grant a marketing authorisation. 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 authorisation 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 authorisation 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 interest for public health and therapeutic intervention, defined by the absence or insufficiency of an appropriate alternative therapeutic approach for the disease to be treated; and anticipation of high therapeutic benefit of the new product. In this circumstance, EMA ensures that the opinion of the CHMP is given within 150 days. The EMA granted an accelerated assessment for patisiran, which was approved in the EU in August 2018 under the centralized procedure.

#### 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 authorisation of a reference product for which regulatory data exclusivity has expired. If a marketing authorisation 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 Committee for Orphan Medicinal Products, or 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 authorisation. During this period, the competent authorities may not accept or approve any similar medicinal product for the same therapeutic indication, unless the second medicinal product is safer, more effective or otherwise clinically superior. 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 orphan designation. Patisiran, approved in the EU in August 2018, as well as vutrisiran, givosiran, lumasiran and fitusiran have been granted orphan medicinal product designation.

#### Post-Approval Controls.

The holder of a marketing authorisation 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 authorisation. 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 U.S. 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. In particular, during 2018, we filed for regulatory approval of ONPATTRO in Japan, Canada and Switzerland and regulatory filings in additional countries are planned for 2019, and will have to follow the specific regulations in Japan, Canada, Switzerland and such other countries, which are complex.

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 U.S. 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 facilities, as well as patisiran formulated bulk drug product for late stage clinical trial use and commercial supply. We have contracted with several third-party contract manufacturing organizations, or CMOs, for the supply of drug substance and finished product to meet our needs for pre-clinical toxicology studies, clinical testing and commercial supply. We expect to continue to rely on third-party CMOs for the supply of drug substance and drug product, including ONPATTRO, as well as other product candidates, for at least the next several years, including to support the potential launch of additional products and to supply the needs of our alliance

partners. In 2015, we amended our manufacturing services 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. Under this agreement, 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 separate commercial manufacturing supply agreements with Agilent for certain products, consistent with certain specified terms, including a specified minimum purchase commitment. Currently, Agilent is the sole manufacturer of the active pharmaceutical ingredient for ONPATTRO for both clinical and commercial use, and in March 2018, we entered into a manufacturing services agreement with Agilent for such commercial supply. Pursuant to the Agilent commercial supply agreement, we are required to provide rolling forecasts for ONPATTRO 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 ONPATTRO in the amounts specified under such firm orders, including a certain percentage of the remaining, non-binding portions of each forecast, as well as a specified number of batches each year. In April 2016, we completed our purchase of a parcel of land in Norton, Massachusetts. We are constructing a cGMP manufacturing facility at this site for drug substance for clinical and commercial use, which we currently expect to be 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 trial use and commercial supply. During 2013, we manufactured our first cGMP batch of ONPATTRO for use in our Phase 2 OLE and Phase 3 clinical trials. We will continue to manufacture commercial supply for patisiran formulated bulk drug product in our facility for the foreseeable future. Commercial quantities of ONPATTRO and any other 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 manufacturing facilities to meet our current research, clinical and commercial needs and the needs of our alliance partners. We believe that the current 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 and our alliance partners' 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 and our alliance partners' 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 successfully overcoming various challenges associated with developing a new class of innovative medicines - such as solving the issue of drug delivery, optimizing our RNAi therapeutics to exhibit potency and durability of effect, and designing and carrying out comprehensive clinical trials to demonstrate the safety and clinical efficacy of our investigational products - we have recently embarked on the next part of the journey: introducing our RNAi therapeutics to as many eligible patients in need as possible. To that end, we have been building a global commercial operation which is designed to be fully integrated and ready to sequentially manage the potential of multiple product launches across multiple geographies. As a now commercial-stage biopharmaceutical company, we are building commercial capability and leveraging the internal knowledge we have accumulated as well as hiring talented people

from industry to enable us to commercialize our products ourselves in key countries globally. The conduct of these commercial activities will continue to be dependent upon regulatory approvals and on agreements that we have made or may make in the future with strategic collaborators, currently as follows with respect to our first approved product and our late-stage clinical programs:

- For ONPATTRO, we have global rights to develop and commercialize both the approved product, ONPATTRO, and vutrisiran, the next potential product in our ATTR amyloidosis franchise;
- For givosiran and lumasiran, we have global rights to develop and commercialize;
- For fitusiran, Sanofi Genzyme has global rights to develop and commercialize fitusiran and any back-ups as a result of the 2018 amendment to the Sanofi Genzyme collaboration and the related product-specific license terms; and
- For inclisiran, we have granted MDCO global rights to develop and commercialize.

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Throughout the development of our product candidates, we have remained focused on keeping patients at the center of everything we do. This patient focus has continued as we have transitioned into commercialization. Moreover, like ONPATTRO, the late stage programs we are advancing to commercialization are focused on orphan diseases, and we have been executing on what we believe to be a proven orphan disease education and commercialization strategy to make ONPATTRO and future orphan products successful. This begins with our Medical Affairs efforts to engage patient groups and communities, improve disease awareness and increase patient diagnosis. We believe our Alnylam Act program and other efforts have supported improvements in diagnosis. Separately, we have a proactive market access strategy that includes using VBAs that we have formed with commercial payers in the U.S. As of the beginning of 2019, we have completed VBAs with several commercial payers, including two of the top five U.S. payers, and have ongoing discussions with multiple commercial payers that, in the aggregate, cover over 90 percent of U.S. patients with commercial insurance. We believe we have also been making strong progress in the EU with government payers. Once a patient is diagnosed and is prescribed ONPATTRO, our own patient services hub, Alnylam Assist, is aimed at supporting patient access and retention in the U.S. We have similar patient support efforts ongoing in Europe and planned for other geographies outside of the U.S. as well.

We are continuing to augment the key components of a global commercial organization with a focus on successfully launching ONPATTRO around the world and preparing for the anticipated commercial launches of additional RNAi therapeutics we are developing, beginning with givosiran, assuming positive complete Phase 3 results and regulatory approval. With respect to ONPATTRO, we continue to build our commercial capabilities with the planned hire of approximately 250 employees deployed in customer facing activities across the world. We have assembled field teams in the U.S. and other major European countries, and we are in the process of expanding these capabilities to additional European countries, as well as Canada, Japan and Brazil, assuming positive regulatory outcomes. We are building a focused commercial team with broad experience in marketing, sales, patient access, patient services, distribution and product reimbursement, in particular for orphan diseases. We are incorporating the appropriate quality systems, compliance policies, systems and procedures, as well as implementing internal systems and infrastructure in order to support global commercial sales, and the establishment of patient-focused programs. Ultimately, we intend to leverage the commercial infrastructure that we have been building for ONPATTRO to also support the potential launches of givosiran, lumasiran and vutrisiran, assuming positive Phase 3 results and regulatory approval. Our objective is to be ready to execute successful product launches. For many territories/countries, we may also elect to utilize strategic partners, distributors or contract sales forces to assist in the commercialization of our products.

## Employees

At January 31, 2019, we had 1,065 employees. 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.

## 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.

The SEC 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>.

## 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,” “may” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these words. Any or all of our forward-looking statements in this annual report on Form 10-K and in any other public statements we make may turn out to be wrong. They can be affected by inaccurate assumptions we might make or by known or unknown risks and uncertainties. Many factors mentioned in the discussion below will be important in determining future results. Consequently, no forward-looking statement can be guaranteed. Actual future results may vary materially from those anticipated in forward-looking statements. We explicitly disclaim any obligation to update any forward-looking statements to reflect events or circumstances that arise after the date hereof. You are advised, however, to consult any further disclosure we make in our reports filed with the SEC.

### Risks Related to Our Business

#### Risks Related to Being a Commercial Company

We have limited experience as a commercial company and the marketing and sale of ONPATTRO or any future products may be unsuccessful or less successful than anticipated.

In August 2018, the FDA approved ONPATTRO (patisiran) lipid complex injection for the treatment of the polyneuropathy of hATTR amyloidosis in adults in the U.S., and the EC granted marketing authorisation for ONPATTRO for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy in the EU. While we have launched ONPATTRO in the U.S. and in several countries in Europe, we have limited experience as a commercial company and there is limited information about our ability to successfully overcome many of the risks and uncertainties encountered by companies commercializing products in the biopharmaceutical industry. We also have several product candidates in late-stage clinical development. To execute our business plan, in addition to successfully marketing and selling ONPATTRO, we will need to successfully:

- execute product development activities using new 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 ONPATTRO, as well as any other products we commercialize;
  - attract and retain customers for our products;
- 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 ONPATTRO or any future products, raise capital, expand our business or continue our operations.

The approach we are taking to discover and develop novel RNAi therapeutics may not lead to products that achieve market acceptance.

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. 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 still 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 and the potential success of any such 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. We have spent and expect to continue to spend large amounts of money developing siRNAs that possess the properties typically required of drugs, and to date, we have received regulatory approval for one product. In addition, the compounds we are developing 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. We conducted a comprehensive evaluation of the revusiran data and reported the results of this evaluation in August 2017, however, our investigation did not result in a conclusive explanation regarding the cause of the mortality imbalance observed in the ENDEAVOUR Phase 3 study. Although we received regulatory approval for ONPATTRO in the U.S. and EU, if we do not succeed in developing multiple products that gain regulatory approval and succeed in the marketplace, we may not become profitable and the value of our common stock could 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 and commercializing additional products 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, 2018, we had an accumulated deficit of \$2.84 billion. Although we have launched ONPATTRO in the U.S. and several countries in Europe, and expect to launch in additional countries during 2019, we may never attain profitability or positive cash flow from operations. For the year ended December 31, 2018, we recognized \$12.5 million in net product revenues from sales of ONPATTRO. 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. In addition to revenues derived from sales of ONPATTRO, and other product candidates that achieve regulatory approval, we anticipate that a portion of any revenues we generate over the next several years will continue to be from alliances with pharmaceutical and biotechnology companies. We 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 expect our operating results to fluctuate in future periods, which may adversely affect our stock price.

Our quarterly operating results have fluctuated in the past, and we believe they will continue to do so in the future. Our operating results may fluctuate due to the level of success of our commercial efforts, as well as the variable nature of our operating expenses as a result of the timing and magnitude of expenditures. In one or more future periods, our results of operations may fall below the expectations of securities analysts and investors. In that event, the market price of our common stock could decline.

We will require substantial additional funds to complete our research, development and commercialization 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 ONPATTRO or any other 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 continued 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 successfully initiate and complete our pre-clinical and clinical studies, obtain regulatory approvals, prepare for global 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 ONPATTRO and our other potential products.

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

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

In April 2016, our subsidiary, Alnylam U.S., Inc., entered into an aggregate of \$150.0 million in term loan agreements related to the build out of our drug substance manufacturing facility. In December 2017, we repaid in full \$120.0 million outstanding under one such term loan agreement. We are the guarantor under the remaining term loan agreement, which matures in April 2021. Interest on the borrowings is calculated based on LIBOR plus 0.45 percent. During an event of default under the remaining 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 agreement are secured by cash collateral in an amount equal to, at any given time, at least 100 percent of the principal amount outstanding under such agreement at such time. The remaining agreement includes 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 lender 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 lender would be entitled to take various actions, including the acceleration of amounts due under the loan. Our ability to satisfy our obligations under this agreement 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, to date, Sanofi Genzyme has exercised its right to purchase an additional 344,448 shares of our common stock in connection with our acquisition of Sirna in March 2014, an aggregate of 401,281 shares of our common stock based on its 2014 and 2015 annual compensation-related rights and an aggregate of 1,042,067 shares of our common stock in connection with our public offerings in January 2015 and May 2017. These purchases allowed Sanofi Genzyme to maintain its ownership level of our outstanding common stock. As of December 31, 2018, Sanofi Genzyme held approximately ten percent of our outstanding common stock. While the exercise of these rights by Sanofi Genzyme has provided us with an additional \$147.7 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. Sanofi Genzyme elected not to exercise its annual compensation-related rights for 2016, 2017 or 2018. Additionally, Sanofi Genzyme elected not to exercise its right to purchase additional shares in connection with our public offerings in November 2017 and January 2019.

If we are unable to obtain additional funding on a timely basis, we may be required to significantly delay or curtail one or more of our research or development programs, delay the build-out of our global commercial infrastructure 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 and/or our projected guidance 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.

Further, from time to time we issue financial guidance relating to our expectations regarding our non-GAAP research and development and selling, general and administrative expenses, and expectations for our cash, cash equivalents and marketable debt securities available for operations, which guidance is based on estimates and the judgment of management. If, for any reason, our expenses differ materially from our guidance or we utilize our cash more quickly than anticipated, we may have to adjust our publicly announced financial guidance. If we fail to meet, or if we are required to change or update any element of, our publicly disclosed financial guidance or other expectations about our business, our stock price could decline.

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

At December 31, 2018, we had \$1.08 billion in cash, cash equivalents and marketable debt securities, excluding the \$44.8 million of restricted investments related to our cash collateral of \$30.0 million under our term loan agreement and \$14.8 million security deposit for 675 West Kendall Street, Cambridge, Massachusetts. We historically have invested these amounts in high-grade corporate notes, commercial paper, securities issued or sponsored by the U.S. government, certificates of deposit and money market funds meeting the criteria of our investment policy, which is focused on the preservation of our capital. Corporate notes may 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.

The effect of comprehensive U.S. tax reform legislation on us, our subsidiaries and our affiliates, whether adverse or favorable, is uncertain.

Our business is subject to numerous international, federal, state, and other governmental laws, rules, and regulations that may adversely affect our operating results, including, taxation and tax policy changes, tax rate changes, new tax laws, or revised tax law interpretations, which individually or in combination may cause our effective tax rate to increase. For example, on December 22, 2017, the President of the United States signed into law the TCJA. Among a number of significant changes to the current U.S. federal income tax rules, the TCJA reduced the marginal U.S.



corporate income tax rate from 35 percent to 21 percent, introduced a capital investment deduction, limited the current deduction for net interest expense, limited the use of net operating losses to offset future taxable income, and made extensive changes in the way in which income earned outside the U.S. is taxed in the U.S. We disclosed the estimated impact of the TCJA in our annual report on Form 10-K that was filed with the SEC on February 15, 2018. As of December 31, 2018, our analysis of the impact of the TCJA was complete and there were no material changes to the provisional amount recorded at December 31, 2017.

### Risks Related to Our Dependence on Third Parties

We may not be able to execute our business strategy if we are unable to maintain existing or enter into new 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 are continuing to advance our sales and distribution capabilities and also have newly established capabilities for marketing, sales 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/or for certain product candidates, 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 U.S., 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. In January 2018, we and Sanofi Genzyme amended our 2014 collaboration to provide that we would develop and commercialize ONPATPRO and vutrisiran globally and Sanofi Genzyme would develop and commercialize fitusiran globally. With respect to our Cardio-Metabolic Disease pipeline, we intend to seek future strategic alliances for these programs, under which we may retain certain product development and commercialization rights, or we may structure as global alliances, as we did in our collaboration with MDCO to advance inclisiran. In March 2018, we entered into a discovery collaboration with Regeneron to identify RNAi therapeutics for NASH and potentially other related diseases, and in November 2018, we and Regeneron entered into a separate, fifty-fifty collaboration to further research, co-develop and commercialize any therapeutic product candidates that emerge from these discovery efforts. In October 2017, we announced an exclusive licensing agreement with Vir for the development and commercialization of RNAi therapeutics for infectious diseases, including chronic HBV infection. We may also seek collaborations, including potentially global alliances, for our CNS and ocular programs in the future.

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 fitusiran worldwide and potentially other of our Genetic Medicine programs in territories outside of the U.S., 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 development and/or commercialization efforts, our future revenues from RNAi therapeutics for these indications may be adversely affected. Sanofi Genzyme also has the right to elect one global license for a future Genetic Medicine program that was not one of our defined Genetic Medicine programs as of the effective date of our 2014 collaboration. If and when Sanofi Genzyme elects to take a global license to one of our programs, we will no longer control the development and potential commercialization of such program and any revenues we receive will depend solely on the success of Sanofi Genzyme's efforts. 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 cemdisiran programs and in early 2018, Sanofi Genzyme elected not to take a global license for our lumasiran program. 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 decisions.

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 POC for our technology in humans, including our ESC+ GalNAc conjugate technology or our alternative conjugate approach for delivering CNS or ocular product candidates, 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. In addition, our decision in September 2017 to temporarily suspend dosing in all ongoing fitusiran studies pending further review of a fatal thrombotic SAE, and agreement with regulatory authorities on a risk mitigation strategy could, notwithstanding the alignment reached with the FDA on a risk mitigation strategy in November 2017 and reinitiation of such studies, contribute to further concerns about the safety of our therapeutic 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, we have formed collaborations to fund all or part of the costs of drug development and commercialization, such as our collaborations with Sanofi Genzyme, MDCO, Vir and Regeneron. 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 materially amends, 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 materially amends or 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. For example, Sanofi Genzyme has the right to terminate its global license agreement for fitusiran at any time upon six months' prior written notice. In addition, 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 on a more expedited timeline, 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 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. Arbutus did not appeal this ruling.

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, or CROs, 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, auditing 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 in compliance with regulatory and other legal requirements and our internal policies and procedures. 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 CROs are required to comply with applicable GCP requirements, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities for all of our product candidates in clinical development, and to implement timely corrective action to any non-compliance. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and trial sites, including in connection with the review of marketing applications. If we or any of our CROs fail to comply with applicable GCP requirements, or fail to take any such corrective action, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, the EMA, the PMDA in Japan or comparable foreign regulatory authorities may require us to take additional action or perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority in the future, 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 stock price would likely be negatively impacted, and 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 continue to commercialize ONPATPRO, continue to develop our current product candidates, apply for regulatory approvals and, if approved, commercialize future products, 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 are constructing a cGMP manufacturing facility for drug substance 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 finished product we will require for any clinical trials that we initiate and to support the commercial launch of ONPATPRO and any of our other product candidates. 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 services 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 product candidates in clinical development, as well as other products the parties may agree upon in the future. We currently rely on Agilent to supply the active pharmaceutical ingredient to support the commercial supply of ONPATTRO and in March 2018, we entered into a manufacturing services agreement with Agilent for such commercial supply. 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 and potentially put at risk commercial supply, 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 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 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 ONPATTRO and believe we have adequate resources to supply our commercial needs. In addition, as noted above, we are developing our own capabilities to manufacture drug substance 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 a lengthy process 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. Any delay or setback in the manufacture of ONPATTRO could impede ongoing commercial supply, which could significantly impact our revenues and operating results.

The manufacturing process for ONPATTRO and any other 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 CMOs 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 our 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 CMO 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:

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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 CMOs, and our products could be the subject of inspections by regulatory authorities that could have a negative outcome and result in delays in supply;

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

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

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If any CMO 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 CMO, 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 CMO 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 CMOs for any reason, we will be required to verify that the new CMO 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 CMO could negatively affect our ability to develop product candidates or commercialize our products in a timely manner or within budget. Furthermore, a CMO may possess technology related to the manufacture of our product candidate that such CMO owns independently. This would increase our reliance on such CMO or require us to obtain a license from such CMO in order to have another CMO manufacture our products or product candidates.

We have limited sales and distribution experience and newly established capabilities for marketing, sales and market access, and expect to continue to invest significant financial and management resources to continue to build these capabilities and to establish a global commercial infrastructure.

We have limited sales and distribution experience and newly established 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, as a result of the January 2018 amendment to our Sanofi Genzyme collaboration, we intend to commercialize ONPATTRO, as well as several of our late-stage product candidates if approved, including givosiran, lumasiran and vutrisiran, on our own globally. Accordingly, we have developed internal sales, distribution and marketing capabilities as part of our core product strategy initially in the U.S. and the EU, and with expansion ongoing in Canada, Switzerland, Central and Eastern Europe, Japan, Brazil and eventually in other major markets in the rest of the world, which will require significant financial and management resources. For those products for which we will perform sales, marketing and distribution functions ourselves, including ONPATTRO and, if approved, givosiran, lumasiran and vutrisiran, and for future products we successfully develop where we may retain certain 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 global capabilities and infrastructure 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/or in any specific geographic region; and
- our direct sales and marketing efforts may not be successful.

If we are unable to continue to develop and scale our own global sales, marketing and distribution capabilities for ONPATTRO and any future products, we will not be able to successfully commercialize our products 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 our term loan agreement 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, medical 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 commercialization, 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 several years 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 attract and reward qualified individuals than we do. In addition, due to the risks associated with developing a new class of medicine, we may experience disappointing results in a clinical program and our stock price may decline as a result, as was the case following our decision in October 2016 to discontinue our revusiran program, and, to less of an extent, following our temporary suspension of dosing in our fitusiran program in September 2017. As a result, we may face additional challenges in attracting and retaining employees. In addition, we may not be successful commercializing our first product and as a result, we may be unable to attract and retain highly qualified sales and marketing professionals to support ONPATTRO and our future products, if approved. Accordingly, we may be unable to attract and retain suitably qualified individuals in order to support our growing research, development and global 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.- and EU-based company primarily involved in discovery, pre-clinical testing and clinical development into a global company that develops and commercializes multiple drugs.

As we continue the commercial launch of ONPATTRO and increase the number of product candidates we are developing, we will also need to expand our operations in the U.S. and continue to build operations in the EU and other geographies, including Japan and Latin America. In August 2018, we received regulatory approval for ONPATTRO in the U.S. and EU, and as a result of the January 2018 amendment to our Sanofi Genzyme collaboration, we now have global development and commercialization rights for ONPATTRO. We also filed for regulatory approvals in Canada, Japan and Switzerland, and plan to file for additional regulatory approvals in additional countries throughout 2019.

As noted above, we grew our workforce significantly from 2016 through 2018, and anticipate continuing to hire additional employees in 2019, including employees in the EU, Japan and other territories, as we focus on the commercialization of ONPATTRO and achieving our Alnylam 2020 strategy. This expected growth is placing a strain on our administrative and operational infrastructure, and we will need to continue to develop additional and/or new infrastructure and capabilities to support our growth and obtain additional space to conduct our operations in the U.S., the EU, Japan and other geographies. 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 continue to expand our global development, regulatory, manufacturing, quality, compliance, and marketing and sales capabilities, or contract with other organizations to provide these capabilities for us. In addition, as our operations expand due to our development progress, we will need to continue 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.

The increasing use of social media platforms presents new risks and challenges.

Social media is increasingly being used to communicate about our clinical development programs and the diseases our investigational RNAi therapeutics are being developed to treat, and we are utilizing what we believe is appropriate social media in connection with our commercialization efforts for ONPATTRO and, we intend to do the same for our future products, if approved. Social media practices in the biopharmaceutical industry continue to evolve and regulations relating to such use are not always clear. This evolution creates uncertainty and risk of noncompliance with regulations applicable to our business, resulting in potential regulatory actions against us. For example, patients may use social media channels to comment on their experience in an ongoing blinded clinical study or to report an alleged AE. When such disclosures occur, there is a risk that we fail to monitor and comply with applicable AE reporting obligations or we may not be able to defend our business or the public's legitimate interests in the face of the political and market pressures generated by social media due to restrictions on what we may say about our investigational products. There is also a risk of inappropriate disclosure of sensitive information or negative or inaccurate posts or comments about us on any social networking website. If any of these events were to occur or we otherwise fail to comply with applicable regulations, we could incur liability, face regulatory actions or incur other harm to our business.

Our business and operations could suffer in the event of system failures or unauthorized or inappropriate use of or access to our systems.

We are increasingly dependent on our information technology systems and infrastructure for our business. We collect, store and transmit sensitive information including intellectual property, proprietary business information and personal information in connection with business operations. The secure maintenance of this information is critical to our operations and business strategy. Some of this information could be an attractive target of criminal attack or unauthorized access and use by third parties with a wide range of motives and expertise, including organized criminal groups, "hacktivists," patient groups, disgruntled current or former employees and others. Cyber-attacks are of ever-increasing levels of sophistication, and despite our security measures, our information technology and infrastructure may be vulnerable to such attacks or may be breached, including due to employee error or malfeasance.

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 or inappropriate access or use, 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, security breach or unauthorized or inappropriate use or access to our systems were to result in a loss of or damage to our data, or inappropriate disclosure of confidential or proprietary information, including but not limited to patient, employee or vendor information, we could incur notification obligations to affected individuals and government agencies, liability, including potential lawsuits from patients, collaborators, employees, stockholders or other third parties and liability under foreign, federal and state laws that protect the privacy and security of personal information, 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/or 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. For example, 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 several internal programs and two partnered programs currently in Phase 3 development, as well as several earlier stage clinical programs.

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 September 2018, we announced topline results of the interim analysis of our ENVISION Phase 3 study of givosiran. Although the clinical data from the interim analysis are encouraging, the data are preliminary in nature, based on a surrogate biomarker that is reasonably likely to predict clinical benefit, and based on a limited number of patients with AHPs. In addition, the favorable interim analysis results from the ENVISION Phase 3 study may not be predictive of the final results, and there can be no guarantee that the final data will be sufficient to serve as the basis for a future NDA, or MAA filing. 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, ONPATPRO and our current product candidates, including givosiran, lumasiran, vutrisiran, fitusiran and inclisiran, 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. We conducted a comprehensive evaluation of the revusiran data and reported the results of our evaluation in August 2017. Following our evaluation, we continue to believe that the decision to discontinue development of revusiran does not affect ONPATPRO or any of our other investigational RNAi therapeutic programs in development. In September 2017, we announced that we had temporarily suspended dosing in all ongoing fitusiran studies pending further review of a fatal thrombotic SAE and agreement with regulatory authorities on a risk mitigation strategy. In December 2017, we reached alignment with study investigators and the FDA on safety measures and a risk mitigation strategy to enable resumption of dosing in clinical studies with fitusiran, including our Phase 2 OLE study, and the ATLAS Phase 3 program, including protocol-specified guidelines and additional investigator and patient education concerning reduced doses of



replacement factor or bypassing agent to treat any breakthrough bleeds in fitusiran studies.

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 or our partners may experience difficulty enrolling our clinical trials, including, but not limited to, the ongoing clinical trials for fitusiran, due to the availability of existing approved treatments, as well as other investigational treatments in development. Moreover, given the temporary suspension of dosing in our fitusiran studies in September 2017 due to a fatal thrombotic SAE, people with hemophilia may be more reluctant to enroll in the ATLAS Phase 3 program of fitusiran. In addition, in November 2018 we announced that due to recruitment challenges, we have discontinued a Phase 2 study of cemdisiran in aHUS and now intend to focus our cemdisiran clinical development efforts in a different indication. Delays or difficulties in patient enrollment or difficulties retaining trial participants, including as a result of the availability of existing or other investigational treatments or safety concerns, 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 September 2017, we announced that we had temporarily suspended dosing in all ongoing fitusiran studies pending further review of a fatal thrombotic SAE that occurred in a patient with hemophilia A without inhibitors who was receiving fitusiran in our Phase 2 OLE study. In addition, 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. Further, a review by us in 2017 of the ENDEAVOUR results subsequent to the completion of follow-up of the patients post-dosing discontinuation revealed an imbalance in new onset or worsening peripheral neuropathy 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 the 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 September 2018, we reported positive topline results from our interim analysis of the ENVISION Phase 3 study of givosiran. As of August 22, 2018, the data cut-off date of the interim analysis, one patient on givosiran discontinued treatment due to an increase in liver transaminase that was greater than eight times the upper limit of normal, a protocol-defined stopping rule. The increase in liver transaminase subsequently resolved.

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 discontinuation of our revusiran program in October 2016 and the temporary suspension of dosing in September 2017 in our fitusiran studies, the occurrence of SAEs and/or 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. The occurrence of SAEs and/or AEs could also result in refusal by the FDA or a foreign regulatory authority 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 U.S., 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;

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- 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, including GCP and cGMP, 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
  - interpretations of data by the FDA and similar foreign regulatory agencies that differ from ours.
- 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 U.S. 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, 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 U.S. 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 the product candidates we are developing will not 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 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 development of our product candidates. In addition, because there may be approved treatments for some of the diseases for which we may seek approval, or treatments in development which are approved by the time we apply for 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.

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Any delay or failure in obtaining required approvals for our product candidates could have a material adverse effect on our ability to generate revenues from any product candidate for which we may seek approval in the future.

Furthermore, any regulatory approval to market any product may be subject to limitations on the approved uses for which we may market the product or the labeling or other restrictions, which could limit each such product's market opportunity and have a negative impact on our results of operations and our stock price. 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 an 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 U.S. and vice versa.

Even if we or our partners obtain regulatory approvals, our marketed drugs will be subject to ongoing regulatory oversight. If we or our partners 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 drugs we or our partners may develop, including ONPATTRO, which was approved in the U.S. and EU in August 2018, 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 ONPATTRO or other drug products required as a condition of approval or agreed to by us. The regulatory approvals that we receive for ONPATTRO, as well as any regulatory approvals we receive for any other 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 good practice quality guidelines and regulations, including 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 U.S., 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 after approval, which may impose further requirements or restrictions on the distribution or use of an approved drug. As ONPATTRO is used commercially, we or others could identify previously unknown side effects or known side effects could be observed as being more frequent or severe than in clinical studies or earlier post-marketing periods, in which case:

- sales of ONPATTRO may be more modest than originally anticipated;
- regulatory approvals for ONPATTRO may be restricted or withdrawn;

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we may decide, or be required, to send product warning letters or field alerts to physicians, pharmacists and hospitals;

• additional nonclinical or clinical studies, changes in labeling, adoption of a REMS, or changes to manufacturing processes, specifications and/or facilities may be required; and

• government investigations or lawsuits, including class action suits, may be brought against us.

Any of the above occurrences could reduce or prevent sales of ONPATTRO, increase our expenses and impair our ability to successfully commercialize ONPATTRO.

The CMO and manufacturing facilities we use to make ONPATTRO and certain of our current product candidates, including our Cambridge facility, our future Norton facility, and Agilent and other CMOs, will also be subject to periodic review and inspection by the FDA and other regulatory agencies. For example, Agilent and our Cambridge-based facility were subject to regulatory inspection by the FDA, the EMA and potentially other regulatory authorities in connection with the review of our NDA and MAA for

ONPATTRO, and may be subject to similar inspection in connection with any subsequent applications for regulatory approval of ONPATTRO filed in other territories. The discovery of any new or previously unknown problems with our facilities or our CMOs, or our or their manufacturing processes or facilities, may result in restrictions on the drug or CMO or facility, including delay in approval or, in the future, withdrawal of the drug from the market. We have developed cGMP capabilities and processes for the manufacture of patisiran formulated bulk drug product for commercial use. In addition, in April 2016, we completed our purchase of a parcel of land in Norton, Massachusetts, where we are constructing a cGMP manufacturing facility for drug substance 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 CMOs entails risks to which we would not be subject if we manufactured products ourselves, including reliance on the CMO for regulatory compliance.

If we or our collaborators, CMOs or service providers fail to comply with applicable continuing regulatory requirements in the U.S. 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 the market perception of such prices and any price increase that we may implement in the future; 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, ONPATTRO utilizes an intravenous mode of administration with pre-medication that physicians and/or patients may not readily adopt, or which may not compete with other available options, including inotersen, marketed by Akcea, which is administered subcutaneously, or tafamidis, marketed in certain countries outside of the U.S. by Pfizer and reportedly available within the U.S. as part of an early access program, which is in pill form. 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 for ONPATTRO, or any future products at the time we commence commercialization, may be materially different from what we expect, including as a result of the indication approved by regulatory authorities, 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. For example, the indication approved by the FDA for ONPATTRO is for the treatment of the polyneuropathy of hATTR amyloidosis and not for the treatment of cardiomyopathy or other manifestations of the disease. In addition, the U.S. label does not include data from the exploratory cardiac endpoints included in our APOLLO Phase 3 study. This could have an adverse impact on the market opportunity for ONPATTRO in the U.S.

We may incur significant liability if enforcement authorities allege or determine that we are engaging in commercial activities or promoting ONPATTRO in a way that violates applicable regulations.

Physicians have the discretion to prescribe drug products for uses that are not described in the product's labeling and that differ from those approved by the FDA or other applicable regulatory agencies. Off-label uses are common across medical specialties. Although the FDA and other regulatory agencies do not regulate a physician's choice of treatments, the FDA and other regulatory agencies regulate a manufacturer's communications regarding off-label use and prohibit off-label promotion, as well as the dissemination of false or misleading labeling or promotional materials. Manufacturers may not promote drugs for off-label uses. Accordingly, we may not promote ONPATTRO in the U.S. for use in any indications other than the treatment of the polyneuropathy of hATTR amyloidosis in adults. The FDA and other regulatory and enforcement authorities actively enforce laws and regulations prohibiting promotion of off-label uses and the promotion of products for which marketing approval has not been obtained. A company that is found to have improperly promoted off-label uses may be subject to significant liability, which may include civil and administrative remedies as well as criminal sanctions.

Notwithstanding regulations related to product promotion, the FDA and other regulatory authorities allow companies to engage in truthful, non-misleading and non-promotional scientific exchange concerning their products. We intend to engage in medical education activities and communicate with healthcare providers in compliance with all applicable laws and regulatory guidance.

In addition, we offer patient support services to assist patients receiving treatment with ONPATTRO. Manufacturers have increasingly become the focus of government investigation of patient support programs based on allegations that through such services illegal inducements are provided to physicians and/or patients, leading to improper utilization of government resources through Medicare, Medicaid and other government programs. Companies that are found to have violated laws such as the federal Anti-Kickback Statute and/or FCA face significant liability, including civil and administrative penalties, criminal sanctions, and potential exclusion from participation in government programs. We have designed our programs in a manner that we believe complies with all applicable laws and regulations and have implemented a robust compliance program to support compliance with such laws.

If we or our collaborators, CMOs or service providers fail to comply with healthcare laws and regulations, or legal obligations related to privacy, data protection and information security, 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, in addition to legal obligations related to privacy, data protection and information security. These laws and regulations include:

•The U.S. federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully 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, including the FCA, 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, making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government, or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government. Manufacturers can be held liable under the FCA even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims. The FCA also permits a private individual acting as a "whistleblower" to bring actions on behalf of the federal government alleging violations of the FCA and to share in any monetary

recovery.

•The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters. Similar to the federal Anti-Kickback Statute, a person or entity can be found guilty of violating HIPAA without actual knowledge of the statute or specific intent to violate it. •HIPAA as amended by the 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.

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The U.S. federal Open Payments requirements were implemented by CMS, pursuant to 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 must 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 as well as ownership and investment interests held by physicians and their immediate family members.

Federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

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.

European Privacy Laws including Regulation 2016/679, known as the General Data Protection Regulation, or the GDPR, and the e-Privacy Directive (2002/58/EC), and the national laws implementing each of them, as well as the privacy laws of Japan and other territories. Failure to comply with our obligations under the privacy regime could expose us to significant fines and/or adverse publicity, which could have material adverse effects on our reputation and business.

Some state laws also require pharmaceutical manufacturers to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, in addition to requiring manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures and pricing information. State and foreign laws also govern the privacy and security of health information, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

In the EU, the GDPR replaced the EU Data Protection Directive on May 25, 2018. The GDPR introduced new data protection requirements in the EU, as well as potential fines for noncompliance of up to the greater of €20,000,000 or four percent of total annual global revenue. The regulation imposes numerous new requirements for the collection, use and disclosure of personal information, including: more stringent requirements relating to data subject consent; what information must be shared with data subjects regarding how their personal information is used; the obligation to notify regulators and affected individuals of personal data breaches; extensive new internal privacy governance obligations; and obligations to honor expanded rights of individuals in relation to their personal information (e.g., the right to access, correct and delete their data). In addition, the GDPR maintains the EU Data Protection Directive's restrictions on cross-border data transfer. The GDPR increases the responsibility and liability of pharmaceutical companies in relation to processing personal data, and companies may be required to put in place additional mechanisms to ensure compliance with the new EU data protection rules. Further, Brexit has created uncertainty with regard to the status of the UK as an "adequate country" for the purposes of data transfers outside the EEA. In particular, it is unclear how data transfers to and from the UK will be regulated. These changes may require us to find alternative bases for the compliant transfer of personal data from the UK to the U.S., and we are monitoring developments in this area.

If our operations are found to be in violation of any of the aforementioned 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. We are continuing to establish our global compliance infrastructure following the launch of ONPATPRO in August 2018 in the U.S. and in October

2018 in the EU and as we prepare for the launch in additional countries, including Japan, Switzerland and Canada, assuming regulatory approvals. 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, CMOs 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 ONPATTRO, or any other future 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, CMOs 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 we market and sell ONPATTRO in the U.S. and EU and as several of our other programs move through 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 such programs for a number of years. We might obtain regulatory approval for a product, including ONPATTRO, 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 ONPATTRO or any future 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. ONPATTRO and other products for which we are able to obtain marketing approval may not be considered cost-effective, and the amount reimbursed may be insufficient to allow us to sell ONPATTRO or any future products on a competitive basis. Increasingly, the third-party payors who pay for or 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. In the U.S., we are negotiating VBAs for ONPATTRO with certain private health insurers. The goal of these agreements is to ensure that we are paid based on the ability of ONPATTRO to deliver results in the real world setting comparable to those demonstrated in clinical trials. Partnering with payors on these agreements is intended to provide more certainty to them for their investment,

and help accelerate coverage decisions for patients. The agreements are structured to link ONPATTRO's performance in real-world use to financial terms. If the price we are able to charge for ONPATTRO or any other 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. In addition, we have stated publicly that we intend to grow through continued scientific innovation rather than arbitrary price increases. Specifically, we have stated that we will not raise the price of any product for which we receive marketing approval over the rate of inflation, as determined by the consumer price index for urban consumers (approximately 2.2 percent currently) absent a significant value driver. Our patient access philosophy could also negatively impact the revenues we are able to generate from the sale of one or more of our products in the future.

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, including ONPATTRO. 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 U.S. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement rates. Our inability to promptly obtain coverage or adequate reimbursement rates from both government-funded and private payors for ONPATTRO or other 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. Specifically, there have been several recent U.S. Congressional inquiries and proposed federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs.

A number of other legislative and regulatory changes in the healthcare system in the U.S. and other major healthcare markets have been proposed or enacted in recent months and 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 U.S. in 2010. These developments could, directly or indirectly, affect our ability to sell ONPATTRO or future products, if approved, at a favorable price.

In particular, in March 2010, the ACA 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. Among the provisions affecting pharmaceutical companies are 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.
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Pharmaceutical companies are required to offer discounts on brand-name drugs to patients who fall within the Medicare Part D coverage gap, commonly referred to as the “donut hole.”

Pharmaceutical companies are required to pay an annual non-tax deductible fee to the federal government based on each company’s market share of prior year total sales of branded products to certain federal healthcare programs, such as Medicare, Medicaid, Department of Veterans Affairs and Department of Defense. Since we expect our branded pharmaceutical sales to constitute a small portion of the total federal 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.

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- The law creates a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected.
- The law expands eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133 percent of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability.
- The law expands the entities eligible for discounts under the Public Health Service Act pharmaceutical pricing program.
  - The law expands healthcare fraud and abuse laws, including the civil FCA and the federal Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance.
- The law establishes new requirements to report financial arrangements with physicians and teaching hospitals and to annually report drug samples that manufacturers and distributors provide to physicians.
- The law establishes a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.
- The law established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery methods.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of two percent per fiscal year, which went into effect in April 2013 and will remain in effect through 2027 unless additional Congressional action is taken. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for ONPATTRO or any of our product candidates for which we may obtain regulatory approval or the frequency with which ONPATTRO or any future product is prescribed or used.

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 U.S.

Members of Congress and the Trump administration have expressed an intent to pass legislation or adopt executive orders to fundamentally change or repeal parts of the ACA. While Congress has not passed repeal legislation to date, the TCJA includes a provision repealing the individual insurance coverage mandate included in ACA, effective January 1, 2019. Further, on January 20, 2017, an Executive Order was signed directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On October 13, 2017, an Executive Order was signed terminating the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. Further, on June 14, 2018 the United States Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than \$12.0 billion in ACA risk corridor payments to third-party payors. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and our business, are not yet known. In addition, CMS has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small

group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. The BBA among other things, amends the ACA effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the “donut hole.” In July 2018, the CMS published a final rule permitting further collections and payments to and from certain ACA qualified health plans and health insurance issuers under the ACA risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. Moreover, CMS issued a final rule in 2018 that will give states greater flexibility, starting in 2020, in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas, or the Texas District Court Judge, ruled that the individual mandate is a critical and inseverable feature of the ACA, and therefore, because it was repealed as part of the TCJA, the remaining provisions of the ACA

are invalid as well. While the Texas District Court Judge issued an order staying the judgment pending appeal in December 2018, and both the Trump Administration and CMS have stated the ruling will have no immediate impact, it is unclear how this decision, subsequent appeals and other efforts to repeal and replace the ACA will impact the ACA and our business. Congress may consider other legislation to replace elements of the ACA. The implications of the ACA, its possible repeal, any legislation that may be proposed to replace the ACA, or the political uncertainty surrounding any repeal or replacement legislation for our business and financial condition, if any, are not yet clear.

The costs of prescription pharmaceuticals in the U.S. has also been the subject of considerable discussion in the U.S., and members of Congress and the Trump administration have stated that they will address such costs through new legislative and administrative measures. To date, there have been several U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, Congress and the Trump administration have each indicated that it will continue to pursue new legislative and/or administrative measures to control drug costs. The Trump administration released a “Blueprint,” or plan, to reduce the cost of drugs. The Trump administration’s Blueprint contains certain measures that the U.S. Department of Health and Human Services is already working to implement. For example, on October 25, 2018, CMS issued an Advanced Notice of Proposed Rulemaking, or ANPRM, indicating it is considering issuing a proposed rule in the spring of 2019 on a model called the International Pricing Index. This model would utilize a basket of other countries’ prices as a reference for the Medicare program to use in reimbursing for drugs covered under Part B. The ANPRM also included an updated version of the Competitive Acquisition Program, as an alternative to current “buy and bill” payment methods for Part B drugs. Such a proposed rule could limit our product pricing and have material adverse effects on our business.

Individual state legislatures have become increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing. Some of these measures include price or patient reimbursement constraints, discounts, restrictions on certain product access, marketing cost disclosure and transparency measures, and, in some cases, measures designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing.

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 U.S. to increase pressure on drug pricing. Such reforms could have an adverse effect on anticipated revenues from ONPATTRO or other 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.

Governments outside the U.S. may impose strict price controls, which may adversely affect our revenues, if any.

The pricing of prescription pharmaceuticals is also subject to governmental control outside the U.S. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of regulatory approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidates to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our ability to generate revenues and become profitable could be impaired.

In some countries, including Member States of the EU, the pricing of prescription drugs is subject to governmental control. Additional countries may adopt similar approaches to the pricing of prescription drugs. In such countries, pricing negotiations with governmental authorities can take considerable time after receipt of regulatory approval for a product. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after coverage and reimbursement have been obtained. Reference pricing used by various countries and parallel distribution, or arbitrage between low-priced and high-priced countries, can further reduce prices. In some countries, we may be required to conduct a clinical study or other studies that compare the cost-effectiveness of a product candidate to other available therapies in order to obtain or maintain reimbursement or pricing approval, which is time-consuming and costly. We cannot be sure that such prices and reimbursement will be acceptable to us or our strategic partners. Publication of discounts by third-party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If pricing is set at unsatisfactory levels or if reimbursement of our products is unavailable or limited in scope or amount, our revenues from sales by us or our strategic partners and the potential profitability of ONPATTRO or any future products in those countries would be negatively affected.

We are subject to governmental regulation and other legal obligations, particularly related to privacy, data protection and information security, and we are subject to consumer protection laws that regulate our marketing practices and prohibit unfair or deceptive acts or practices. Our actual or perceived failure to comply with such obligations could harm our business.

The GDPR imposes strict requirements on controllers and processors of personal data, including special protections for “special category data,” which includes health, biometric and genetic information of data subjects located in the EU. Further, GDPR provides a broad right for EU Member States to create supplemental national laws, such as laws relating to the processing of health, genetic and biometric data, which could further limit our ability to use and share such data or could cause our costs to increase, and harm our business and financial condition. GDPR grants individuals the opportunity to object to the processing of their personal information, allows them to request deletion of personal information in certain circumstances, and provides the individual with an express right to seek legal remedy in the event the individual believes his or her rights have been violated. Further, the GDPR imposes strict rules on the transfer of personal data out of the EU to the U.S. or other regions that have not been deemed to offer “adequate” privacy protections.

Failure to comply with the requirements of the GDPR and the related national data protection laws of the EU Member States, which may deviate slightly from the GDPR, may result in fines of up to four percent of total global annual revenue, or €20,000,000, whichever is greater, and in addition to such fines, we may be the subject of litigation and/or adverse publicity, which could have material adverse effect on our reputation and business. As a result of the implementation of the GDPR, we are required to put in place additional mechanisms to ensure compliance with the new data protection rules. For example, the GDPR requires us to make more detailed disclosures to data subjects, requires disclosure of the legal basis on which we can process personal data, may make it harder for us to obtain valid consent for processing, will require the appointment of a data protection officer where sensitive personal data (i.e., health data) is processed on a large scale, introduces mandatory data breach notification requirements throughout the EU, imposes additional obligations on us when we are contracting with service providers and requires us to adopt appropriate privacy governance including policies, procedures, training and data audit.

We are subject to the supervision of local data protection authorities in those jurisdictions where we are monitoring the behavior of individuals in the EU (i.e., undertaking clinical trials). We depend on a number of third parties in relation to the provision of our services, a number of which process personal data of EU individuals on our behalf. With each such provider we enter or intend to enter into contractual arrangements under which they are contractually obligated to only process personal data according to our instructions, and conduct or intend to conduct diligence to ensure that they have sufficient technical and organizational security measures in place.

We are also subject to evolving European privacy laws on electronic marketing and cookies. The EU is in the process of replacing the e-Privacy Directive (2002/58/EC) with a new set of rules taking the form of a regulation, which will be directly implemented in the laws of each European member state, without the need for further enactment. The draft ePrivacy Regulation imposes strict opt-in marketing rules with limited exceptions for business-to-business communications, alters rules on third-party cookies, web beacons and similar technology and significantly increases potential fines to the same levels as GDPR (i.e., the greater of €20,000,000 or four percent of total global annual revenue). While the e-Privacy Regulation was originally intended to be adopted on May 25, 2018 (alongside the GDPR), it is still going through the European legislative process and commentators now expect it to be adopted during the middle or second half of 2020.

There is significant uncertainty related to the manner in which data protection authorities will seek to enforce compliance with GDPR. Further, Brexit has created uncertainty with regard to the status of the UK as an ‘adequate country’ for the purposes of data transfers outside the EEA. In particular, it is unclear how data transfers to and from the UK will be regulated. Enforcement uncertainty and the costs associated with ensuring GDPR and e-Privacy

compliance may be onerous and may adversely affect our business, financial condition, results of operations and prospects.

Compliance with U.S. and international data protection laws and regulations could require us to take on more onerous obligations in our contracts, restrict our ability to collect, use and disclose data, or in some cases, impact our ability to operate in certain jurisdictions. Failure to comply with these laws and regulations could result in government enforcement actions (which could include civil, criminal and administrative penalties), private litigation, and/or adverse publicity and could negatively affect our operating results and business. Moreover, clinical trial subjects, employees and other individuals about whom we or our potential collaborators obtain personal information, as well as the providers who share this information with us, may limit our ability to collect, use and disclose the information. Claims that we have violated individuals' privacy rights, failed to comply with data protection laws, or breached our contractual obligations, even if we are not found liable, could be expensive and time-consuming to defend and could result in adverse publicity that could harm our business.

Our ability to obtain services, reimbursement or funding from the federal government may be impacted by possible reductions in federal spending and services, and any inability on our part to effectively adapt to such changes could substantially affect our financial position, results of operations and cash flows.

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 two 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. Due to legislation amending the statute, including the BBA, these reductions will stay in effect through 2027 unless additional Congressional action is taken. 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 the NIH 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 ONPATTRO and any other products we may develop.

In addition, in the case of any U.S. federal government shutdown, now or in the future, that continued for a prolonged period of time, FDA review and approval processes, and FDA interactions during clinical development, could be delayed. Resolving such delays could force us or our collaborators to incur significant costs, could limit our allowed activities or the allowed activities of our collaborators, could diminish any competitive advantages that we or our collaborators may attain or could adversely affect our business, financial condition, results of operations and prospects, the value of our common stock and our ability to bring new products to market as forecasted. Even without such delay, there is no guarantee we will receive approval for our product candidates on a timely basis, or at all.

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 conducted a comprehensive evaluation of available revusiran data. We reported the results of this evaluation in August 2017, however, our investigation did not result in a conclusive explanation regarding the cause of the mortality imbalance observed in the ENDEAVOUR Phase 3 study. In addition, in September 2017, we announced that we had temporarily suspended dosing in all ongoing fitusiran studies pending further review of a fatal thrombotic SAE and agreement with regulatory authorities on a risk mitigation strategy. 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 our clinical trials, including the revusiran and fitusiran studies, it is possible that product liability claims will be asserted against us relating to the worsening of a patient's condition, injury or death alleged to have been caused by one of our product candidates, including revusiran or fitusiran. Such claims might not be fully covered by product liability insurance. If we succeed in marketing products, including ONPATTRO, 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, including the marketing and sale of ONPATTRO. 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 U.S. 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 ONPATTRO or future 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, could reduce or eliminate royalty payments to us from third party licensors 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 U.S. 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 U.S. 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 U.S. 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.

Failure to obtain and maintain all available regulatory exclusivities, broad patent scope and to maximize patent term restoration or extension on patents covering our products may lead to loss of exclusivity and early generic entry resulting in a loss of market share and/or revenue.

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, Cancer Research Technology Limited, Ionis, 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 U.S. 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, re-examination 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.

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There are many issued and pending patents that claim aspects of oligonucleotide chemistry and modifications that we may need for our siRNA therapeutic candidates or marketed products, including ONPATTRO. 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. In addition, there may be issued and pending patent applications that may be asserted against us in a court proceeding or otherwise based upon the asserting party's belief that we may need such patents for our siRNA therapeutic candidates or marketed products, including ONPATTRO. Thus, it is possible that one or more organizations will hold patent rights to which we may need a license, or hold patent rights which could be asserted against us. If those organizations refuse to grant us a license to such patent rights on reasonable terms and/or a court rules that we need such patent rights that have been asserted against us and we are not able to obtain a license on reasonable terms, we may be unable to market products, including ONPATTRO, or perform research and development or other activities covered by such patents. For example, during 2017 and 2018, Silence filed claims in several jurisdictions, including the High Court of England and Wales, and named us and our wholly owned subsidiary Alnylam UK Ltd. as co-defendants. Silence alleged various claims, including that ONPATTRO infringed one or more Silence patents. There were also a number of related actions brought by us or Silence in connection with this intellectual property dispute. In December 2018, we entered into a Settlement and License Agreement with Silence, resolving all ongoing claims, administrative proceedings, and regulatory proceedings worldwide between us regarding, among other issues, patent infringement, patent invalidity and breach of contract. For a discussion of the Silence litigation proceedings, please read Note 9, Commitments and Contingencies – Litigation, to our consolidated financial statements included in Part I, Item I, "Financial Statements," of this annual report on Form 10-K.

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. For example, in October 2017 Silence sued us in the UK alleging that ONPATTRO and other investigational RNAi therapeutics we or MDCO are developing infringed one or more Silence patents. 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. We and Dicerna settled the ongoing litigation between us in April 2018 and in December 2018 we and Silence settled all ongoing litigation between us. 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 fourth quarter of 2012.

In protecting our intellectual patent rights through litigation or other means, a third party may claim that we have improperly asserted our rights against them. For example, in August 2017, Dicerna successfully added counterclaims against us in the above-referenced trade secret lawsuit alleging that our lawsuit represented abuse of process and claiming tortious interference with its business. In addition, in August 2017, Dicerna filed a lawsuit against us in the United States District Court of Massachusetts alleging attempted monopolization by us under the Sherman Antitrust Act. As noted above, in April 2018, we and Dicerna settled the ongoing litigation between us.

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 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 was 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, the court granted our motions for summary judgment, and dismissed Utah's state law damages claims as well. During the pendency of this litigation, as well as the Arbutus and Dicerna litigation described above, we incurred significant costs, and in each case, the litigation diverted the attention of our management and other resources that would otherwise have been engaged in other activities.

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, development and commercialization 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, commercializing and protecting our RNAi technology, as well as ONPATTRO and any other 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. Moreover, we could incur significant costs and/or disruption to our business and distraction of our management defending against any breach of such licenses alleged by the licensor. For example, in 2013, Arbutus 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. Arbutus did not appeal this ruling. In addition, in June 2018, Ionis sent us a notice claiming that it is owed payments under our second amended and restated strategic collaboration and license agreement as a result of the January 2018 amendment of our collaboration agreement with Sanofi Genzyme and the related Exclusive TTR License and AT3 License Terms. Ionis claims it is owed technology access fees based on rights granted and amounts paid to us in connection with the Sanofi Genzyme restructuring. In November 2018, we received notice that Ionis had filed a Demand for Arbitration with the Boston office of the American Arbitration Association against us, asserting, among other things, breach of contract. In December 2018, we filed our answer to Ionis's Demand for Arbitration. While we dispute that additional technology access fees are owed to Ionis, there can be no assurance that we will resolve this matter favorably or that it will not have a material adverse impact on our future results of operations.

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 ONPATTRO or 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 ONPATTRO or other 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. There are a number of drugs currently under development, which 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 developed ONPATTRO for the treatment of hATTR amyloidosis. In August 2018, the FDA approved ONPATTRO lipid complex injection for the treatment of the polyneuropathy of hATTR amyloidosis in adults, and the EC granted marketing authorisation for ONPATTRO for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy. We are aware of other approved products used to treat this disease, including tafamidis, marketed by Pfizer in Europe and certain countries outside the U.S., and inotersen, developed by Ionis and licensed to Akcea, which is now approved in the U.S., the EU and Canada, as well as product candidates in various stages of clinical development, including an additional investigational drug being developed by Ionis. In addition, in August 2018, Pfizer announced the primary results from a Phase 3 study of tafamidis in patients with TTR cardiomyopathy. In June 2017 and May 2018, respectively, the FDA granted Fast Track and Breakthrough Therapy designations for tafamidis for TTR amyloid cardiomyopathy and in March 2018, the Ministry of Labor Health and Welfare in Japan granted SAKIGAKE designation to tafamidis for this indication. In January 2019, Pfizer announced that the FDA had accepted two NDAs based on two forms of tafamidis. Finally, we are aware that Eidos Therapeutics, Inc. completed a Phase 2 clinical trial of AG10, a TTR stabilizer, in ATTR-CM and plans to initiate a Phase 3 clinical trial of AG10 in ATTR-PN patients in the first half of 2019. While we believe that ONPATTRO will have a competitive product profile, it is possible it will not compete favorably with these products and product candidates, or others, and, as a result, may not achieve commercial success. Moreover, positive data and/or the commercial success of competitive products could negatively impact our stock price.

If we continue to 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;

the price of our products relative to alternative approved therapies;  
reimbursement coverage; and  
patent position.

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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. In addition, our competitors may develop strategic alliances with or receive funding from larger pharmaceutical or biotechnology companies, providing them with an advantage over us. 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 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, but are not limited to, Takeda, Marina, Arrowhead, and its subsidiary, Calando, Quark, Silence, Arbutus, Sylentis, Dicerna, WAVE, Arcturus, and Genevant Sciences, launched by Arbutus and Roivant Sciences. In addition, we granted licenses or options for licenses to Ionis, 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, Takeda has obtained a non-exclusive license, and Arrowhead, as the assignee of Novartis Pharma AG, has obtained specific exclusive licenses for 30 gene targets, that include access 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. Akcea has received marketing approval for an antisense drug, inotersen that was developed by Ionis, in the U.S., the EU and Canada, for the treatment of hATTR amyloidosis. Several antisense drugs developed by Ionis have been approved and are currently marketed, and Ionis has multiple antisense product candidates in clinical trials. 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 sector in particular has 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.

Our stock price may fluctuate for many reasons, including as a result of public announcements regarding the progress of our development and commercialization efforts or the development and commercialization 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 and in September 2017, following our temporary suspension of dosing in our fitusiran program, our stock also declined, although to a lesser extent. 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.

For example, a class action complaint was filed on September 26, 2018 in the United States District Court for the Southern District of New York, entitled Caryl Hull Leavitt v. Alnylam Pharmaceuticals, Inc., et. al., Case No. 18-CV-8845. The complaint alleges that we and our Chief Executive Officer and our Chief Financial Officer violated certain federal securities laws, specifically under Sections 10(b) and 20(a) of the Exchange Act, and Rule 10b-5 promulgated thereunder. The plaintiff seeks unspecified damages on behalf of a purported class of purchasers of our common stock between February 15, 2018 and September 12, 2018. We believe that the allegations contained in the complaint are without merit and intend to defend the case vigorously. However, whether or not the plaintiff's claims are successful, this type of litigation is often expensive and diverts management's attention and resources, which could adversely affect the operation of our business. If we are ultimately required to pay significant defense costs, damages or settlement amounts, such payments could adversely affect our operations.

We may be the target of similar litigation in the future. Any future litigation could result in substantial costs and divert our management's attention and resources, which could cause serious harm to our business, operating results and financial condition. We maintain liability insurance; however, if any costs or expenses associated with this or any other litigation exceed our insurance coverage, we may be forced to bear some or all of these costs and expenses directly, which could be substantial.

Sales of 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.

As of December 31, 2018, Sanofi Genzyme held approximately ten 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 then current 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.

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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, UK. A description of certain of the facilities we lease as of January 31, 2019 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	January 2034	Two five-year terms
101 Main Street Cambridge, Massachusetts	Additional office space	72,000	June 2021 and March 2024	One five-year term on each lease
		295,000	January 2034	Two five-year terms



675 West Kendall Street Cambridge, Massachusetts	Future corporate headquarters and research facility*				
665 Concord Avenue  Cambridge, Massachusetts	cGMP manufacturing	15,000	August 2022	One five-year term	
Grafenauweg 4	International headquarters	14,500	March 2023	One five-year term	
6300 Zug Braywick Gate	Office space	21,500	May 2026	None	
Braywick Road, Maidenhead  Berkshire, United Kingdom					

\*We intend to move our corporate headquarters and research facility to this location in 2019. The lease term commenced on May 1, 2018 and monthly rent payments commenced on February 1, 2019, upon substantial completion of the building improvements, and will continue through January 2034.

In addition to the locations above, we also maintain small offices in multiple locations in and outside of the U.S. to support our operations and growth.

In April 2016, we completed the purchase of 12 acres of undeveloped land in Norton, Massachusetts. We are constructing a manufacturing facility at this site for drug substance 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 9, 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 MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND  
5. ISSUER PURCHASES OF EQUITY SECURITIES

Market Information

Our common stock trades on The Nasdaq Global Select Market under the symbol "ALNY."

Holders of record

At January 31, 2019, there were 31 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.

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, 2018. The information required by this item relating to our equity compensation plans is incorporated herein by reference to the information contained under the section captioned "Equity Compensation Plan Information" of the Proxy Statement.

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## Stock Performance Graph

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

The comparative stock performance graph below compares the five-year cumulative total stockholder return (assuming reinvestment of dividends, if any) from investing \$100 on December 31, 2013, to the close of the last trading day of 2018, in each of our common stock and the selected indices. The stock price performance reflected in the graph below is not necessarily indicative of future price performance.

## Comparison of Five-Year Cumulative Total Return

Among Alnylam Pharmaceuticals, Inc.,

Nasdaq Composite Total Return and Nasdaq Biotechnology Total Return

	12/31/2013	12/31/2014	12/31/2015	12/30/2016	12/29/2017	12/31/2018
Alnylam Pharmaceuticals, Inc.	\$ 100.00	\$ 150.86	\$ 146.41	\$ 58.23	\$ 197.59	\$ 113.39
Nasdaq Composite Total Return	\$ 100.00	\$ 114.75	\$ 122.74	\$ 133.62	\$ 173.22	\$ 168.30
Nasdaq Biotechnology Total Return	\$ 100.00	\$ 134.40	\$ 150.22	\$ 118.15	\$ 143.71	\$ 130.97

## ITEM 6. SELECTED CONSOLIDATED FINANCIAL DATA

The following selected consolidated financial data for each of the five years in the period ended December 31, 2018 are derived from our audited consolidated financial statements. The selected consolidated financial data set forth below should be read in conjunction with “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and the financial statements, and the related Notes, included elsewhere in this annual report on Form 10-K. Historical results are not necessarily indicative of future results.

## Selected Consolidated Financial Data

(In thousands, except per share data)

	Year Ended December 31,				
	2018 (3)	2017	2016	2015	2014
<b>Statements of Comprehensive Loss Data:</b>					
Revenues	\$74,908	\$89,912	\$47,159	\$41,097	\$50,561
Costs and expenses (1) (2)	889,581	590,000	471,746	337,105	455,541
Loss from operations	(814,673)	(500,088)	(424,587)	(296,008)	(404,980)
Net loss	\$(761,497)	\$(490,874)	\$(410,108)	\$(290,073)	\$(360,395)
Net loss per common share — basic and diluted	\$(7.57 )	\$(5.42 )	\$(4.79 )	\$(3.45 )	\$(4.85 )
Weighted-average common shares outstanding — basic					
and diluted	100,590	90,554	85,596	83,992	74,278

(1) Stock-based compensation expenses included in operating costs and expenses

	\$157,752	\$92,819	\$75,528	\$45,783	\$33,061
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(2) Operating costs and expenses for the year ended December 31, 2014 included a \$220.8 million charge to in process research and development expenses in connection with our acquisition of the Sirna RNAi assets from Merck.

(3) On January 1, 2018, we adopted the new revenue standard by applying the modified retrospective method to all contracts that were not completed as of January 1, 2018. Please read Note 2 to our consolidated financial statements included in Part II, Item 8, “Financial Statements and Supplementary Data,” of this annual report on Form 10-K for further discussion of our adoption of the new revenue standard.

	December 31,				
	2018	2017	2016	2015	2014
<b>Balance Sheet Data:</b>					
Cash, cash equivalents and marketable debt securities	\$1,082,949	\$1,704,537	\$942,601	\$1,280,951	\$881,929
Restricted investments	44,825	30,000	150,000	—	—
Working capital	1,021,202	1,620,489	540,178	1,043,289	651,033
Total assets	1,574,802	1,994,730	1,262,810	1,386,510	1,079,595
Long-term debt	30,000	30,000	150,000	—	—

Total stockholders' equity	1,301,965	1,766,431	920,221	1,264,714	936,267
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## ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

### Overview

We are a global commercial-stage biopharmaceutical company developing novel therapeutics based on RNAi. RNAi is a naturally occurring biological pathway within cells for sequence-specific silencing and regulation of gene expression. By harnessing the RNAi pathway, we have developed a new class of innovative medicines, known as RNAi therapeutics. RNAi therapeutics are comprised of siRNA, and function upstream of conventional medicines by potently silencing mRNA that encode for disease-causing proteins, thus preventing them from being made. We believe this is a revolutionary approach with the potential to transform the care of patients with genetic and other diseases. Our efforts to advance this revolutionary approach culminated with the approval in 2018 of the first ever RNAi therapeutic, ONPATTRO, for the treatment of the polyneuropathy of hATTR amyloidosis in adults in the U.S. and for the treatment of hATTR amyloidosis in adults with Stage 1 or Stage 2 polyneuropathy in the EU.

Our research and development strategy is to target genetically validated liver-expressed genes that have been implicated in the cause or pathway of human disease. We utilize a LNP or GalNAc conjugate approach to enable hepatic delivery of siRNAs. For delivery to the CNS and eye (ocular delivery), we intend to utilize an alternative conjugate approach. Our focus is on clinical indications where there is a high unmet need, 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.

We are committed to the advancement of our Alnylam 2020 strategy of building a multi-product, commercial biopharmaceutical company with a sustainable pipeline of RNAi therapeutics to address the needs of patients who have limited or inadequate treatment options. Specifically, our broad pipeline of investigational RNAi therapeutics is focused in four STArS: Genetic Medicines; Cardio-Metabolic Diseases; Hepatic Infectious Diseases; and CNS/Ocular Diseases. In August 2018, we received regulatory approval for ONPATTRO from the FDA for the treatment of the polyneuropathy of hATTR amyloidosis in adults. Also, in August 2018, the EC granted marketing authorisation for ONPATTRO for the treatment of hATTR amyloidosis in adults with Stage 1 or Stage 2 polyneuropathy. We began selling ONPATTRO in the U.S. in August 2018 and in Germany in October 2018, and are now marketing ONPATTRO in several additional countries in Europe. During 2018, we also submitted regulatory applications for the approval of ONPATTRO in Japan, Canada and Switzerland. Regulatory filings in additional markets in Europe and elsewhere are planned throughout 2019.

In January 2019, we sold 5,000,000 shares of our common stock through an underwritten public offering at a price to the public of \$77.50 per share. As a result of the offering, we received aggregate net proceeds of approximately \$382 million.

We have incurred significant losses since we commenced operations in 2002 and expect such losses to continue for the foreseeable future. At December 31, 2018, we had an accumulated deficit of \$2.84 billion. Historically, we have generated losses principally from costs associated with research and development activities, acquiring, filing and expanding intellectual property rights, and selling, general and administrative costs. As a result of planned expenditures for research and development activities relating to our research platform, our drug development programs, including clinical trial and manufacturing costs, the establishment of late stage clinical and commercial capabilities, including global operations, continued management and growth of our patent portfolio, collaborations and general corporate activities, we expect to incur additional operating losses for the foreseeable future. We also anticipate that our operating results will fluctuate for the foreseeable future. Therefore, period-to-period comparisons should not be relied upon as predictive of the results in future periods.

We currently have programs focused on a number of therapeutic areas and, as noted above, in August 2018, received regulatory approval from the FDA and EC for our first product, ONPATTRO. As a result of the regulatory approval of ONPATTRO, we began to generate net revenues from product sales during the third quarter of 2018. However, our ongoing development efforts may not be successful and we may not be able to commence sales of any other products and/or successfully market and sell ONPATTRO or any other approved products in the future. A substantial portion of our total revenues in recent years has been derived from collaboration revenues from strategic alliances with Sanofi Genzyme and MDCO. In addition to revenues from the commercial sale of ONPATTRO and potentially from sales of future products, we expect our sources of potential funding for the next several years to continue to be derived in part from existing and new strategic alliances, which may include license and other fees, funded research and development, milestone payments and royalties on product sales by our licensors, and proceeds from the sale of equity or debt.

#### Research and Development

Since our inception, we have focused on drug discovery and development programs. Research and development expenses represent a substantial percentage of our total operating expenses, as reflected by our broad pipeline of clinical development programs, which includes multiple programs in late-stage development.



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

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

### Strategic Alliances

Our business strategy is to develop and commercialize a broad pipeline of RNAi therapeutic products directed towards our four STArS. As part of this strategy, we have entered into, and expect to enter into additional, collaboration and licensing agreements as a means of obtaining resources, capabilities and funding to advance our investigational RNAi therapeutic programs.

Our collaboration strategy is to form alliances that create significant value for ourselves and our collaborators in the advancement of RNAi therapeutics as a new class of innovative medicines. Specifically, with respect to our Genetic Medicine pipeline, we formed a broad strategic alliance with Sanofi Genzyme in 2014 pursuant to which we retain development and commercial rights for our current and future Genetic Medicine products in the U.S., 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 Sanofi Genzyme Territory, subject to certain broader rights. In January 2018, we and Sanofi Genzyme amended our 2014 Sanofi Genzyme collaboration and entered into the Exclusive TTR License with respect to all TTR products, including ONPATPRO, vutrisiran and any back-up products, and the AT3 License Terms with respect to fitusiran and any back-up products. The 2018 amendment, together with the Exclusive TTR License and the AT3 License Terms, revised the terms and conditions of the 2014 collaboration to (i) provide us with the exclusive right to pursue the further global development and commercialization of all TTR products, including ONPATPRO, vutrisiran and any back-up products, (ii) provide Sanofi Genzyme the exclusive right to pursue the further global development and commercialization of fitusiran and any back-up products and (iii) terminate the previous co-development and co-commercialization rights related to revusiran, vutrisiran and fitusiran under the 2014 Sanofi Genzyme collaboration. Sanofi Genzyme continues to have the right to opt into our other rare genetic disease programs for development and commercialization in territories outside of the Alnylam Territory as contemplated in the 2014 Sanofi Genzyme collaboration, as well as one right to a global license.

With respect to our Cardio-Metabolic pipeline, we intend to seek future strategic alliances for these programs, under which we may retain certain product development and commercialization rights, or we may structure as global alliances, as we did in our collaboration with MDCO to advance inclisiran. In March 2018, we entered into a discovery collaboration with Regeneron to identify RNAi therapeutics for NASH and potentially other related diseases, and in November 2018, we and Regeneron entered into a separate, fifty-fifty collaboration to further research, co-develop and commercialize any therapeutic product candidates that emerge from these discovery efforts.

With respect to our Hepatic Infectious Disease pipeline, in October 2017, we announced an exclusive licensing agreement with Vir for the development and commercialization of RNAi therapeutics for infectious diseases, including chronic HBV infection.

We may also seek future collaborations, including potentially global licenses, for one or more programs in our early stage CNS/ocular pipeline.

#### Critical Accounting Policies and Estimates

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

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## Revenue Recognition

We began to record revenues from product sales in the third quarter of 2018 subsequent to the approval of ONPATTRO by the FDA in August 2018. Prior to the third quarter of 2018, all of our revenues were derived from collaboration agreements that we have entered into with leading pharmaceutical and life sciences companies, including Sanofi Genzyme and MDCO. The terms of our collaboration agreements may include consideration such as non-refundable license fees, funding of research and development services, payments due upon the achievement of clinical and pre-clinical performance-based development milestones, regulatory milestones, manufacturing services, sales-based milestones and royalties on product sales.

On January 1, 2018, we adopted the new revenue standard, discussed below under the heading “Recent Accounting Pronouncements,” which amended revenue recognition principles and provides a single, comprehensive set of criteria for revenue recognition within and across all industries. Our adoption of the new revenue standard had a material impact on our consolidated financial statements, as discussed below under the heading “Recent Accounting Pronouncements.” This new revenue standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments. The new revenue standard provides a five-step framework whereby revenue is recognized when control of promised goods or services is transferred to a customer at an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. To determine revenue recognition for arrangements that we determine are within the scope of the new revenue standard, we perform the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) we satisfy a performance obligation. We only apply the five-step model to contracts when collectability of the consideration to which we are entitled in exchange for the goods or services we transfer to the customer is determined to be probable. At contract inception, once the contract is determined to be within the scope of the new revenue standard, we assess whether the goods or services promised within each contract are distinct and, therefore, represent a separate performance obligation. Goods and services that are determined not to be distinct are combined with other promised goods and services until a distinct bundle is identified. We then allocate the transaction price (the amount of consideration we expect to be entitled to from a customer in exchange for the promised goods or services) to each performance obligation and recognize the associated revenue when (or as) each performance obligation is satisfied. Our estimate of the transaction price for each contract includes all variable consideration to which we expect to be entitled.

Amounts are recorded as accounts receivable when our right to consideration is unconditional. We do not assess whether a contract has a significant financing component if the expectation at contract inception is that the period between payment by the customer and the transfer of the promised goods or services to the customer will be one year or less. We expense incremental costs of obtaining a contract as and when incurred if the expected amortization period of the asset that we would have recognized is one year or less or the amount is immaterial. At December 31, 2018, we had not capitalized any costs to obtain any of our contracts.

During 2018, all of our net revenues from collaborators were attributed to the U.S. and the majority of our net product revenues were attributed to the U.S. During 2017 and 2016, all of our revenues were attributed to the U.S. and consisted solely of net revenues from collaborators.

## Product revenues, net

In the third quarter of 2018, following FDA approval in August 2018, we began to ship ONPATTRO in the U.S. to specialty pharmacies, or SPs, and a specialty distributor, or SD, referred to as our customers. Our U.S. customers subsequently resell ONPATTRO to health care providers. We also received approval from the EC in August 2018 and

launched ONPATTRO in several countries in Europe during the fourth quarter of 2018, where we primarily sell to government-owned and supported customers, including hospitals. We recognize product revenues, net of variable consideration related to certain allowances and accruals, in our consolidated financial statements at the time of sale. In the event the variable consideration is constrained, we include an amount to the extent it is probable that a significant reversal in the amount of cumulative revenue recognized will not occur in a future reporting period. We use the expected value method to estimate variable consideration related to ONPATTRO sales. We do not have any material constraints on our variable consideration included within the transaction price of our ONPATTRO revenue arrangements. Each unit of ONPATTRO that is ordered by our customers represents a separate performance obligation that is completed when control of the product is transferred to our customer, which occurs upon delivery of the product to the customer. We record revenues, net of variable consideration and any applicable constraint, at that point in time. We record shipping and handling costs within cost of goods sold on our consolidated statements of comprehensive loss. We classify payments to distributors and other customers in the distribution channel for services that have a separate benefit and fair value as selling, general and administrative expenses on our consolidated statements of comprehensive loss. We have elected to exclude taxes collected from our customers and remitted to governmental authorities from the measurement of the transaction price. We periodically evaluate the creditworthiness of our customers.

The following are the components of variable consideration related to product revenues. We record reserves, based on contractual terms, for these components related to product sold during the reporting period, as well as our estimate of product that remains in the distribution channel inventory at the end of the reporting period that we expect will be sold to qualified healthcare providers. On a quarterly basis, we update our estimates and record any needed adjustments in the period we identify the adjustments.

**Chargebacks:** We estimate obligations resulting from contractual commitments with the government and other entities to sell products to qualified healthcare providers at prices lower than the list prices charged to the SD who purchases ONPATTRO from us. The SD charges us for the difference between what the SD pays to us for the product and the selling price to the qualified healthcare providers.

**Rebates:** We are subject to discount obligations under government programs, including Medicaid in the U.S. and similar programs in certain countries in Europe. We are also subject to potential rebates in connection with our value-based agreements with certain commercial payors. We record reserves for rebates in the same period the related product revenue is recognized, resulting in a reduction of ONPATTRO product revenues and a current liability that is included in accrued expenses on our consolidated balance sheet. Our estimate for rebates is based on statutory discount rates and expected utilization.

**Trade discounts and allowances:** We provide customary invoice discounts on ONPATTRO sales to our customers for prompt payment and we pay fees for distribution services, such as fees for certain data that customers provide to us. We estimate our customers will earn these discounts and fees, and deduct these discounts and fees in full from gross ONPATTRO revenues and accounts receivable at the time we recognize the related revenues.

**Product returns:** ONPATTRO may be returned if it is damaged, defective or expired, with “expired” defined as having three months or less to expiry or within three months past expiry. We estimate the amount of product that will be returned using a probability-weighted estimate, initially calculated based on a portfolio of data from similar products and industry experience for SP products. Based on the distribution model for ONPATTRO, contractual inventory limits with our customers, the price of ONPATTRO and limited contractual return rights, we believe there will be minimal ONPATTRO returns. We have recorded an initial refund liability for our estimate of ONPATTRO returns related to sales during the year ended December 31, 2018. We will update our estimated refund liability, on at least a quarterly basis, based on actual shipments of ONPATTRO subject to contractual return rights, changes in expectations about the amount of estimated refunds or actual returns as data is known.

**Other incentives:** Other incentives include co-payment assistance we provide to patients with commercial insurance that have coverage and reside in states that allow co-payment assistance. We estimate the average co-payment assistance amounts for ONPATTRO based on expected customer demographics and record any such amounts within accrued expenses on our consolidated balance sheet.

During 2018, we recorded product revenues, net, of \$12.5 million, which consist of commercial sales of ONPATTRO in the U.S. and several countries in Europe.

#### Revenues from Collaborators

We recognize the transaction price allocated to upfront license payments as revenue upon delivery of the license to the customer and resulting ability of the customer to use and benefit from the license, if the license is determined to be distinct from the other performance obligations identified in the contract. If the license is considered to not be distinct from other performance obligations, we utilize judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied (i) at a point in time, but only for licenses determined to be distinct from other performance obligations in the contract, or (ii) over time; and, if over time, the

appropriate method of measuring progress for purposes of recognizing revenue from license payments. We evaluate the measure of progress each reporting period and, if necessary, adjust the measure of performance and related revenue recognition.

Many of our collaboration agreements entitle us to additional payments upon the achievement of performance-based milestones. These milestones are generally categorized into three types: development milestones, which are generally based on the advancement of our pipeline and initiation of clinical trials; regulatory milestones, which are generally based on the submission, filing or approval of regulatory applications such as an NDA in the U.S.; and sales-based milestones, which are generally based on meeting specific thresholds of sales in certain geographic areas. For each collaboration that includes development milestone payments, we evaluate whether it is probable that the consideration associated with each milestone will not be subject to a significant reversal in the cumulative amount of revenue recognized. Amounts that meet this threshold are included in the transaction price using the most likely amount method, whereas amounts that do not meet this threshold are considered constrained and excluded from the transaction price until they meet this threshold. Milestones tied to regulatory approval, and therefore not within our control, are considered constrained until such approval is received. Upfront and ongoing development milestones per our collaboration agreements are not subject to

refund if the development activities are not successful. At the end of each subsequent reporting period, we re-evaluate the probability of a significant reversal of the cumulative revenue recognized for our milestones, and, if necessary, adjust our estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues from collaborators and loss in the period of adjustment. We exclude sales-based royalties and milestone payments from the transaction price until the sale occurs (or, if later, the underlying performance obligation to which some or all of the royalty has been allocated has been satisfied, or partially satisfied), because the license to our intellectual property is deemed to be the predominant item to which the royalties relate as it is the primary driver of value. Currently, we have not recognized any royalty revenue resulting from any of our agreements.

The new revenue standard, which was adopted in January 2018, requires us to allocate the arrangement consideration on a relative standalone selling price basis for each performance obligation after determining the transaction price of the contract and identifying the performance obligations to which that amount should be allocated. The relative standalone selling price is defined in the new revenue standard as the price at which an entity would sell a promised good or service separately to a customer. If other observable transactions in which we have sold the same performance obligation separately are not available, we are required to estimate the standalone selling price of each performance obligation. Key assumptions to determine the standalone selling price may include forecasted revenues, development timelines, reimbursement rates for personnel costs, discount rates and probabilities of technical and regulatory success.

Whenever we determine that a contract should be accounted for as a combined performance obligation over time, we determine the period over which the performance obligations will be performed and revenue will be recognized. Revenue is recognized using a cost-to-cost input model. Direct labor hours or full-time equivalents are typically used as the measure of performance. Significant management judgment is required in determining the level of effort required under an arrangement and the period over which we are expected to complete our performance obligations under an arrangement.

We evaluate our collaborative agreements for proper classification in our consolidated statements of comprehensive loss based on the nature of the underlying activity. Transactions between collaborators recorded in our consolidated statements of comprehensive loss are recorded on either a gross or net basis, depending on the characteristics of the collaborative relationship. We generally reflect amounts due under our collaborative agreements related to cost-sharing of development activities as revenue if we have a vendor-customer relationship with our collaborator. Costs incurred or shared with our collaboration partners that are deemed to be joint-risk sharing activities are recorded as an adjustment to the related operating expense captions.

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

Consideration that does not meet the requirements to satisfy the above revenue recognition criteria is recorded as deferred revenue in the accompanying consolidated balance sheets. Although we follow detailed guidelines in measuring revenue, certain judgments affect the application of our revenue policy. For example, in connection with our existing collaboration agreements, we have recorded on our consolidated balance sheets short-term and long-term

deferred revenue based on our best estimate of when such revenue will be recognized. Short-term deferred revenue consists of amounts that are expected to be recognized as revenue in the next 12 months. Amounts that we expect will not be recognized within the next 12 months are classified as long-term deferred revenue. However, this estimate is based on our current operating plan and, if our operating plan should change in the future, we may recognize a different amount of deferred revenue over the next 12-month period.

The estimate of deferred revenue also reflects management's estimate of the periods of our involvement in certain of our collaborations. Our performance obligations under these collaborations consist of participation on steering committees and the performance of other research and development services. In certain instances, the timing of satisfying these obligations can be difficult to estimate. Accordingly, our estimates may change in the future. Such changes to estimates would result in a change in revenue recognition amounts. If these estimates and judgments change over the course of these agreements, it may affect the timing and amount of revenue that we recognize and record in future periods. At December 31, 2018, we had short-term and long-term deferred revenue of \$3.5 million and \$0.5 million, respectively, all of which was related to our collaboration with Vir.



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, referred to as the 2014 Sanofi Genzyme collaboration. The 2014 Sanofi Genzyme collaboration superseded and replaced the previous collaboration between us and Sanofi Genzyme entered into in October 2012 to develop and commercialize RNAi therapeutics targeting TTR for the treatment of hereditary ATTR amyloidosis, including patisiran and revusiran, in Japan and the Asia-Pacific region.

On January 6, 2018, we and Sanofi Genzyme entered into an amendment to our 2014 Sanofi Genzyme collaboration. In connection and simultaneously with entering into the amendment to the 2014 Sanofi Genzyme collaboration, we and Sanofi Genzyme also entered into the Exclusive TTR License and the AT3 License Terms. As a result, we have the exclusive right to pursue the further global development and commercialization of all TTR products, including ONPATTRO, vutrisiran and any back-up products, and Sanofi Genzyme has the exclusive right to pursue the further global development and commercialization of fitusiran and any back-up products.

The January 2018 transaction was subject to customary closing conditions and clearances, including clearance under the Hart-Scott-Rodino Antitrust Improvements Act, and closed during the first quarter of 2018.

Under the 2012 Sanofi Genzyme agreement, Sanofi Genzyme paid us an upfront cash payment of \$22.5 million. We were also entitled to receive certain milestone payments under the 2012 Sanofi Genzyme agreement. In the fourth quarter of 2013, we earned \$11.0 million in patisiran development milestones under the 2012 Sanofi Genzyme agreement.

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

In January 2014, we entered into the 2014 Sanofi Genzyme collaboration. As noted above, the 2014 Sanofi Genzyme collaboration superseded and replaced the 2012 Sanofi Genzyme agreement and was amended in January 2018, at which time we also entered into the Exclusive TTR License and the AT3 License Terms. Under the 2014 Sanofi Genzyme collaboration, we retain full product rights in the Alnylam Territory, while Sanofi Genzyme will obtain exclusive rights to develop and commercialize collaboration products in the Sanofi Genzyme Territory, together with worldwide rights for one product. Upon the effective date of the 2014 Sanofi Genzyme collaboration, Sanofi Genzyme expanded the scope of its regional license and collaboration for patisiran for the Sanofi Genzyme Territory. We and Sanofi Genzyme also expanded our existing collaboration on revusiran, to include a co-development/co-commercialize license and collaboration in the Alnylam Territory. In October 2016, we discontinued our revusiran clinical development program. In September 2015, Sanofi Genzyme elected to opt into our fitusiran clinical development program under the regional license terms and began funding the program under the regional license terms in January 2016. In November 2016, Sanofi Genzyme exercised its right to co-develop and co-commercialize fitusiran in the Alnylam Territory, while retaining its rights to exclusively develop and

commercialize the product in the Sanofi Genzyme Territory. Sanofi Genzyme shared in fifty percent of the global development costs for fitusiran in accordance with the co-development/co-commercialize license terms. In connection with the exercise of this right, Sanofi Genzyme paid us approximately \$6.0 million in January 2017 for its incremental share of co-development costs incurred from January 2016 through September 2016.

Sanofi Genzyme's rights with respect to patisiran and fitusiran were modified in connection with the 2018 amendment, the Exclusive TTR License and the AT3 License Terms. Sanofi Genzyme continues to have the right to opt into our future rare genetic disease programs for development and commercialization in the Sanofi Genzyme Territory as contemplated in the 2014 Sanofi Genzyme collaboration, as well as one right to a global license. In connection with the 2018 amendment, the Exclusive TTR License and the AT3 License Terms, we and Sanofi Genzyme terminated the co-development and co-commercialization rights related to revusiran, vutrisiran and fitusiran under the original 2014 Sanofi Genzyme collaboration. No future rights will be granted to Sanofi Genzyme for co-development and co-commercialization under the 2014 Sanofi Genzyme collaboration, as amended. Please read Note 4 to our consolidated financial statements included in Part II, Item 8, "Financial Statements and Supplementary Data," of this annual report on Form 10-K for our discussion of the terms of the Exclusive TTR License and the AT3 License Terms.

Sanofi Genzyme will be required to make payments totaling up to \$75.0 million per regional product, consisting of up to \$55.0 million in development milestones and \$20.0 million in commercial milestones. Sanofi Genzyme will also be required to pay tiered double-digit royalties up to twenty percent for each regional product based on annual net sales, if any, of such regional product by

Sanofi Genzyme, its affiliates and sublicensees. In consideration for the rights granted to Sanofi Genzyme under the co-development/co-commercialize license terms, Sanofi Genzyme was required to make certain milestone payments for fitusiran, and, prior to the discontinuation of our revusiran clinical development program, was required to make certain milestone payments for revusiran. In December 2014, we earned a development milestone payment of \$25.0 million based upon the initiation of the first global Phase 3 clinical trial for revusiran. Finally, with respect to its one global product right, Sanofi Genzyme will be required to make payments totaling up to \$200.0 million for such global product, including up to \$100.0 million in development milestones and \$100.0 million in commercial milestones. Sanofi Genzyme will also be required to pay tiered double-digit royalties up to twenty percent for such global product based on annual net sales, if any, of such global product by Sanofi Genzyme, its affiliates and sublicensees.

Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any additional milestone payments or any royalty payments from Sanofi Genzyme under the 2014 Sanofi Genzyme collaboration, as amended, or any royalty payments under the AT3 License Terms.

As noted above, the Sanofi Genzyme collaboration originally entered into in 2012 was materially modified during its term when the agreement was amended in 2014, prior to our adoption of the new revenue standard on January 1, 2018. In accordance with the new revenue standard, we evaluated the Sanofi Genzyme collaboration with the aggregate effect of all modifications when identifying performance obligations, determining the transaction price and allocating the transaction price. We determined that certain promises included in these agreements are within the scope of the new revenue standard since Sanofi Genzyme is a customer with respect to the license of the rights to its territories. We also determined, however, that certain aspects of these agreements are within the scope of the collaboration accounting guidance with respect to co-commercialization activities as these activities are joint risk-sharing and are not reflective of a vendor-customer relationship. We apply the new revenue standard to all promises associated with the transfer of goods and services to a customer.

We concluded that Sanofi Genzyme meets the definition of a customer as we were delivering intellectual property and know-how rights as well as research and development activities for the TTR programs and fitusiran programs in support of territories in which we are not jointly sharing the risks and rewards. We concluded that the accounting for the original 2014 Sanofi Genzyme collaboration, and the collaboration, as amended, should be assessed as separate contracts for (i) the patisiran and revusiran (TTR) programs, upon the initiation of the 2014 Sanofi Genzyme collaboration, and (ii) the subsequent opt-in by Sanofi Genzyme for the fitusiran program. In addition, we determined that the Sanofi Genzyme collaboration met the requirements to be accounted for as a contract, including that it is probable that we will collect the consideration to which we are entitled in exchange for the goods or services that will be delivered to Sanofi Genzyme. We identified contract promises or deliverables for licenses to our intellectual property and know-how rights, associated development activities, joint steering committee participation and information exchange. We determined that, pursuant to the new revenue standard (and consistent with our accounting prior to the adoption of the new revenue standard), the performance obligations were not separately identifiable and were not distinct (and did not have standalone value) due to the specialized nature of the services to be provided by us and the dependent relationship between the performance obligations. Given this fact pattern, we concluded each of the TTR and fitusiran contracts have a single identified or combined performance obligation.

When applying the previous revenue standard, we determined that the co-commercialization activities prior to the 2018 amendment were within the scope of the collaboration accounting standard since both parties would actively participate in the co-commercialization and be subject to significant risks and rewards. As a result of this determination, we recorded any payments or cash receipts for these joint risk-sharing activities as an adjustment to the related operations expense captions. The amounts recorded as a reduction of our selling, general and administrative activities were not material.

The transaction price as of January 1, 2018 of \$127.6 million for the 2014 Sanofi Genzyme collaboration related to the license to the TTR programs included the \$22.5 million upfront payment and \$11.0 million of development milestone payments earned under the now superseded 2012 Sanofi Genzyme agreement, a \$25.0 million development milestone payment for revusiran achieved in 2014, the estimated patisiran and revusiran cost-share reimbursements, net of payments to Sanofi Genzyme, of \$63.6 million and \$57.0 million, respectively, and the \$51.5 million equity discount related to the stock purchase agreement, described below. Since the fair value of the stock at the time of closing was more than the consideration received by us by \$51.5 million, we reduced the transaction price of the license and collaboration contract, treating the equity discount in a manner consistent with a payment to the customer. The transaction price related to our license to the fitusiran program as of January 1, 2018, accounted for as a separate agreement, included estimated fitusiran development cost-share reimbursements of \$147.3 million, net of payments to Sanofi Genzyme. There are no refund provisions in the agreement and, therefore, none of the consideration received to date has been excluded from the transaction price calculation. None of the unearned milestones as of January 1, 2018 were included in the transaction price, as all unearned milestone amounts were not considered likely of achievement. We considered several factors, including that achievement of the milestones is outside our control and contingent upon success in clinical trials and regulatory decisions and the licensee's efforts. Any consideration related to sales-based royalties (including milestones) will be recognized when the related sales occur as they were determined to relate predominantly to the license granted to Sanofi Genzyme and as a result have also been excluded from the transaction price.

We allocated the transaction price to the combined performance obligation. We have determined that this combined performance obligation is satisfied over time based on our performance that is creating or enhancing an asset that Sanofi Genzyme controls. In this instance, Sanofi Genzyme received control over the asset, or the licensed intellectual property, and know-how, at the time the contract was executed since the licensed intellectual property and know-how meet the definition of functional intellectual property per the new revenue standard, which defines functional intellectual property as intellectual property that derives a substantial portion of its utility from its standalone functionality rather than the entity's ongoing activities (thus, once the asset is fully developed, our ongoing involvement is not required for the licensee to derive value). The other promises included in the performance obligation, however, are enhancing the controlled asset, and thus the combined performance obligation is being satisfied over time.

The new revenue standard requires a single method of measuring performance for each performance obligation satisfied over time. Since we do not have a reliable method of estimating progress based upon its outputs, it was determined that the most reliable method of estimating progress would be using a cost-to-cost input method. We have determined that our completion of certain clinical and regulatory development tasks is relevant and directly related to our progress in completing the combined performance obligation. As such, we measured our progress upon adoption and will continue to measure our progress during each reporting period based upon the amount of development costs incurred divided by the total amount of development costs expected to be incurred over the course of the agreement. We exclude costs that are not related to our completion of this performance obligation, such as the completion of tasks (and incurring of costs) associated with the marketing and commercialization of the drug. We estimated our internal costs during the last three years, excluding non-reimbursable costs that were not deemed to directly relate to the delivery of the development services to Sanofi Genzyme. Historically, we have been unable to reliably measure our performance based upon our lack of historical experience in completing the development of a drug candidate and have, as a result, defaulted to straight-line attribution for many of our licensing agreements. At the time of adoption of the new revenue standard, however, we have completed a substantial portion of our development obligations and determined we have sufficient information to estimate the remaining development costs for the fitusiran program and sufficient experience to reasonably estimate our development costs.

We determined that the 2018 amendment, together with the Exclusive TTR License and the AT3 License Terms, referred to as the 2018 restructured agreement, are included in the scope of the modification provisions of the new revenue standard. We had identified that the agreement for the TTR programs under the 2014 Sanofi Genzyme collaboration should be accounted for separately from any subsequent option exercises, including with respect to fitusiran. Therefore, we concluded it is appropriate to account for the 2018 restructured agreement as two separate modifications to the 2014 Sanofi Genzyme collaboration: one related to the TTR programs and one related to the fitusiran program. Our conclusions related to scoping under the prior revenue standard are consistent with the new revenue standard.

As noted above, the 2018 amendment, together with the Exclusive TTR License, provide us with the exclusive right to pursue the further global development and commercialization of all TTR products, including ONPATTRO. We are responsible for all development and commercialization costs for ONPATTRO and vutrisiran. As of the 2018 restructured agreement, we are no longer required to complete the delivery of any of the performance obligations under the agreement related to the TTR programs. As a result, the transaction price prior to the 2018 amendment has been reduced as we are no longer entitled to cost-share reimbursements or any of the previously constrained consideration, such as milestones and royalties. Since the 2018 amendment affected the transaction price but did not add any incremental and distinct performance obligations, we concluded this amendment should be accounted for as a change to the existing agreement and recorded the revenue on a cumulative catch-up basis. At the time of the 2018 amendment, we had \$2.9 million in revenue deferred as a contract liability on our consolidated balance sheet related to this contract for TTR programs, all of which we recognized in the first quarter of 2018 under a cost-to-cost input model as we no longer expected to incur costs associated with the delivery of goods or services. If we had not adopted

the new revenue standard, at the time of the 2018 restructured agreement, we would have had \$25.8 million of deferred revenues on our consolidated balance sheet that would have been recognized in full upon the date of the 2018 restructured agreement as we would have similarly concluded there were no ongoing deliverables under the 2018 restructured agreement related to the TTR programs. We expect to record future royalties payable to Sanofi Genzyme with respect to any sales of ONPATTRO within cost of goods sold on our consolidated statements of comprehensive loss as Sanofi Genzyme is no longer considered our customer after the 2018 restructured agreement for sales of all TTR products, including ONPATTRO, and as such, these royalty payments are outside of the scope of the new revenue standard, including with respect to principal versus agent guidance.

The 2018 amendment, together with the AT3 License Terms, as noted above, provide Sanofi Genzyme the exclusive right to pursue the further global development and commercialization of fitusiran and any back-up products and terminates the previous co-development and co-commercialization rights related to fitusiran under the 2014 Sanofi Genzyme collaboration. The 2018 restructured agreement provides a broader license that permits global development, manufacturing and commercialization, and we were required to facilitate the transfer of all ongoing activities, contracts, intellectual property, know-how and other materials and information related to fitusiran to Sanofi Genzyme.

In connection with the 2018 restructured agreement for fitusiran, we funded development and commercialization costs for fitusiran through the transition period, which was completed in 2018, up to a limit of \$50.0 million. The only milestone under the 2018 restructured agreement, which was achieved in the first quarter of 2018, was considered variable consideration for the license and

transition services related to the fitusiran program. We agreed to reimburse Sanofi Genzyme for certain transition activities that are reflected as a reduction in the transaction price. As a result, the transaction price has been reduced as we are no longer entitled to cost-share reimbursements or any of the previously constrained consideration, such as milestones and royalties.

We concluded that the modification that resulted from the 2018 restructured agreement related to fitusiran would be treated as a termination and replacement of the 2014 Sanofi Genzyme collaboration and accounted for prospectively as the remaining license and transition services are considered distinct from that under the agreement prior to this modification. However, the incremental consideration under the 2018 restructured agreement does not directly reflect the standalone selling price of the incremental performance obligation. Therefore, we concluded the 2018 restructured agreement for fitusiran should be accounted for on a prospective basis. At the time of the 2018 amendment, we had \$0.6 million in revenue deferred as a contract liability on our consolidated balance sheet related to the 2014 Sanofi Genzyme collaboration for the fitusiran program. The transaction price of the 2018 restructured agreement for fitusiran is \$37.6 million, primarily related to the \$50.0 million milestone that was achieved in the first quarter of 2018, offset by consideration paid to Sanofi Genzyme for its transition activities that were accounted for as a reduction of the transaction price. Consistent with our accounting prior to this 2018 modification, we are applying the sales-based royalty under the new revenue standard to exclude from the transaction price the royalties earned on Sanofi Genzyme's sales of fitusiran as we have determined in the context of all the performance obligations, including those delivered prior to the 2018 modification, that the value of the broader license will continue to represent a substantial portion of the value provided to Sanofi Genzyme; and therefore the license to the intellectual property is the predominant item to which the royalty relates.

We have determined that Sanofi Genzyme's right to purchase additional clinical and commercial material from us reflects optional purchases that are distinct from other performance obligations. Revenues associated with these purchases will be recognized in accordance with the right to invoice practical expedient and as Sanofi Genzyme obtains control of any purchased material.

We recognized the transaction price of the 2018 restructured agreement related to fitusiran under a separate cost-to-cost input model as we performed transition services over the transition period, which was completed in 2018. We measured our performance based on a percentage of our costs expected to be incurred in connection with the transition. During the transition, we incurred a total cost of \$38.0 million. During the year ended December 31, 2018, under a cost-to-cost input model, we recognized revenues of \$37.6 million related to the 2018 restructured agreement for fitusiran. If we had not adopted the new revenue standard, at the time of the 2018 restructured agreement, we would have had \$23.4 million of deferred revenues on our consolidated balance sheet, that would have represented an incremental \$22.8 million to the transaction price. Similar to under the new revenue standard, we consider the 2018 restructured agreement related to fitusiran to include a combined performance obligation. Under the prior revenue standard and our historical practice to account for contract modifications, we would apply a separate model to the consideration. Historically, we have measured our performance under our models based on the passage of time due to our inability to estimate performance under another method. However, as a result of the 2018 restructured agreement related to fitusiran, we have the ability to measure our performance under the prior revenue standard based on costs expected to be incurred, and therefore measure performance under the prior standard consistent with that of the new revenue standard. Under the prior revenue standard, we would have recorded revenues of \$60.3 million in the year ended December 31, 2018, related to fitusiran.

We determined that the opt-in rights that Sanofi Genzyme continues to have for future Genetic Medicine programs represent separate and additional optional purchases that Sanofi Genzyme may receive from us in future periods.

The Medicines Company. In February 2013, we and MDCO entered into a license and collaboration agreement pursuant to which we granted to MDCO an exclusive, worldwide license to develop, manufacture and commercialize

RNAi therapeutics targeting PCSK9 for the treatment of hypercholesterolemia and other human diseases, including inclisiran. MDCO paid us an upfront cash payment of \$25.0 million. Upon achievement of certain milestones, we will be entitled to receive milestone payments, up to an aggregate of \$180.0 million, including up to \$30.0 million in specified development milestones, \$50.0 million in specified regulatory milestones and \$100.0 million in specified commercialization milestones. In addition, we will be entitled to royalties ranging from the low- to high- teens based on annual worldwide net sales, if any, of licensed products by MDCO, its affiliates and sublicensees, subject to reduction under specified circumstances. To date, we have earned two development milestones totaling \$30.0 million under the MDCO agreement. We could potentially earn the next development milestone payment of \$25.0 million based upon regulatory approval of an NDA for inclisiran in the U.S. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any additional milestone payments or any royalty payments from MDCO.

Under the MDCO agreement, we had responsibility for the development of inclisiran until Phase 1 Completion, as defined in the MDCO agreement, at our cost, up to an agreed upon initial development cost cap. In late 2015, MDCO assumed responsible for all development and commercialization of inclisiran, at its sole cost. The collaboration between us and MDCO is governed by a joint steering committee that is comprised of an equal number of representatives from each party.

We were solely responsible for obtaining supply of finished product reasonably required for the conduct of our obligations under the initial development plan through Phase 1 Completion, and for supplying MDCO with finished product reasonably required



for the first Phase 2 clinical trial of inclisiran conducted by MDCO, at our expense, subject to certain caps. In April 2016, we and MDCO entered into a supply and technical transfer agreement to provide for our supply of inclisiran to MDCO, in accordance with the terms of the MDCO agreement. MDCO now has the sole right and responsibility to manufacture and supply inclisiran for development and commercialization under the MDCO development plan, subject to the terms of the MDCO agreement and the supply and technical transfer agreement.

In accordance with the new revenue standard, we evaluated the MDCO agreement and concluded that MDCO meets the definition of a customer and that the MDCO agreement is a contract. We determined the transaction price, identified the performance obligations and allocated the transaction price to each performance obligation. We also determined that substantially all of our performance obligations are within the scope of the new revenue standard as they relate to the delivery of goods and services to a customer for that customer's use in monetizing an asset. Specifically, we concluded that MDCO meets the definition of a customer as we are delivering intellectual property and know-how rights as well as research and development activities. In addition, we determined that the MDCO agreement met the requirements to be accounted for as a contract, including that it is probable that we will collect the consideration to which we are entitled in exchange for the goods or services that will be delivered to MDCO. We identified contract promises or deliverables for licenses to our intellectual property development and manufacturing know-how rights, associated development activities, joint steering committee participation and information exchange. In connection with the supply and technical transfer agreement, we assessed the new revenue standard to conclude if this modification should be accounted for as a separate contract or as a modification to the existing contract. We determined that the modification should not be treated as a separate agreement as the related performance obligations are not distinct as the value produced by these promises are highly dependent on the other promises in the contract. We determined that, pursuant to the new revenue standard (and consistent with our accounting prior to the adoption of the new revenue standard), the performance obligations were not separately identifiable and were not distinct (and did not have standalone value) due to the specialized nature of the services to be provided by us and the dependent relationship between the performance obligations. Given this fact pattern, we have concluded the MDCO agreement has a single identified or combined performance obligation.

The transaction price as of January 1, 2018 of \$72.9 million for the MDCO agreement included the \$25.0 million upfront payment, \$30.0 million of development milestones and \$17.9 million of cost reimbursement. There are no refund provisions in the MDCO agreement and, therefore, none of the consideration received to date has been excluded from the transaction price calculation. None of the unearned milestones as of January 1, 2018 were included in the transaction price, as all unearned milestone amounts were not considered likely of achievement. We considered several factors, including that achievement of the milestones is outside our control and contingent upon success in clinical trials and regulatory decisions and the licensee's efforts. Any consideration related to sales-based royalties (including milestones) will be recognized when the related sales occur as they were determined to relate predominantly to the license granted to MDCO and as a result have also been excluded from the transaction price.

Under the previous accounting standard, the initial upfront payment of \$25.0 million from MDCO was initially recorded as deferred revenue. During the fourth quarter of 2014, we recognized as revenue a portion of the \$10.0 million milestone payment earned in December 2014 equal to the percentage of the performance period completed when the milestone was earned. During the fourth quarter of 2017, we recognized as revenue a portion of the \$20.0 million milestone payment earned in November 2017 equal to the percentage of the performance period completed when the milestone was earned.

We allocated the transaction price to the combined performance obligation. We have determined that this combined performance obligation is satisfied over time based on our performance that is creating or enhancing an asset that MDCO controls. In this instance, MDCO received control over the asset, or the licensed intellectual property, and know-how, at the time the contract was executed since the licensed intellectual property and know-how meet the definition of functional intellectual property per the new revenue standard, which defines functional intellectual

property in that it derives a substantial portion of its utility from its standalone functionality rather than the entity's ongoing activities (thus, once the asset is fully developed, our ongoing involvement is not required for the licensee to derive value). The other promises included in the performance obligation, however, are enhancing the controlled asset, and thus the combined performance obligation is being satisfied over time.

The new revenue standard requires a single method of measuring performance for each performance obligation satisfied over time. Since we do not have a reliable method of estimating progress based upon its outputs, it was determined that the most reliable method of estimating progress would be using a cost-to-cost input method. We have determined that our completion of certain clinical and regulatory development tasks is relevant and directly related to our progress in completing the combined performance obligation. As such, we measured our progress upon adoption and will continue to measure our progress during each reporting period based upon the amount of development costs incurred divided by the total amount of development costs expected to be incurred over the course of the agreement. We exclude costs that are not related to our completion of this performance obligation, such as the completion of tasks (and incurring of costs) associated with the marketing and commercialization of the drug. We estimated our internal costs during the last three years, excluding non-reimbursable costs that were not deemed to directly relate to the delivery of the development services to MDCO. Historically, we have been unable to reliably measure our performance based upon our lack of historical experience in completing the development of a drug candidate and have, as a result, defaulted to straight-line attribution for many of our licensing

agreements. At the time of adoption of the new revenue standard, however, we have completed a substantial portion of our development obligations and determined we have sufficient information to estimate the remaining development costs for the inclisiran program and sufficient experience to reasonably estimate our development costs.

We recognized the transaction price as we satisfied our performance obligations over time. Beginning with the inception of the MDCO agreement and through the year end December 31, 2017, we incurred \$17.8 million of the \$17.9 million of total costs expected. If we had not adopted the new revenue standard, we would have had \$5.7 million of deferred revenues on our consolidated balance sheet as of January 1, 2018. We completed the performance obligations identified in the MDCO agreement, including the supply and technical transfer agreement, during 2018, although we may receive additional orders for supply. We consider such orders as promised goods to be distinct from the other performance obligations since MDCO now has the ability to begin manufacturing on its own through its own vendors. Such option orders will be treated as separate agreements and any associated revenue will be recognized upon transfer of control.

### Inventory

We capitalize inventory costs that are expected to be sold commercially once we determine there is a high probability that the inventory costs will be recovered through commercial sale based on the review of several factors, including (i) the likelihood that all required regulatory approvals will be obtained, (ii) the expected timing of validation (if not yet completed) of manufacturing processes in the associated facility, (iii) the expected expiration of the inventory, (iv) logistical or commercial constraints that may impede the timely distribution and sale of the product, including transport requirements and reimbursement status, (v) history of approvals of similar products or formulations and (vi) potential legal challenges. Prior to the capitalization of inventory costs, we record such costs as research and development expenses on our consolidated statements of comprehensive loss.

On a quarterly basis, we evaluate the recoverability of capitalized inventory using significant judgements, estimates and assumptions, primarily those related to commercial sales forecasts and product shelf life. In the event we determine our capitalized inventory to be impaired, we would reduce our inventory to net realizable value. Through December 31, 2018, we had not identified any impairment of our capitalized inventory.

### Accounting for Income Taxes

Accounting for income taxes requires a two-step approach to recognize and measure uncertain tax positions. The first step is to evaluate the tax position for recognition by determining if, based on the technical merits, it is more likely than not that the position will be sustained upon audit, including resolution of related appeals or litigation processes, if any. The second step is to measure the tax benefit as the largest amount that is more than 50 percent likely of being realized upon ultimate settlement. We re-evaluate these uncertain tax positions on a quarterly basis. This evaluation is based on factors including, but not limited to, changes in facts or circumstances, changes in tax law, and effectively settled issues under audit and new audit activity. Any change in these factors could result in the recognition of a tax benefit or an additional charge to the tax provision.

As of December 31, 2018, we have recorded no interest and penalty expense related to uncertain tax positions.

On December 22, 2017, the President of the United States signed into law the TCJA tax reform legislation. The TCJA makes significant changes in U.S. tax law including a reduction in the corporate tax rates, changes to net operating loss carryforwards and carrybacks, and a repeal of the corporate alternative minimum tax. The TCJA reduced the U.S. corporate tax rate from the current rate of 35 percent down to 21 percent starting on January 1, 2018. As a result of the enacted law, we were required to revalue deferred tax assets and liabilities at 21 percent. This revaluation resulted in a provision of \$227.9 million to income tax expense in continuing operations and a corresponding reduction in the

valuation allowance for the year ended December 31, 2017. As a result, there was no impact to our consolidated statements of comprehensive loss due to the reduction in tax rates. The other provisions of the TCJA did not have a material impact on our consolidated financial statements. Our final determination of the TCJA impact and the remeasurement of our deferred assets and liabilities was completed prior to the deadline of one year from the enactment of the TCJA. For the year ended December 31, 2018, there were no material changes to our analysis originally performed as of December 31, 2017.

We operate in the U.S., as well as in several countries outside of the U.S., where our income tax returns are subject to audit and adjustment by local tax authorities. The nature of the uncertain tax positions is often very complex and subject to change, and the amounts at issue can be substantial. We develop our cumulative probability assessment of the measurement of uncertain tax positions using internal experience, judgment and assistance from professional advisors. We refine estimates as we become aware of additional information. Any outcome upon settlement that differs from our current estimate may result in additional tax expense in future periods. At December 31, 2018, we had no unrecognized tax benefits.

We account for income taxes under the asset and liability method. Under this method, deferred tax assets and liabilities are recognized for the estimated future tax consequences attributable to differences between financial statement carrying amounts of existing assets and liabilities and their respective tax basis. Deferred tax assets and liabilities are measured using enacted rates in effect for the year in which these temporary differences are expected to be recovered or settled. Valuation allowances are provided if, based on the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized.

During 2018, we recorded a provision for income taxes of \$0.8 million. There was no provision for income taxes recorded during the years ended December 31, 2017 or 2016.

At December 31, 2018, we had a valuation allowance against our net deferred tax assets to the extent it is more likely than not that the assets will not be realized. At December 31, 2018, we had federal and state net operating loss carryforwards of \$1.9 billion and \$1.6 billion, respectively, to reduce future taxable income that will expire at various dates through 2038. At December 31, 2018, approximately \$0.5 billion of our federal net operating loss carryforward can be carried forward indefinitely. At December 31, 2018, we had federal and state research and development, including Orphan Drug, and state investment tax credit carryforwards of \$208.0 million and \$16.2 million, respectively, available to reduce future tax liabilities that expire at various dates through 2038. At December 31, 2018, we had alternative minimum tax credits of \$0.8 million that will either be available to reduce future regular tax liabilities or be fully refundable in 2021. We have a valuation allowance against the net operating loss and credit deferred tax assets as it is unlikely that we will realize these assets. Ownership changes, as defined in the Internal Revenue Code, including those resulting from the issuance of common stock in connection with our public offerings, may limit the amount of net operating loss and tax credit carryforwards that can be utilized to offset future taxable income or tax liability. The amount of the limitation is determined in accordance with Section 382 of the Internal Revenue Code. We have performed an analysis of ownership changes through December 31, 2018. Based on this analysis, we do not believe that any of our tax attributes will expire unutilized due to Section 382 limitations.

#### Accounting for Stock-Based Compensation

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

For time-based stock option awards granted during the year ended December 31, 2018, we used a weighted-average expected stock-price volatility assumption of 66 percent. Our expected life assumption is based on our historical data. Our weighted-average expected term was 5.8 years for the year ended December 31, 2018. We utilize a dividend yield of zero based on the fact that we have never paid cash dividends and currently have no intention to pay cash dividends. The risk-free interest rate used for each grant is based on the U.S. Treasury yield curve in effect at the time of grant for instruments with a similar expected life.

The fair value of restricted stock awards granted to employees is based upon the quoted closing market price per share on the date of grant. Expense for time-based restricted stock awards is recognized over the vesting period.

We have performance conditions included in certain of our stock option and restricted stock awards that are based upon the achievement of pre-specified clinical development, regulatory and/or commercial events. As the outcome of each event has inherent risk and uncertainties and a positive outcome may not be known until the event is achieved,

we begin to recognize the value of the performance-based stock option and restricted stock awards when we determine the achievement of each performance condition is deemed probable, which often is not until the condition is achieved. This determination requires significant judgment by management. At the probable date, we record a cumulative expense catch-up, with remaining expense amortized over the remaining service period.

At December 31, 2018, the estimated fair value of time-based unvested employee stock options was \$156.2 million, net of estimated forfeitures. We will recognize this amount over the weighted-average remaining vesting period of approximately three years for these awards. At December 31, 2018, the estimated fair value of performance-based unvested employee stock options and restricted stock units was \$59.3 million, net of estimated forfeitures. Stock-based employee compensation expense was \$157.8 million for the year ended December 31, 2018. However, we cannot currently predict the total amount of stock-based compensation expense to be recognized in any future period because such amounts will depend on levels of stock-based payments granted in the future as well as the portion of the awards that actually vest, including our performance-based awards. We estimate forfeitures at the time of grant and revise, if necessary, in subsequent periods if actual forfeitures differ from those estimates. The term “forfeitures” is distinct from “cancellations” or “expirations” and represents only the unvested portion of the surrendered stock option. We have applied an

annual forfeiture rate to all unvested employee stock options and restricted stock awards at December 31, 2018 based on an analysis of our historical forfeitures. Ultimately, the actual expense recognized over the vesting period will only be for those shares that vest.

#### Estimated Liability for Development Costs

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

#### Results of Operations

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

Description	Year Ended December 31,		
	2018	2017	2016
Revenues	\$74,908	\$89,912	\$47,159
Operating costs and expenses	889,581	590,000	471,746
Loss from operations	(814,673)	(500,088)	(424,587)
Net loss	\$(761,497)	\$(490,874)	\$(410,108)

#### Discussion of Results of Operations

##### Revenues

The following table summarizes our total consolidated revenues for the periods indicated, in thousands, together with the changes, in thousands:

Description	Years Ended December 31,			Dollar Change	
	2018	2017	2016	2018 compared to 2017	2017 compared to 2016
Product revenues, net	\$12,535	\$—	\$—	\$12,535	\$—
Net revenues from collaborators	62,373	89,912	47,159	(27,539)	42,753
Total revenues	\$74,908	\$89,912	\$47,159	\$(15,004)	\$42,753

Product revenues, net. We began to record net product revenues following regulatory approval of ONPATTRO in the U.S. and EU in August 2018 and its subsequent commercial launch in the U.S. and several countries in Europe during the third and fourth quarters of 2018, respectively. During 2018, we recognized \$12.5 million of net product revenues related to sales of ONPATTRO in the U.S. and several countries in Europe. We expect net product revenues to increase during 2019 as compared to 2018 primarily due to a full year of ONPATTRO sales in the U.S. and several countries in Europe in 2019, as well as expected product launches in additional territories, assuming regulatory approvals.

Net revenues from collaborators. The following table summarizes our total consolidated net revenues from collaborators under our research and development collaborations, for the periods indicated, in thousands, together with the changes, in thousands:

Description	Year Ended December 31,			Dollar Change	
	2018	2017	2016	2018 compared to 2017	2017 compared to 2016
Sanofi Genzyme	\$46,000	\$54,625	\$32,015	\$(8,625 )	\$ 22,610
Vir	12,778	1,464	—	11,314	1,464
MDCO	2,789	30,217	11,220	(27,428)	18,997
Other	806	3,606	3,924	(2,800 )	(318 )
Total net revenues from collaborators	\$62,373	\$89,912	\$47,159	\$(27,539)	\$ 42,753



The following table summarizes our total consolidated net revenues from collaborators under our research and development collaborations, under the prior revenue standard, for the periods indicated, in thousands, together with the changes, in thousands:

Description	Year Ended December 31,			Dollar Change	
	2018	2017	2016	2018 compared to 2017	2017 compared to 2016
Sanofi Genzyme	\$91,738	\$54,625	\$32,015	\$37,113	\$ 22,610
Vir	12,778	1,464	—	11,314	1,464
MDCO	7,184	30,217	11,220	(23,033)	18,997
Other	806	3,606	3,924	(2,800 )	(318 )
Total net revenues from collaborators	\$ 112,506	\$ 89,912	\$ 47,159	\$ 22,594	\$ 42,753

Net revenues from collaborators decreased during the year ended December 31, 2018 as compared to the year ended December 31, 2017 as a result of a decrease in reimbursable activities under our MDCO and Sanofi Genzyme agreements, as well as the adoption of the new revenue standard, partially offset by work performed under our collaboration with Vir. Upon our adoption of the new revenue standard on January 1, 2018, we recorded a cumulative reduction of \$45.7 million of deferred revenues related to our collaboration with Sanofi Genzyme, resulting in a remaining balance of \$3.5 million. As a result, we recorded significantly lower revenues related to our collaboration with Sanofi Genzyme during the year ended December 31, 2018 than we would have recorded under the prior revenue standard.

Net revenues from collaborators increased during the year ended December 31, 2017 as compared to the year ended December 31, 2016 due primarily to increased services performed by us in connection with our clinical development programs for which Sanofi Genzyme had opted in and the achievement of a \$20.0 million milestone under our agreement with MDCO in early November 2017.

Assuming that we do not enter into any new collaborative agreements during 2019, we expect net revenues from collaborators to decrease during 2019 as compared to 2018 due primarily to lower reimbursable activities under our existing collaborations. We had \$4.0 million of deferred revenue at December 31, 2018 related to our collaboration with Vir. At December 31, 2017, prior to the adoption of the new revenue standard, we had \$84.8 million of deferred revenue, which consisted of payments we have received from collaborators, primarily Sanofi Genzyme, MDCO and Kyowa Hakko Kirin Co., Ltd., but had not yet recognized pursuant to our revenue recognition policies. As a result of our adoption of the new revenue standard on January 1, 2018, we recorded a cumulative reduction of \$68.2 million of deferred revenue with a corresponding adjustment to accumulated deficit in the first quarter of 2018. Please read Note 2 to our consolidated financial statements included in Part II, Item 8, “Financial Statements and Supplementary Data,” of this annual report on Form 10-K for our discussion of recent accounting pronouncements for the impact of this new accounting standard.

#### Operating costs and expenses

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

Description	% of Total			% of Total			Dollar Change		
	2018	Operating Costs and Expenses	2017	2016	Operating Costs and Expenses	2017	2018	2017	2016
Cost of goods sold	\$1,802	0	% \$—	0	% \$—	0	% \$1,802	\$—	
Research and development	505,420	57	% 390,635	66	% 382,392	81	% 114,785	8,243	
Selling, general and administrative	382,359	43	% 199,365	34	% 89,354	19	% 182,994	110,011	
Total operating costs and expenses	\$889,581	100	% \$590,000	100	% \$471,746	100	% \$299,581	\$118,254	

Cost of goods sold. Cost of goods sold includes the cost of producing and distributing inventories that are related to ONPATTRO product revenues during the year ended December 31, 2018 (including salary-related and stock-based compensation expenses for employees involved with ONPATTRO production and distribution) and third-party royalties payable on our net product revenues for ONPATTRO. We began capitalizing ONPATTRO inventory costs during the third quarter of 2018 in connection with FDA approval and based upon our expectation that these costs are recoverable through commercialization of ONPATTRO. Prior to the capitalization of ONPATTRO inventory costs, such costs were recorded as research and development expenses in our consolidated statements of comprehensive loss. During the year ended December 31, 2018, we recorded \$1.8 million of cost of goods sold, including \$1.0 million related to third-party royalties. The cost of goods sold during the year ended December 31, 2018 only reflects a

portion of the manufacturing cost of ONPATTRO and third-party royalties. Utilizing the average cost per unit of ONPATTRO manufactured, cost of goods sold with respect to manufacturing costs for the year ended December 31, 2018 would have been approximately \$0.5 million, which would have resulted in \$2.3 million of costs of goods sold during the year ended December 31, 2018. At December 31, 2018, we had \$17.3 million of zero-cost inventory that we expect to sell over the next 16 to 18 months. We estimate cost of goods sold as a percentage of ONPATTRO product revenues, net will be in the mid- to high teens subsequent to the utilization of our zero-cost ONPATTRO inventory. The range is affected by our estimate of material costs from our suppliers and the level of fixed overhead costs estimated in relation to our future sales levels.

We expect that cost of goods sold will increase during 2019 as compared to 2018 primarily as a result of an expected increase in ONPATTRO sales.

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

Description	% of		% of		% of		Dollar Change	
	2018	Expense	2017	Expense	2016	Expense	2018	2017
		Category		Category		Category	compared	compared
							to 2017	to 2016
Research and development								
Compensation and related	\$ 116,350	23 %	\$ 100,728	26 %	\$ 87,124	23 %	\$ 15,622	\$ 13,604
Clinical trial	88,431	17 %	87,730	22 %	92,383	24 %	701	(4,653 )
Manufacturing	84,840	17 %	54,681	14 %	56,348	15 %	30,159	(1,667 )
Stock-based compensation	80,509	16 %	51,872	13 %	42,946	11 %	28,637	8,926
External services	55,165	11 %	38,675	10 %	48,624	13 %	16,490	(9,949 )
Facilities-related	42,159	8 %	31,022	8 %	30,032	8 %	11,137	990
Lab supplies and materials	12,827	3 %	10,513	3 %	8,917	2 %	2,314	1,596
Other	25,139	5 %	15,414	4 %	16,018	4 %	9,725	(604 )
Total research and development expenses	\$ 505,420	100 %	\$ 390,635	100 %	\$ 382,392	100 %	\$ 114,785	\$ 8,243

Research and development expenses increased significantly during the year ended December 31, 2018 as compared to the year ended December 31, 2017 due primarily to increased manufacturing expenses as a result of our late stage programs. In addition, stock-based compensation expense increased significantly related to the accounting for performance-based stock awards as a result of the approval and launch of ONPATTRO and clinical achievements with respect to our givosiran Phase 3 study. External services expenses increased during the year ended December 31, 2018

as a result of increased pre-clinical services related to early stage programs to support our Alnylam 2020 strategy, as well as increased expenses related to regulatory submissions. In addition, compensation and related expenses increased as a result of an increase in headcount during the period as we continue to expand and advance our development pipeline.

Research and development expenses increased slightly during the year ended December 31, 2017 as compared to the year ended December 31, 2016 due primarily to increased compensation and related expenses as a result of an increase in headcount during the period as we expanded and advanced our development pipeline, partially offset by decreases in external services expenses related to pre-clinical activities and clinical trial expenses as a result of our decision in October 2016 to discontinue development of revusiran. In addition, stock-based compensation expenses increased during the year ended December 31, 2017 as a result of increased expense related to the accounting for performance-based stock option awards.

During the years ended December 31, 2018, 2017 and 2016, in connection with advancing activities under our collaboration agreements, we incurred significant research and development expenses, primarily related to external development and manufacturing services. The 2018 amendment to the 2014 Sanofi Genzyme collaboration, together with the Exclusive TTR License and the AT3 License Terms, provide us with the exclusive right to pursue the further global development and commercialization of all TTR products and any back-up products and provide Sanofi Genzyme with the exclusive right to pursue the further global development and commercialization of all fitusiran and any back-up products. As a result, we expect costs incurred under our collaboration agreements to decrease. The following table summarizes the expenses incurred under our collaboration agreements by collaboration partner for the periods indicated, in thousands:

	Years Ended December 31,		
	2018	2017	2016
Sanofi Genzyme	\$43,219	\$184,703	\$160,580
Vir	16,071	2,060	—
MDCO	1,869	5,527	1,275
Ionis	3,247	3,250	525
Total	\$64,406	\$195,540	\$162,380

We expect to continue to devote a substantial portion of our resources to research and development expenses to support our goals for 2020. We expect that research and development expenses will increase during 2019 as compared to 2018 as we continue to develop our pipeline and advance our product candidates into later-stage development, hire additional employees and prepare regulatory submissions. However, we expect that certain expenses will be variable depending on the timing of manufacturing batches, clinical trial enrollment and results, regulatory review of our product candidates and programs, and stock-based compensation expenses due to our determination regarding the probability of vesting for performance-based awards.

A significant portion of our research and development costs are not tracked by project as they benefit multiple projects or our technology platform. However, certain of our collaboration agreements contain cost-sharing arrangements pursuant to which certain costs incurred under the project are reimbursed. Costs reimbursed under the agreements typically include certain direct external costs and a negotiated full-time equivalent labor rate for the actual time worked on the project. As a result, although a significant portion of our research and development expenses are not tracked on a project-by-project basis, we do track direct external costs attributable to, and the actual time our employees worked on, our collaborations.

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

Description	2018	% of Expense	Category	2017	% of Expense	Category	2016	% of Expense	Dollar Change	
									2018	2017
									to 2017	to 2016
Selling, general and administrative										
Consulting and professional services	\$137,201	36 %		\$68,847	35 %		\$25,310	28 %	\$68,354	\$43,537
Compensation and related	107,376	28 %		60,289	30 %		20,967	24 %	47,087	39,322
Stock-based compensation	77,243	20 %		40,947	21 %		32,582	36 %	36,296	8,365
Facilities-related	25,658	7 %		11,130	6 %		5,547	6 %	14,528	5,583
Other	34,881	9 %		18,152	8 %		4,948	6 %	16,729	13,204
Total selling, general and administrative	\$382,359	100 %		\$199,365	100 %		\$89,354	100 %	\$182,994	\$110,011

administrative expenses

Selling, general and administrative expenses increased significantly during the year ended December 31, 2018 as compared to the year ended December 31, 2017 due primarily to an increase in commercial and medical affairs headcount and commercial-related services to support corporate growth and prepare for the launch of ONPATTRO in 2018 in the U.S. and several countries in Europe, and potential additional country launches of ONPATTRO in 2019, as well as future worldwide product launches assuming regulatory approval of givosiran and other product candidates. In addition, selling, general and administrative expenses increased due to an increase in stock-based compensation expense related to the accounting for performance-based stock awards as a result of the approval and launch of ONPATTRO and clinical achievements with respect to our givosiran Phase 3 study.

Selling, general and administrative expenses increased significantly during the year ended December 31, 2017 as compared to the year ended December 31, 2016 due primarily to an increase in commercial and medical affairs headcount and commercial-related services to support corporate growth and prepare for potential commercial product launches. In addition, stock-based compensation expenses increased during the year ended December 31, 2017 as a result of increased expense related to the accounting for performance-based stock option awards.

We expect that selling, general and administrative expenses will increase during 2019 as compared to 2018 as we continue to grow our operations, including the continued build-out of our global commercial infrastructure and field team to support ONPATTRO

and potentially additional product launches, but expect that stock-based compensation expenses will be variable due to our determination regarding the probability of vesting for performance-based awards.

**Gain on litigation settlement.** In April 2018, we and Dicerna entered into a Settlement Agreement resolving all ongoing litigation between the companies. As a result, during the year ended December 31, 2018, we recorded \$20.6 million as a gain on litigation settlement, classified as other income on our consolidated statements of comprehensive loss, that includes the \$10.0 million valuation of Dicerna common stock received at the settlement date, the \$2.0 million upfront cash payment received in the second quarter of 2018, and \$8.6 million, which represented the discounted present value of the \$13.0 million cash payment due from Dicerna by April 18, 2022 under the terms of the Settlement Agreement. During the fourth quarter of 2018, in connection with the completion of business development activities by Dicerna, the \$13.0 million cash payment became due and we accreted the remaining discount and recorded \$4.0 million in interest income on our consolidated statements of comprehensive loss. In future periods, there will be no additional charges recorded to gain on litigation settlement related to the Settlement Agreement. For a discussion of the terms of the Settlement Agreement, please read Note 2 and Note 9 to our consolidated financial statements included in Part II, Item 8, "Financial Statements and Supplementary Data," of this annual report on Form 10-K.

#### Liquidity and Capital Resources

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

	Year Ended December 31,		
	2018	2017	2016
Net loss	\$(761,497)	\$(490,874 )	\$(410,108)
Adjustments to reconcile net loss to net cash used in			
operating activities	153,782	110,990	85,188
Changes in operating assets and liabilities	45,099	(2,902 )	17,219
Net cash used in operating activities	(562,616)	(382,786 )	(307,701)
Net cash provided by (used in) investing activities	272,945	(290,361 )	142,591
Net cash provided by financing activities	65,470	1,124,891	177,832
Net (decrease) increase in cash, cash equivalents and			
restricted cash	(224,201)	451,744	12,722
Cash, cash equivalents and restricted cash, beginning			
of period	646,832	195,088	182,366
Cash, cash equivalents and restricted cash, end of period	\$422,631	\$646,832	\$195,088

Since we commenced operations in 2002, we have generated significant losses. At December 31, 2018, we had an accumulated deficit of \$2.84 billion. At December 31, 2018, we had cash, cash equivalents and marketable debt securities of \$1.08 billion, excluding the \$44.8 million of restricted investments, compared to \$1.70 billion at December 31, 2017, excluding the \$30.0 million of restricted investments.

In May 2017, we sold an aggregate of 5,000,000 shares of our common stock through an underwritten public offering at a price to the public of \$71.87 per share. As a result of the offering, we received aggregate net proceeds of \$355.2

million, after deducting underwriting discounts and commissions and other offering expenses of \$4.2 million. In November 2017, we sold an aggregate of 6,440,000 shares of our common stock through an underwritten public offering at a price to the public of \$125.00 per share. As a result of the offering, which included the full exercise of the underwriters' option to purchase additional shares, we received aggregate net proceeds of \$784.5 million, after deducting underwriting discounts and commissions and other offering expenses of \$20.5 million. In January 2019, we sold an aggregate of 5,000,000 shares of our common stock through an underwritten public offering at a price to the public of \$77.50 per share. As a result of the offering, we received aggregate net proceeds of \$381.9 million, after deducting underwriting discounts and commissions and other estimated offering expenses of \$5.6 million.

We intend to use the proceeds from the January 2019 public offering for general corporate purposes, including advancing the ongoing commercialization of ONPATTRO in the U.S. and Europe and, assuming favorable regulatory reviews, the potential expansion into additional countries, development efforts directed towards the potential expansion of the ONPATTRO label in the U.S., continuing to advance our late stage clinical pipeline and preparing for the potential global launch of several additional products, continuing investment in our early stage pipeline, including our CNS and ocular programs, clinical trial costs and other research and development expenses, continued growth of our manufacturing, quality, commercial and medical affairs capabilities to support our commercialization efforts, potential acquisitions, investments or licenses in businesses, products or technologies that are complementary to our business, working capital, capital expenditures, and general and administrative expenses.



Sanofi Genzyme has certain rights to purchase additional shares from us under our investor agreement. In connection with our May 2017 public offering described above, Sanofi Genzyme exercised its right to purchase directly from us, in a concurrent private placement, 297,501 shares of common stock at the public offering price resulting in \$21.4 million in proceeds to us. In addition, Sanofi Genzyme also has the right at the beginning of each year to purchase a number of shares of our common stock based on the number of shares we issued during the previous year for compensation-related purposes. Sanofi Genzyme exercised this right to purchase directly from us 205,030 shares of our common stock in February 2016 for \$14.3 million. As of December 31, 2018, Sanofi Genzyme held approximately ten percent of our outstanding common stock.

We invest primarily in money market funds, U.S. government-sponsored enterprise securities, U.S. treasury securities, high-grade corporate notes, certificates of deposit and commercial paper. Corporate notes may also include foreign bonds denominated in U.S. dollars. Our investment objectives are, primarily, to assure liquidity and preservation of capital and, secondarily, to obtain investment income. All of our investments in marketable debt securities are recorded at fair value and are available-for-sale. Fair value is determined based on quoted market prices and models using observable data inputs. We have not recorded any impairment charges to our marketable debt securities during the three years ended December 31, 2018.

#### Operating activities

We have required significant amounts of cash to fund our operating activities as a result of net losses since our inception. Cash used in operating activities is adjusted for non-cash items to reconcile net loss to net cash used in operating activities. These non-cash adjustments have historically included stock-based compensation and depreciation and amortization, and for year ended December 31, 2018 included a gain related to common stock received as part of a litigation settlement.

We expect that we will require significant amounts of cash to fund our operating activities for the foreseeable future as we continue to execute on our Alnylam 2020 strategy through the advancement of our research, development, pre-commercial and commercial initiatives. The actual amount of overall expenditures will depend on numerous factors, including the timing of expenses, the timing and terms of collaboration agreements or other strategic transactions, if any, and the timing and progress of our research, development and commercialization efforts.

The increase in net cash used in operating activities for the year ended December 31, 2018 compared to the year ended December 31, 2017 and for the year ended December 31, 2017 compared to the year ended December 31, 2016 was due primarily to our net loss.

#### Investing activities

For the years ended December 31, 2018, 2017 and 2016, net cash provided by or used in investing activities included purchases of property, plant and equipment of \$126.9 million, \$104.2 million and \$64.6 million, respectively, primarily in connection with construction of our drug substance manufacturing facility. In addition, in connection with the commencement of our lease for 675 West Kendall Street in Cambridge, Massachusetts in May 2018, we were required to provide a \$14.8 million security deposit that is recorded as restricted investments on our consolidated balance sheet as of December 31, 2018. For the year ended December 31, 2016, there were \$150.0 million of purchases of restricted investments related to our term loan agreements with Bank of America N.A., or BOA, and Wells Fargo Bank, National Association, or Wells. In December 2017, we repaid in full \$120.0 million outstanding under the BOA term loan agreement. For the years ended December 31, 2018, 2017 and 2016, net cash provided by or used in investing activities included activities related to our marketable debt securities in accordance with management of our liquidity needs.

### Financing activities

For the year ended December 31, 2018, net cash of \$65.5 million provided by financing activities was due primarily to proceeds received from the issuance of common stock in connection with stock option exercises and the purchase of shares under our employee stock purchase plan. For the year ended December 31, 2017, net cash of \$1.12 billion provided by financing activities was due primarily to proceeds of \$1.14 billion received from our May and November 2017 underwritten public offerings. For the year ended December 31, 2016, net cash of \$177.8 million provided by financing activities was due primarily to our term loan agreements with BOA and Wells.

### Operating Capital Requirements

We currently have programs focused on a number of therapeutic areas and, in August 2018, received our first product approvals in the U.S. and EU for ONPATTRO. As a result, we began to generate net revenues from product sales during the third quarter of 2018. However, our ongoing development efforts may not be successful and we may not be able to commence sales of any other products in the future. In addition, we anticipate that we will continue to generate significant losses for the foreseeable future as a result of planned expenditures for research and development activities relating to our research platform, our drug development

programs, including clinical trial and manufacturing costs, the establishment of late stage clinical and commercial capabilities, including global operations, continued management and growth of our intellectual property including our patent portfolio, collaborations and general corporate activities. In addition, we are expanding our manufacturing capabilities, including through construction of a drug substance manufacturing facility in Norton, Massachusetts. In April 2016, our subsidiary, Alnylam U.S., Inc., entered into an aggregate of \$150.0 million in term loan agreements related to the build out of our new drug substance manufacturing facility. In December 2017, we repaid in full \$120.0 million outstanding under one of these term loan agreements. Interest on the borrowings was and is calculated based on LIBOR plus 0.45 percent and obligations were and 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 agreements at such time. We are the guarantor under the remaining term loan agreement, which matures in April 2021.

Based on our current operating plan, we believe that our cash, cash equivalents and marketable debt securities at December 31, 2018, together with the proceeds from our public offering in January 2019 and the cash we expect to generate from product sales and under our current alliances, will be sufficient to enable us to advance our Alnylam 2020 strategy for at least the next 24 months from the filing of this annual report on Form 10-K. For reasons discussed below, we may require significant additional funds earlier than we currently expect in order to continue to commercialize ONPATTRO and to develop, conduct clinical trials for, manufacture and, if approved, commercialize additional product candidates.

In the future, we may seek additional funding through new collaborative arrangements and public or private financings. Additional funding may not be available to us on acceptable terms or at all. Moreover, the terms of any additional financing may further adversely affect the holdings or the rights of our stockholders. For example, if we raise additional funds by issuing equity securities, further dilution to our existing stockholders will result. In addition, as a condition to providing additional funds to us, future investors may demand, and may be granted, rights superior to those of existing stockholders. 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 and our ability to achieve our goals 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. Even if we are able to raise additional funds in a timely manner, our future capital requirements may vary from what we expect and will depend on many factors, including:

- our continued 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 successfully initiate and complete our pre-clinical and clinical trials, obtain regulatory approvals, prepare for global 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 ONPATTRO and our other potential products.

Off-Balance Sheet Arrangements

In connection with our license agreements with Max Planck relating to the Tuschl I and II patent applications, we are required to indemnify Max Planck for certain damages arising in connection with the intellectual property rights licensed under the agreements. Under this indemnification agreement with Max Planck, we are responsible for paying the costs of any litigation relating to the license agreements or the underlying intellectual property rights, including the costs associated with certain litigation regarding the Tuschl patents, which was settled in 2011. In connection with the settlement of the litigation regarding the Tuschl patents, we also agreed to indemnify Whitehead, MIT and UMass for certain costs associated with defending the Utah litigation described above in Part I, Item 1A, "Risk Factors." In connection with our research agreement with Acuitas, we agreed to indemnify Acuitas for certain legal costs,

subject to certain exceptions and limitations, associated with certain litigation with Arbutus, which has been settled. These indemnification costs are charged to selling, general and administrative expense. In addition, we are a party to a number of agreements entered into in the ordinary course of business, which contain typical provisions that obligate us to indemnify the other parties to such agreements upon the occurrence of certain events. These indemnification obligations are considered off-balance sheet arrangements in accordance with GAAP. To date, other than certain costs associated with certain previously settled litigation related to the Tuschl patents and the litigation with Arbutus, and certain defense costs related to the Utah litigation, we have not encountered material costs as a result of such obligations and have not accrued any liabilities related to such obligations in our consolidated financial statements. Please read Note 9 to our consolidated financial statements included in Part II, Item 8, “Financial Statements and Supplementary Data,” of this annual report on Form 10-K for further discussion of these indemnification agreements.

### Contractual Obligations

In the table below, we set forth our enforceable and legally binding obligations and future commitments at December 31, 2018. Some of the figures that we include in this table are based on management’s estimates and assumptions about these obligations, including their duration, the possibility of renewal, anticipated actions by third parties and other factors. Because these estimates and assumptions are necessarily subjective, the obligations we will actually pay in future periods may vary from those reflected in the table.

Contractual Obligations	Payments Due by Period				Total
	2019	2020 and 2021	2022 and 2023	After 2023	
Facility lease obligations(1)	\$ 32,228	\$ 69,236	\$ 70,096	\$ 390,455	\$ 562,015
Long-term debt(2)	903	31,277	—	—	32,180
Technology license commitments(3)	1,453	1,540	1,070	525	4,588
Total contractual cash obligations	\$ 34,584	\$ 102,053	\$ 71,166	\$ 390,980	\$ 598,783

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

(2)In April 2016, our subsidiary, Alnylam U.S., Inc., entered into a \$30.0 million term loan agreement with Wells, for which we are the guarantor, related to the build out of our new drug substance manufacturing facility, that matures in April 2021. Interest payments are included in the table above and are calculated based on LIBOR plus 0.45 percent. The obligations under the term loan agreement are secured by cash collateral in an amount equal to, at any given time, at least 100 percent of the principal amount of the term loan outstanding at such time. We include estimates for interest in “Long-term debt,” which are equivalent to our expectations for the probable outcome of variable interest rates that are dependent on various future events and market interest rates.

(3)Relates to our fixed payment obligations under license agreements.

The table above excludes approximately \$297.6 million of cancellable commitments related to clinical and manufacturing-related agreements. We in-license technology from a number of sources, including Ionis, Merck and Arbutus. In addition, we have collaboration agreements relating to the research, development and commercialization of certain of our product candidates. Pursuant to these agreements, we will be required to make additional payments, including in some cases milestone payments if and when we achieve specified development, regulatory and commercialization events, as well as royalty payments on ONPATTRO and potentially other products, if approved. Amounts related to contingent milestone payments are not considered contractual obligations as they are contingent upon the successful achievement of such milestones. Based on our current development plans as of December 31, 2018, potential future milestone payments to third parties could equal up to \$53.7 million, including \$9.9 million in development milestones, \$40.2 million in regulatory milestones and \$3.6 million in commercial milestones. These milestones generally become due and payable upon achievement. Because the achievement of these milestones was

not considered probable as of December 31, 2018, such contingencies have not been recorded in our consolidated financial statements.

#### Recent Accounting Pronouncements

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

#### ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

As part of our investment portfolio, we own financial instruments that are sensitive to market risks. The investment portfolio is used to preserve our capital until it is required to fund operations, including our research, development and commercial activities. Our marketable debt securities consist of primarily U.S. government-sponsored enterprise securities, U.S. treasury securities, high-grade corporate notes, and commercial paper. Corporate notes may also include foreign bonds denominated in U.S. dollars. All of our investments in debt securities are classified as available-for-sale and are recorded at fair value. Our available-for-sale investments in debt securities are sensitive to changes in interest rates and changes in the credit ratings of the issuers. Interest rate changes would result in a change in the net fair value of these financial instruments due to the difference between the market interest rate and the market interest rate at the date of purchase of the financial instrument. If market interest rates were to increase immediately and

uniformly by 50 basis points, or one-half of a percentage point, from levels at December 31, 2018, the net fair value of our interest-sensitive financial instruments would have resulted in a hypothetical decline of \$0.9 million. We currently do not seek to hedge this exposure to fluctuations in interest rates. A downgrade in the credit rating of an issuer of a debt security or further deterioration of the credit markets could result in a decline in the fair value of the debt instruments. Our investment guidelines prohibit investment in auction rate securities and we do not believe we have any direct exposure to losses relating from mortgage-based securities or derivatives related thereto such as credit-default swaps. As we build our foreign operations, we face exposure to movements in foreign currency exchange rates, primarily the Euro, Swiss Franc and British Pound against the U.S. dollar. We will continue to evaluate strategies to mitigate foreign exchange risk, including the implementation of a foreign currency hedging program. Historically, foreign currency fluctuations have not been material. We did not record any impairment charges to our marketable debt securities during the year ended December 31, 2018.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA  
INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

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## Management's Annual Report on Internal Control Over Financial Reporting

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

- Pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of our assets;
- Provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that our receipts and expenditures are being made only in accordance with authorizations of management and directors; and
- Provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on the financial statements.

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

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2018. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in Internal Control-Integrated Framework (2013).

Based on our assessment, our management concluded that, as of December 31, 2018, our internal control over financial reporting is effective based on those criteria.

The effectiveness of our internal control over financial reporting as of December 31, 2018 has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in their report. This report appears on page 99.

Report of Independent Registered Public Accounting Firm

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

Opinions on the Financial Statements and Internal Control over Financial Reporting

We have audited the accompanying consolidated balance sheets of Alnylam Pharmaceuticals, Inc. and its subsidiaries (the "Company") as of December 31, 2018 and 2017, and the related consolidated statements of comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2018, including the related notes (collectively referred to as the "consolidated financial statements"). We also have audited the Company's internal control over financial reporting as of December 31, 2018, based on criteria established in Internal Control - Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO).

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of the Company as of December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2018 in conformity with accounting principles generally accepted in the United States of America. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2018, based on criteria established in Internal Control - Integrated Framework (2013) issued by the COSO.

Change in Accounting Principle

As discussed in Note 2 to the consolidated financial statements, the Company changed the manner in which it accounts for revenue from contracts with customers in 2018.

Basis for Opinions

The Company's management is responsible for these consolidated financial statements, for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Management's Annual Report on Internal Control over Financial Reporting. Our responsibility is to express opinions on the Company's consolidated financial statements and on the Company's internal control over financial reporting based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud, and whether effective internal control over financial reporting was maintained in all material respects.

Our audits of the consolidated financial statements included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating

the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

#### Definition and Limitations of Internal Control over Financial Reporting

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

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

/s/PricewaterhouseCoopers LLP

Boston, Massachusetts

February 14, 2019

We have served as the Company's auditor since 2003.

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## ALNYLAM PHARMACEUTICALS, INC.

## CONSOLIDATED BALANCE SHEETS

(In thousands, except share and per share amounts)

	December 31,	
	2018	2017
<b>ASSETS</b>		
Current assets:		
Cash and cash equivalents	\$420,146	\$645,361
Marketable debt securities	662,803	1,045,257
Marketable equity securities	1,206	—
Accounts receivable, net	18,760	34,002
Inventory	24,068	—
Prepaid expenses and other current assets	73,713	40,120
<b>Total current assets</b>	<b>1,200,696</b>	<b>1,764,740</b>
Marketable debt securities	—	13,919
Property, plant and equipment, net	320,658	181,900
Restricted investments	44,825	30,000
Other assets	8,623	4,171
<b>Total assets</b>	<b>\$1,574,802</b>	<b>\$1,994,730</b>
<b>LIABILITIES AND STOCKHOLDERS' EQUITY</b>		
Current liabilities:		
Accounts payable	\$59,708	\$28,355
Accrued expenses	112,719	72,203
Deferred rent	3,571	1,988
Deferred revenue	3,496	41,705
<b>Total current liabilities</b>	<b>179,494</b>	<b>144,251</b>
Deferred rent, net of current portion	57,920	6,626
Deferred revenue, net of current portion	458	43,075
Long-term debt	30,000	30,000
Other liabilities	4,965	4,347
<b>Total liabilities</b>	<b>272,837</b>	<b>228,299</b>
Commitments and contingencies (Note 9)		
Stockholders' equity:		
Preferred stock, \$0.01 par value per share, 5,000,000 shares authorized and no		
shares issued and outstanding at December 31, 2018 and 2017	—	—
Common stock, \$0.01 par value per share, 125,000,000 shares authorized;		
101,177,007 shares issued and outstanding at December 31, 2018; 99,666,549		
shares issued and outstanding at December 31, 2017	1,011	997
Additional paid-in capital	4,175,139	3,947,552
Accumulated other comprehensive loss	(33,213 )	(34,433 )
Accumulated deficit	(2,840,972)	(2,147,685)

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Total stockholders' equity	1,301,965	1,766,431
Total liabilities and stockholders' equity	\$1,574,802	\$1,994,730

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

## ALNYLAM PHARMACEUTICALS, INC.

## CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS

(In thousands, except per share amounts)

	Year Ended December 31,		
	2018	2017	2016
<b>Revenues:</b>			
Product revenues, net	\$12,535	\$—	\$—
Net revenues from collaborators	62,373	89,912	47,159
Total revenues	74,908	89,912	47,159
<b>Costs and expenses:</b>			
Cost of goods sold	1,802	—	—
Research and development(1)	505,420	390,635	382,392
Selling, general and administrative(1)	382,359	199,365	89,354
Total costs and expenses	889,581	590,000	471,746
Loss from operations	(814,673)	(500,088)	(424,587)
<b>Other income (expense):</b>			
Interest income	29,262	12,236	8,308
Other income (expense)	4,173	(3,022)	6,171
Gain on litigation settlement	20,564	—	—
Total other income	53,999	9,214	14,479
Loss before income taxes	(760,674)	(490,874)	(410,108)
Provision for income taxes	(823)	—	—
Net loss	\$(761,497)	\$(490,874)	\$(410,108)
Net loss per common share — basic and diluted	\$(7.57)	\$(5.42)	\$(4.79)
Weighted-average common shares used to compute basic and diluted net loss			
per common share	100,590	90,554	85,596
<b>Comprehensive loss:</b>			
Net loss	\$(761,497)	\$(490,874)	\$(410,108)
Unrealized gain (loss) on marketable securities, net of tax	1,220	(2,886)	(30,833)
Reclassification adjustment for realized loss (gain) on marketable securities	—	—	—
included in net loss	—	1,894	(6,977)
Comprehensive loss	\$(760,277)	\$(491,866)	\$(447,918)

(1) Stock-based compensation expenses included in operating costs and expenses are as follows:

Research and development	\$80,509	\$51,872	\$42,946
Selling, general and administrative	77,243	40,947	32,582

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



## ALNYLAM PHARMACEUTICALS, INC.

## CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY

(In thousands, except share amounts)

	Common Stock		Additional Paid-in Capital	Accumulated		Total Stockholders' Equity
	Shares	Amount		Comprehensive Income (Loss)	Accumulated Deficit	
Balance at December 31, 2015	85,090,968	\$ 851	\$2,506,197	\$ 4,369	\$(1,246,703 )	\$ 1,264,714
Exercise of common stock options, net of tax withholdings	559,344	5	11,603	—	—	11,608
Issuance of common stock under other types of equity plans	75,453	1	3,647	—	—	3,648
Issuance of common stock under equity plans, net of tax withholdings	10,549	—	(314 )	—	—	(314 )
Issuance of common stock to Sanofi Genzyme	205,030	2	14,299	—	—	14,301
Stock-based compensation expense related to equity-classified awards	—	—	74,182	—	—	74,182
Other comprehensive loss, net of tax	—	—	—	(37,810 )	—	(37,810 )
Net loss	—	—	—	—	(410,108 )	(410,108 )
Balance at December 31, 2016	85,941,344	859	2,609,614	(33,441 )	(1,656,811 )	920,221
Exercise of common stock options	1,841,566	19	80,527	—	—	80,546
Issuance of common stock under other types of equity plans	134,615	2	5,905	—	—	5,907
Issuance of common stock under equity plans, net of tax withholdings	11,523	—	(707 )	—	—	(707 )
Issuance of common stock to Sanofi Genzyme	297,501	3	21,378	—	—	21,381
Issuance of common stock, net of offering costs	11,440,000	114	1,139,511	—	—	1,139,625
Stock-based compensation expense related to	—	—	91,324	—	—	91,324

equity-classified						
awards						
Other comprehensive loss, net of tax	—	—	—	(992 )	—	(992 )
Net loss	—	—	—	—	(490,874 )	(490,874 )
Balance at December 31, 2017	99,666,549	997	3,947,552	(34,433 )	(2,147,685 )	1,766,431
Cumulative effect adjustment from the adoption of new revenue standard	—	—	—	—	68,210	68,210
Exercise of common stock options, net of tax withholdings	1,267,728	12	60,731	—	—	60,743
Issuance of common stock under other types of equity plans	108,539	1	8,984	—	—	8,985
Issuance of common stock under equity plans, net of tax withholdings	134,191	1	(770 )	—	—	(769 )
Stock-based compensation expense related to equity-classified awards	—	—	158,642	—	—	158,642
Other comprehensive gain, net of tax	—	—	—	1,220	—	1,220
Net loss	—	—	—	—	(761,497 )	(761,497 )
Balance at December 31, 2018	101,177,007	\$ 1,011	\$ 4,175,139	\$ (33,213 )	\$ (2,840,972 )	\$ 1,301,965

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

## ALNYLAM PHARMACEUTICALS, INC.

## CONSOLIDATED STATEMENTS OF CASH FLOWS

(In thousands)

	Year Ended December 31,		
	2018	2017	2016
<b>Cash flows from operating activities:</b>			
Net loss	\$(761,497 )	\$(490,874 )	\$(410,108 )
<b>Adjustments to reconcile net loss to net cash used in operating activities:</b>			
Depreciation, amortization and accretion, net	6,435	13,367	15,130
Stock-based compensation	157,752	92,819	75,528
Non-cash gain on litigation settlement	(10,000 )	—	—
Charge for 401(k) company stock match	3,159	2,302	1,507
Fair value adjustments on marketable equity securities	(3,564 )	1,894	(6,977 )
Other	—	608	—
<b>Changes in operating assets and liabilities:</b>			
Proceeds from landlord lease incentive for tenant improvements	25,350	—	2,145
Accounts receivable, net	15,242	(10,668 )	(15,036 )
Inventory	(22,645 )	—	—
Prepaid expenses and other assets	(35,067 )	(20,711 )	(5,276 )
Accounts payable	15,478	(4,939 )	10,098
Accrued expenses and other	59,357	31,568	10,673
Deferred revenue	(12,616 )	1,848	14,615
Net cash used in operating activities	(562,616 )	(382,786 )	(307,701 )
<b>Cash flows from investing activities:</b>			
Purchases of property, plant and equipment	(126,887 )	(104,209 )	(64,557 )
Purchases of restricted investments	(14,825 )	—	(150,000 )
Purchases of marketable debt securities	(1,104,046)	(903,457 )	(759,310 )
Sales and maturities of marketable securities	1,518,703	597,305	1,116,458
Sale of restricted investments	—	120,000	—
Net cash provided by (used in) investing activities	272,945	(290,361 )	142,591
<b>Cash flows from financing activities:</b>			
Proceeds from exercise of stock options and other types of equity	68,939	84,142	14,127
Proceeds from issuance of common stock, net of offering costs	—	1,139,625	—
Proceeds from issuance of common stock to Sanofi Genzyme	—	21,381	14,301
Proceeds from issuance of long-term debt	—	—	150,000
Repayment of long-term debt	—	(120,000 )	—
Payments for repurchase of common stock for employee tax			
withholding	(3,469 )	(257 )	(596 )
Net cash provided by financing activities	65,470	1,124,891	177,832
Net (decrease) increase in cash, cash equivalents and restricted cash	(224,201 )	451,744	12,722
Cash, cash equivalents and restricted cash, beginning of period	646,832	195,088	182,366
Cash, cash equivalents and restricted cash, end of period	\$422,631	\$646,832	\$195,088
<b>Supplemental disclosure of cash flows:</b>			

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Cash paid for interest	\$775	\$2,430	\$1,096
Cash paid for income taxes	\$1,066	\$114	\$111
Supplemental disclosure of noncash investing and financing activities:			
Capital expenditures included in accounts payable and accrued expenses	\$33,274	\$8,176	\$33,153
Fair value of common stock received in the period for collaboration			
agreement in other assets	\$1,327	\$2,700	\$—
Receipt of common stock for exercises of stock options	\$2,420	\$653	\$1,260
Repurchase of common stock for employee tax withholding in accrued			
expenses	\$—	\$450	\$—

The following table provides a reconciliation of cash, cash equivalents and restricted cash reported within our consolidated balance sheets that sum to the total of the same such amounts shown in the consolidated statements of cash flows:

	Year Ended December 31,		
	2018	2017	2016
Cash and cash equivalents	\$420,146	\$645,361	\$193,617
Restricted cash included in prepaid expenses and other current assets	225	—	—
Restricted cash included in long-term other assets	2,260	1,471	1,471
Total cash, cash equivalents, and restricted cash shown in the consolidated			
statements of cash flows	\$422,631	\$646,832	\$195,088

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

ALNYLAM PHARMACEUTICALS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. NATURE OF BUSINESS

We commenced operations on June 14, 2002 as a biopharmaceutical company seeking to develop and commercialize novel therapeutics based on RNA interference, or RNAi. We are committed to the advancement of our company strategy of building a multi-product, commercial biopharmaceutical company with a sustainable pipeline of RNAi therapeutics to address the needs of patients who have limited or inadequate treatment options. Since inception, we have focused on discovering, developing and commercializing RNAi therapeutics by establishing and maintaining a strong intellectual property position in the RNAi field, establishing strategic alliances with leading pharmaceutical and life sciences companies, generating revenues through licensing agreements, and ultimately developing and commercializing RNAi therapeutics globally, either independently or with our strategic partners. We have devoted substantially all of our efforts to business planning, research, development, manufacturing and early commercial efforts, acquiring, filing and expanding intellectual property rights, recruiting management and technical staff, and raising capital. In late 2017, we filed a new drug application, or NDA, and a marketing authorisation application, or MAA, seeking regulatory approval of ONPATTRO<sup>®</sup> (patisiran), our first product, in the U.S. and Europe, respectively. In August 2018, we received approval for ONPATTRO from the United States Food and Drug Administration, or FDA, and began commercializing and generating product revenues in the U.S. In August 2018, we also received approval of ONPATTRO from the European Commission, or EC, and in October 2018, began commercializing and generating product revenues outside of the U.S. During 2018, we also submitted regulatory applications for the approval of ONPATTRO in Japan, Canada and Switzerland, and we plan to make regulatory filings in additional markets in Europe and elsewhere throughout 2019.

We are subject to risks common to companies in our industry including, but not limited to, uncertainties relating to conducting clinical research and development, the manufacture and supply of products for clinical and commercial use, obtaining and maintaining regulatory approvals and pricing and reimbursement for our products, market acceptance, managing global growth and operating expenses, availability of additional capital, competition, obtaining and enforcing patents, stock price volatility, dependence on collaborative relationships and third-party service providers, dependence on key personnel, potential litigation, product liability claims and government investigations.

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Basis of Presentation and Principles of Consolidation

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

Use of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the United States of America, or GAAP, requires management to make estimates and assumptions that affect the reported

amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of revenues and expenses during the reporting period. In our consolidated financial statements, there are significant estimates and assumptions related to our inventory valuation and related reserves, income taxes, revenue recognition, research and development expenses, and stock-based compensation. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable. Actual results could differ from those estimates.

#### Liquidity

Based on our current operating plan, we believe that our cash, cash equivalents and marketable debt securities at December 31, 2018, together with the cash we expect to generate from product sales and under our current alliances, will be sufficient to enable us to advance our Alnylam 2020 strategy for at least the next 12 months from the filing of this annual report on Form 10-K.

## Concentrations of Credit Risk and Significant Customers

Financial instruments that potentially expose us to concentrations of credit risk consist primarily of cash, cash equivalents and marketable debt securities. At December 31, 2018 and 2017, substantially all of our cash, cash equivalents and marketable debt securities were invested in money market funds, certificates of deposit, commercial paper, corporate notes, U.S. government-sponsored enterprise securities and U.S. treasury securities through highly rated financial institutions. Corporate notes may also include foreign bonds denominated in U.S. dollars. Investments are restricted, in accordance with our investment policy, to a concentration limit per issuer.

In recent periods, our revenues have been generated primarily from collaborations with strategic partners, including Sanofi Genzyme, the specialty care global business unit of Sanofi, Vir Biotechnology, Inc., or Vir, and The Medicines Company, or MDCO. We began to record product revenues in the second half of 2018 following the approval of ONPATTRO by the FDA and the EC in August 2018 and subsequent launches of ONPATTRO in the U.S. and several countries in Europe. For the year ended December 31, 2018, our gross accounts receivable, net were composed primarily of payments due from a distributor for sales of ONPATTRO. For the year ended December 31, 2017, our gross accounts receivable were composed primarily of a milestone payment due from MDCO and expense reimbursement due from Sanofi Genzyme.

The following table summarizes customers that represent greater than 10 percent of our consolidated total gross revenues for the periods indicated:

	Year Ended December 31,		
	2018	2017	2016
Sanofi Genzyme	58%	61 %	68 %
Vir Biotechnology	16%	*	N/A
Distributor A	13%	N/A	N/A
MDCO	*	34 %	24 %

\*Represents 10 percent or less

The following table summarizes customers with amounts due that represent greater than 10 percent of our gross accounts receivable balance, at the periods indicated:

	At December 31,	
	2018	2017
Distributor A	44 %	N/A
Sanofi Genzyme	29 %	39 %
MDCO	*	59 %



\*Represents 10 percent or less  
Fair Value Measurements

The fair value is the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. In general, fair values determined by Level 1 inputs utilize quoted prices (unadjusted) in active markets for identical assets or liabilities. Fair values determined by Level 2 inputs utilize data points that are observable, such as quoted prices (adjusted), interest rates and yield curves. Fair values determined by Level 3 inputs utilize unobservable data points for the asset or liability, and include situations where there is little, if any, market activity for the asset or liability. The fair value hierarchy level is determined by the lowest level of significant input.

#### Investments in Marketable Securities and Cash Equivalents

We invest our excess cash balances in short-term and long-term marketable debt securities. We classify our investments in marketable debt securities as either held-to-maturity or available-for-sale based on facts and circumstances present at the time we purchased the securities. At each balance sheet date presented, we classified all of our investments in debt securities as available-for-sale. We report available-for-sale debt securities at fair value at each balance sheet date and include any unrealized holding gains and losses (the adjustment to fair value) in accumulated other comprehensive income (loss), a component of stockholders' equity. At December 31, 2018, the balance in our accumulated other comprehensive loss was composed solely of activity related to our marketable debt securities and our investment in equity securities of Regulus Therapeutics Inc., or Regulus. Realized gains and losses are determined using the specific identification method and are included in other income (expense). We did not recognize any realized gains or losses from sales of our available-for-sale debt securities during the years ended December 31, 2018, 2017 or 2016, and as a

result, did not reclassify any amount out of accumulated other comprehensive loss for the respective period related to our available-for-sale debt securities. If any adjustment to fair value reflects a decline in the value of the marketable debt securities, we consider all available evidence to evaluate the extent to which the decline is “other than temporary,” including our intention to sell and, if so, mark the investment to market through a charge to our consolidated statements of comprehensive loss. We did not record any impairment charges related to our marketable debt securities during the years ended December 31, 2018, 2017 or 2016. Our marketable debt securities are classified as cash equivalents if the original maturity, from the date of purchase, is 90 days or less, and as marketable debt securities if the original maturity, from the date of purchase, is in excess of 90 days. Our cash equivalents are generally composed of commercial paper, corporate notes, U.S. government-sponsored enterprise securities, U.S. treasury securities and money market funds.

Upon the adoption of the new accounting standard, discussed below under the heading “Recent Accounting Pronouncements,” effective January 1, 2018, we measure marketable equity investments (except those accounted for under the equity method of accounting or those that result in consolidation of an investee), which have readily available prices, at fair value with changes in fair value recognized in other income (expense) on our consolidated statements of comprehensive loss. Prior to January 1, 2018, we recognized unrealized gains and losses on our marketable equity securities through accumulated other comprehensive income (loss) on our consolidated balance sheets.

During the second quarter of 2017, we sold all our remaining holdings in Regulus. We accounted for our investment in Regulus as an available-for-sale marketable equity security. We recognized \$1.9 million of realized losses and \$7.0 million of realized gains from sales of our Regulus available-for-sale securities as other income (expense) in our consolidated statement of comprehensive loss during the year ended December 31, 2017 and 2016, respectively. Intraproduct tax allocation rules require us to allocate our provision for income taxes between continuing operations and other categories of earnings, such as other comprehensive income. In periods in which we have a year-to-date pre-tax loss from continuing operations and pre-tax income in other categories of earnings, such as other comprehensive income, we must allocate the tax provision to the other categories of earnings. We then record a related tax benefit in continuing operations. Upon sales of our marketable equity securities, we apply the aggregate portfolio approach to recognize the related tax provision or benefit into income (loss) from continuing operations. As a result, the disproportionate tax effect remains in accumulated other comprehensive income (loss) as long as we maintain an investment portfolio. At December 31, 2018 and 2017, there was \$32.8 million of accumulated other comprehensive loss, net of tax, recorded on our consolidated balance sheets related to our investment in Regulus.

#### Accounts Receivable

We record accounts receivable net of customer allowances for distribution services, prompt payment discounts and chargebacks based on contractual terms. As of December 31, 2018, we determined an allowance for doubtful accounts was not required based upon our review of contractual payment terms and individual customer circumstances. We have standard payment terms that generally require payment within approximately 30 to 50 days. Accounts receivable, net on our consolidated balance sheets also includes billed and unbilled collaboration receivables.

#### Inventory

Prior to initial regulatory approval, we expense costs relating to the production of inventory as research and development expenses on our consolidated statements of comprehensive loss in the period incurred, unless we believe regulatory approval and subsequent commercialization of the product candidate is probable and we expect the future economic benefit from sales of the product to be realized, at which point we capitalize the costs as inventory.

Inventory is measured at the lower of cost or estimated net realizable value. We use a standard cost basis, which approximates average cost determined on a first-in, first-out basis. Inventory costs include all raw materials, direct conversion costs and overhead. Raw and intermediate materials that may be used for either research and development or commercial purposes are classified as inventory until the material is consumed or otherwise allocated for research and development. If the material is used for research and development, it is expensed as research and development once that determination is made.

We capitalize inventory costs that are expected to be sold commercially once we determine there is a high probability that the inventory costs will be recovered through commercial sale based on the review of several factors, including (i) the likelihood that all required regulatory approvals will be obtained, (ii) the expected timing of validation of manufacturing processes in the associated facility (if not yet completed), (iii) the expected expiration of the inventory, (iv) logistical or commercial constraints that may impede the timely distribution and sale of the product, including transport requirements and reimbursement status, (v) the history of approvals of similar products or formulations, and (vi) potential legal challenges.

We reduce our inventory to net realizable value for potentially excess, dated or obsolete inventory based on our quarterly assessment of the recoverability of our capitalized inventory. Through December 31, 2018, we had not identified any impairment of our capitalized inventory.

### Property, Plant and Equipment

Property, plant and equipment are stated at cost, net of accumulated depreciation. Depreciation expense is recorded on a straight-line basis over the estimated useful life of the asset. Leasehold improvements are amortized over the shorter of the asset's estimated useful life or the lease term. Construction in progress reflects amounts incurred for construction or improvements of property, plant or equipment that have not been placed in service. Costs of construction of certain long-lived assets include capitalized interest, which is amortized over the estimated useful life of the related asset. The cost and accumulated depreciation of assets retired or sold are removed from the respective asset category, and any gain or loss is recognized in our consolidated statements of comprehensive loss.

The estimated useful lives of property, plant and equipment are as follows:

Asset Category	Useful Life
Laboratory equipment	5 years
Computer equipment and software	3-10 years
Furniture and fixtures	5 years
Leasehold improvements	Shorter of asset life or lease term
Land	—
Construction in progress	—

### Estimated Liability for Development Costs

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

### Revenue Recognition

We began to record revenues from product sales in the third quarter of 2018 subsequent to the approval of ONPATTRO by the FDA in August 2018. Prior to the third quarter of 2018, all of our revenues were derived from collaboration agreements that we have entered into with leading pharmaceutical and life sciences companies, including Sanofi Genzyme and MDCO. The terms of our collaboration agreements may include consideration such as non-refundable license fees, funding of research and development services, payments due upon the achievement of clinical and pre-clinical performance-based development milestones, regulatory milestones, manufacturing services, sales-based milestones and royalties on product sales.

On January 1, 2018, we adopted the new revenue standard, discussed below under the heading “Recent Accounting Pronouncements,” which amended revenue recognition principles and provides a single, comprehensive set of criteria for revenue recognition within and across all industries. Our adoption of the new revenue standard had a material impact on our consolidated financial statements, as discussed below under the heading “Recent Accounting Pronouncements.” This new revenue standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments. The new revenue standard provides a five-step framework whereby revenue is recognized when control of promised goods or services is transferred to a customer at an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. To determine revenue recognition for arrangements that we determine are within the scope of the new revenue standard, we perform the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) we satisfy a performance obligation. We only apply the five-step model to contracts when collectability of the consideration to which we are entitled in exchange for the goods or services we transfer to the customer is determined to be probable. At contract inception, once the contract

is determined to be within the scope of the new revenue standard, we assess whether the goods or services promised within each contract are distinct and, therefore, represent a separate performance obligation. Goods and services that are determined not to be distinct are combined with other promised goods and services until a distinct bundle is identified. We then allocate the transaction price (the amount of consideration we expect to be entitled to from a customer in exchange for the promised goods or services) to each performance obligation and recognize the associated revenue when (or as) each performance obligation is satisfied. Our estimate of the transaction price for each contract includes all variable consideration to which we expect to be entitled.

Amounts are recorded as accounts receivable when our right to consideration is unconditional. We do not assess whether a contract has a significant financing component if the expectation at contract inception is that the period between payment by the customer and the transfer of the promised goods or services to the customer will be one year or less. We expense incremental costs of obtaining a contract as and when incurred if the expected amortization period of the asset that we would have recognized is one year or less or the amount is immaterial. At December 31, 2018, we had not capitalized any costs to obtain any of our contracts.

#### Product revenues, net

In the third quarter of 2018, following FDA approval in August 2018, we began to ship ONPATTRO in the U.S. to specialty pharmacies, or SPs, and a specialty distributor, or SD, referred to as our customers. Our U.S. customers subsequently resell ONPATTRO to health care providers. We also received approval from the EC in August 2018 and launched ONPATTRO in several countries in Europe during the fourth quarter of 2018, where we primarily sell to government-owned and supported customers, including hospitals. We recognize product revenues, net of variable consideration related to certain allowances and accruals, in our consolidated financial statements at the time of sale. In the event the variable consideration is constrained, we include an amount to the extent it is probable that a significant reversal in the amount of cumulative revenue recognized will not occur in a future reporting period. We use the expected value method to estimate variable consideration related to ONPATTRO sales. We do not have any material constraints on our variable consideration included within the transaction price of our ONPATTRO revenue arrangements. Each unit of ONPATTRO that is ordered by our customers represents a separate performance obligation that is completed when control of the product is transferred to our customer, which occurs upon delivery of the product to the customer. We record revenues, net of variable consideration and any applicable constraint, at that point in time. We record shipping and handling costs within cost of goods sold on our consolidated statements of comprehensive loss. We classify payments to distributors and other customers in the distribution channel for services that have a separate benefit and fair value as selling, general and administrative expenses on our consolidated statements of comprehensive loss. We have elected to exclude taxes collected from our customers and remitted to governmental authorities from the measurement of the transaction price. We periodically evaluate the creditworthiness of our customers.

The following are the components of variable consideration related to product revenues. We record reserves, based on contractual terms, for these components related to product sold during the reporting period, as well as our estimate of product that remains in the distribution channel inventory at the end of the reporting period that we expect will be sold to qualified healthcare providers. On a quarterly basis, we will update our estimates and record any needed adjustments in the period we identify the adjustments.

**Chargebacks:** We estimate obligations resulting from contractual commitments with the government and other entities to sell products to qualified healthcare providers at prices lower than the list prices charged to the SD who purchases ONPATTRO from us. The SD charges us for the difference between what the SD pays to us for the product and the selling price to the qualified healthcare providers.

**Rebates:** We are subject to discount obligations under government programs, including Medicaid in the U.S. and similar programs in certain countries in Europe. We are also subject to potential rebates in connection with our value-based agreements with certain commercial payors. We record reserves for rebates in the same period the related product revenue is recognized, resulting in a reduction of ONPATTRO product revenues and a current liability that is included in accrued expenses on our consolidated balance sheet. Our estimate for rebates is based on statutory discount rates and expected utilization.

**Trade discounts and allowances:** We provide customary invoice discounts on ONPATTRO sales to our customers for prompt payment and we pay fees for distribution services, such as fees for certain data that customers provide to us. We estimate our customers will earn these discounts and fees, and deduct these discounts and fees in full from gross ONPATTRO revenues and accounts receivable at the time we recognize the related revenues.

**Product returns:** ONPATTRO may be returned if it is damaged, defective or expired, with “expired” defined as having three months or less to expiry or within three months past expiry. We estimate the amount of product that will be returned using a probability-weighted estimate, initially calculated based on a portfolio of data from similar products and industry experience for SP products. Based on the distribution model for ONPATTRO, contractual inventory limits with our customers, the price of ONPATTRO

and limited contractual return rights, we believe there will be minimal ONPATTRO returns. We have recorded an initial refund liability for our estimate of ONPATTRO returns related to sales during the year ended December 31, 2018. We will update our estimated refund liability, on at least a quarterly basis, based on actual shipments of ONPATTRO subject to contractual return rights, changes in expectations about the amount of estimated refunds or actual returns, as data is known.

**Other incentives:** Other incentives include co-payment assistance we provide to patients with commercial insurance that have coverage and reside in states that allow co-payment assistance. We estimate the average co-payment assistance amounts for ONPATTRO based on expected customer demographics and record any such amounts within accrued expenses on our consolidated balance sheet.

#### Revenues from Collaborators

We recognize the transaction price allocated to upfront license payments as revenue upon delivery of the license to the customer and resulting ability of the customer to use and benefit from the license, if the license is determined to be distinct from the other performance obligations identified in the contract. If the license is considered to not be distinct from other performance obligations, we exercise judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied (i) at a point in time, but only for licenses determined to be distinct from other performance obligations in the contract, or (ii) over time; and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from license payments. We evaluate the measure of progress each reporting period and, if necessary, adjust the measure of performance and related revenue recognition.

Many of our collaboration agreements entitle us to additional payments upon the achievement of performance-based milestones. These milestones are generally categorized into three types: development milestones, which are generally based on the advancement of our pipeline and initiation of clinical trials; regulatory milestones, which are generally based on the submission, filing or approval of regulatory applications such as an NDA in the U.S.; and sales-based milestones, which are generally based on meeting specific thresholds of sales in certain geographic areas. For each collaboration that includes development milestone payments, we evaluate whether it is probable that the consideration associated with each milestone will not be subject to a significant reversal in the cumulative amount of revenue recognized. Amounts that meet this threshold are included in the transaction price using the most likely amount method, whereas amounts that do not meet this threshold are considered constrained and excluded from the transaction price until they meet this threshold. Milestones tied to regulatory approval, and therefore not within our control, are considered constrained until such approval is received. Upfront and ongoing development milestones per our collaboration agreements are not subject to refund if the development activities are not successful. At the end of each subsequent reporting period, we re-evaluate the probability of a significant reversal of the cumulative revenue recognized for our milestones, and, if necessary, adjust our estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues from collaborators and loss in the period of adjustment. We exclude sales-based royalties and milestone payments from the transaction price until the sale occurs (or, if later, the underlying performance obligation to which some or all of the royalty has been allocated has been satisfied, or partially satisfied), because the license to our intellectual property is deemed to be the predominant item to which the royalties relate as it is the primary driver of value. Currently, we have not recognized any royalty revenue resulting from any of our agreements.

The new revenue standard, which was adopted in January 2018, requires us to allocate the arrangement consideration on a relative standalone selling price basis for each performance obligation after determining the transaction price of the contract and identifying the performance obligations to which that amount should be allocated. The relative standalone selling price is defined in the new revenue standard as the price at which an entity would sell a promised good or service separately to a customer. If other observable transactions in which we have sold the same performance



obligation separately are not available, we are required to estimate the standalone selling price of each performance obligation. Key assumptions to determine the standalone selling price may include forecasted revenues, development timelines, reimbursement rates for personnel costs, discount rates and probabilities of technical and regulatory success.

Whenever we determine that a contract should be accounted for as a combined performance obligation over time, we determine the period over which the performance obligations will be performed and revenue will be recognized. Revenue is recognized using a cost-to-cost input model. Direct labor hours or full-time equivalents are typically used as the measure of performance. Significant management judgment is required in determining the level of effort required under an arrangement and the period over which we are expected to complete our performance obligations under an arrangement.

We evaluate our collaborative agreements for proper classification in our consolidated statements of comprehensive loss based on the nature of the underlying activity. Transactions between collaborators recorded in our consolidated statements of comprehensive loss are recorded on either a gross or net basis, depending on the characteristics of the collaborative relationship. We generally reflect amounts due under our collaborative agreements related to cost-sharing of development activities as revenue if we have a vendor-customer relationship with our collaborator. Costs incurred or shared with our collaboration partners that are deemed to be joint-risk sharing activities are recorded as an adjustment to the related operating expense captions.

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

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

The estimate of deferred revenue also reflects management's estimate of the periods of our involvement in certain of our collaborations. Our performance obligations under these collaborations consist of participation on steering committees and the performance of other research and development services. In certain instances, the timing of satisfying these obligations can be difficult to estimate. Accordingly, our estimates may change in the future. Such changes to estimates would result in a change in revenue recognition amounts. If these estimates and judgments change over the course of these agreements, it may affect the timing and amount of revenue that we recognize and record in future periods. At December 31, 2018, we had short-term and long-term deferred revenue of \$3.5 million and \$0.5 million, respectively, all of which was related to our collaboration with Vir.

#### Cost of Goods Sold

Cost of goods sold includes the cost of producing and distributing inventories that are related to product revenues during the respective period (including salary-related and stock-based compensation expenses for employees involved with production and distribution, freight and indirect overhead costs), third-party royalties payable on our net product revenues and amortization of intangible assets associated with ONPATTRO. Cost of goods sold may also include costs related to excess or obsolete inventory adjustment charges, abnormal costs, unabsorbed manufacturing and overhead costs, and manufacturing variances.

#### Other Income

As described more fully below in Note 9, in April 2018, we and Dicerna Pharmaceuticals, Inc., or Dicerna, entered into the Settlement Agreement resolving all ongoing litigation between the companies. As a result, during the second quarter of 2018, we recorded \$20.6 million as a gain on litigation settlement classified as other income on our consolidated statements of comprehensive loss, that includes the \$10.0 million valuation of Dicerna common stock received at the settlement date, the \$2.0 million upfront cash payment received in the second quarter of 2018, and \$8.6 million, which represented the discounted present value of the \$13.0 million cash payment due from Dicerna by April 18, 2022 under the terms of the Settlement Agreement. During the fourth quarter of 2018, in connection with the completion of certain business development activities by Dicerna, the \$13.0 million cash payment, included in prepaid expenses and other current assets on our consolidated balance sheet, became due and we accreted the remaining

discount and recorded \$4.0 million in interest income on our consolidated statements of comprehensive loss. Total other income on our consolidated statements of comprehensive loss also includes interest income related to our interest-bearing cash equivalents and marketable debt securities.

#### Income Taxes

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

Accounting for income taxes requires a two-step approach to recognize and measure uncertain tax positions. The first step is to evaluate the tax position for recognition by determining if, based on the technical merits, it is more likely than not that the position will be sustained upon audit, including resolution of related appeals or litigation processes, if any. The second step is to measure the tax benefit as the largest amount that is more than 50 percent likely of being realized upon ultimate settlement. We re-evaluate these uncertain tax positions on a quarterly basis. This evaluation is based on factors including, but not limited to, changes in facts or circumstances, changes in tax law, effectively settled issues under audit and new audit activity. Any change in these factors could result in the recognition of a tax benefit or an additional charge to the tax provision.

As of December 31, 2018, we have recorded no interest and penalty expense related to uncertain tax positions.

#### Research and Development Expenses

We record research and development expenses as incurred. Included in research and development expenses are wages, stock-based compensation expenses, benefits and other operating costs, facilities, supplies, external services, clinical trial and manufacturing costs, costs related to our collaboration arrangements and overhead directly related to our research and development operations, as well as costs to acquire technology licenses.

We have entered into several license agreements for rights to utilize certain technologies. The terms of the licenses may provide for upfront payments, annual maintenance payments, milestone payments based upon certain specified events being achieved and royalties on product sales. We charge costs to acquire and maintain licensed technology that has not reached technological feasibility and does not have alternative future use to research and development expense as incurred. During the years ended December 31, 2018, 2017 and 2016, we charged to research and development expense costs associated with license fees of \$8.0 million, \$7.7 million and \$2.4 million, respectively.

#### Stock-Based Compensation

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

The fair value of restricted stock awards granted to employees is based upon the quoted closing market price per share on the date of grant. Expense for time-based restricted stock awards is recognized over the vesting period.

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

#### Comprehensive Loss

Comprehensive loss is comprised of net loss and certain changes in stockholders' equity that are excluded from net loss. We include foreign currency translation adjustments in other comprehensive loss if the functional currency is not the U.S. dollar. We include unrealized gains and losses on certain marketable securities in other comprehensive loss, including changes in the value of our marketable debt securities.

#### Net Loss Per Common Share

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

common share.

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

	At December 31,		
	2018	2017	2016
Options to purchase common stock	12,573	11,239	12,270
Unvested restricted common stock	36	149	171
	12,609	11,388	12,441

## Segment Information

We operate in a single reporting segment, the discovery, development and commercialization of RNAi therapeutics. During 2018, all of our net revenues from collaborators were attributed to the U.S. and the majority of our net product revenues were attributed to the U.S. During 2017 and 2016, all of our revenues were attributed to the U.S. and consisted solely of net revenues from collaborators. At December 31, 2018 and 2017, substantially all of our consolidated property, plant and equipment, net was from U.S. operations.

## Recent Accounting Pronouncements

In May 2014, the Financial Accounting Standards Board, or FASB, issued a new revenue recognition standard, which we refer to as the new revenue standard, which amends revenue recognition principles and provides a single, comprehensive set of criteria for revenue recognition within and across all industries. The new revenue standard provides a five-step framework whereby revenue is recognized when control of promised goods or services are transferred to a customer at an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. The new revenue standard also requires enhanced disclosures pertaining to revenue recognition in both interim and annual periods. In August 2015, the FASB deferred the effective date of the new revenue standard from January 1, 2017 to January 1, 2018. In March 2016, the FASB issued amendments to clarify the implementation standard on principal versus agent considerations. In April 2016, the FASB issued amendments to clarify the standard on accounting for licenses of intellectual property and identifying performance obligations. In May 2016, the FASB issued amendments related to collectibility, non-cash consideration, the presentation of sales and other similar taxes collected from customers and transition. The new revenue standard allows for adoption using a full retrospective method or a modified retrospective method. On January 1, 2018, we adopted the new revenue standard by applying the modified retrospective method to all contracts that were not completed as of January 1, 2018. As a result, while reporting periods beginning on our adoption of the new revenue standard are presented under the new revenue standard, prior period amounts have not been adjusted and continue to be presented under the revenue standard in effect prior to January 1, 2018. For contracts that were modified prior to our adoption of the new revenue standard, we reflected the aggregate effect of all modifications that occurred before the beginning of the earliest period presented when identifying performance obligations and allocating the transaction price in accordance with an available practical expedient. Our implementation approach included performing a detailed review of our collaboration agreements not completed as of the transition date. In addition, we designed internal controls to enable the preparation of financial information and have reached conclusions on key accounting assessments related to the new revenue standard, including our assessment that the impact of accounting for costs incurred to obtain a contract is immaterial. There was no impact to cash from or used in operating, financing or investing activities on our consolidated statement of cash flows as a result of the adoption of the new revenue standard.

The following table summarizes the cumulative effect to our consolidated balance sheet upon the adoption of the new revenue standard on January 1, 2018, in thousands:

	Balance at		Balance at
	December		January 1,
	31,		2018
Consolidated Balance Sheet	2017	Adjustments	2018

Deferred revenue, current portion	\$41,705	\$ (34,463 )	\$7,242
Deferred revenue, net of current portion	\$43,075	\$ (33,747 )	\$9,328
Accumulated deficit	\$(2,147,685)	\$ 68,210	\$(2,079,475)

The adoption of the new revenue standard resulted in a cumulative reduction of \$68.2 million of deferred revenue with a corresponding adjustment to the opening balance of accumulated deficit recorded in the first quarter of 2018. This adjustment is due primarily to the application of the new revenue standard to our collaboration agreements with Sanofi Genzyme, MDCO and Kyowa Hakko Kirin Co., Ltd., or Kyowa Hakko Kirin. In addition, as a result of the cumulative reduction in deferred revenue, our corresponding deferred tax asset was reduced by \$13.6 million, which was offset by a corresponding decrease to our valuation allowance. These offsetting adjustments were recorded to our accumulated deficit in the first quarter of 2018.

A substantial portion of the incremental \$68.2 million adjustment is the result of the application of the new revenue standard regarding how entities should measure progress in satisfying performance obligations and the contract's transaction price. In particular, for Sanofi Genzyme and MDCO, the adoption of the new revenue standard resulted in the recognition of previously deferred revenue of \$45.7 million and \$4.5 million, respectively, due to the change in the way we measure our performance under each agreement, from a straight-line method to a cost-to-cost input model. As a result, at January 1, 2018, the balance of remaining deferred revenues was \$3.5 million and \$1.2 million, respectively, related to Sanofi Genzyme and MDCO. In addition, the adoption of the new revenue standard resulted in the recognition of \$15.5 million of previously deferred revenue related to our Kyowa Hakko Kirin agreement. Under the revenue standard in effect at the time that agreement was executed, we had been unable to reasonably estimate our period of performance under the Kyowa Hakko Kirin agreement as we were unable to estimate the timeline of our deliverables related to the fixed-price option granted to Kyowa Hakko Kirin for any additional compounds, an obligation that was bundled with all other deliverables into a single unit of accounting. Under the new revenue standard, two distinct performance

obligations were identified. The first distinct performance obligation included a license to our program targeting respiratory syncytial virus, or RSV, infection, related know-how and updates, manufacturing supply services and joint steering committee services. The second distinct performance obligation included the fixed-price option to a future follow-on compound. We allocated all consideration to the first performance obligation because the second performance obligation was deemed to have a de minimis relative selling price due to its low likelihood of occurring, in part due to our discontinuation of our RSV program. Given this fact pattern, because we do not expect to incur any future costs related to our RSV program, we concluded our performance obligations were complete in the period prior to our adoption of the new revenue standard and therefore, there would not be a future significant reversal of revenue. As a result, we recorded the \$15.5 million of deferred revenue as of December 31, 2017 as an adjustment to the opening balance of our accumulated deficit on January 1, 2018.

In accordance with the new revenue standard requirements, the following tables summarize the impact of adoption on our consolidated balance sheet and consolidated statement of comprehensive loss, in thousands:

	At December 31, 2018		
	Balances		
	Without		
	Adoption of		
		New	Effect of
	As	Revenue	Change
	Reported	Standard	Higher/(Lower)
Consolidated Balance Sheet			
Deferred revenue, current portion	\$3,496	\$3,496	\$ —
Deferred revenue, net of current portion	\$458	\$18,451	\$ (17,993 )
Accumulated deficit	\$(2,840,972)	\$(2,859,049)	\$ (18,077 )

  

	Year Ended December 31, 2018		
	Balances		
	Without		
	Adoption of		
		New	Effect of
	As	Revenue	Change
	Reported	Standard	Higher/(Lower)
Consolidated Statement of Comprehensive Loss			
Net revenues from collaborators	\$62,373	\$112,506	\$ (50,133 )
Net loss	\$(761,497)	\$(711,364)	\$ 50,133
Net loss per common share - basic and diluted	\$(7.57 )	\$(7.07 )	\$ 0.50



The impact of our adoption of the new revenue standard did not have a material impact on the amount of net product revenues recognized during the year ended December 31, 2018.

In January 2016, the FASB issued a new standard on recognition and measurement of financial assets and financial liabilities. The new standard impacts the accounting for equity investments, financial liabilities under the fair value option, and the presentation and disclosure requirements for financial instruments. All equity investments in unconsolidated entities (other than those accounted for under the equity method of accounting) will generally be measured at fair value with changes in fair value recognized through earnings. There is no longer an available-for-sale classification (changes in fair value reported in other comprehensive income (loss)) for equity securities with readily determinable fair values. For equity investments that do not have readily determinable fair values, such as privately issued corporate equity securities, we have elected the measurement alternative. As a result, we will record these investments at cost, less any impairment, and adjust for observable price changes in orderly transactions for identical or similar investments of the same issuer. At December 31, 2018 and December 31, 2017, we did not have material equity investments without readily determinable fair values. In addition, the FASB clarified the need for a valuation allowance on deferred tax assets resulting from unrealized losses on available-for-sale debt securities. In general, the new standard requires modified retrospective application to all outstanding instruments, with a cumulative effect adjustment recorded to opening retained earnings. This standard became effective for us on January 1, 2018. This standard did not have a significant impact on our consolidated financial statements and related disclosures.

In February 2016, the FASB issued a new leasing standard which generally requires lessees to recognize operating and financing lease liabilities and corresponding right-of-use assets on the consolidated balance sheet and to provide enhanced disclosures surrounding the amount, timing and uncertainty of cash flows arising from leasing arrangements. We adopted the new standard on January 1, 2019, using a modified retrospective basis and will not restate comparative periods. Presentation of leases within the consolidated statements of comprehensive loss and consolidated statements of cash flows will be generally consistent with the current lease accounting guidance. We did not elect the package of practical expedients permitted under the transition guidance, however the adoption of the new standard will not change the classification of any of our leases. We elected to combine lease and non-lease components and to keep leases with an initial term of 12 months or less off the consolidated balance sheet and recognize the associated lease payments in the consolidated statements comprehensive loss on a straight-line basis over the lease term. We expect to recognize approximately \$290 million as total lease liabilities and approximately \$230 million as total right-of-use assets on our consolidated balance sheet as of January 1, 2019. The adoption of this standard is not expected to have a significant impact on our consolidated statements of comprehensive loss and consolidated statements of cash flows.

In November 2016, the FASB issued a new standard that requires restricted cash and restricted cash equivalents be included with cash and cash equivalents when reconciling the total beginning and ending amounts for the periods shown on the consolidated statements of cash flows. The new standard became effective for us on January 1, 2018 using a retrospective transition method for each period presented. For the years ended December 31, 2017 and 2016, our restricted cash and restricted cash equivalents were not significant. This standard did not have a significant impact on our consolidated financial statements and related disclosures.

In March 2017, the FASB issued a new standard that amends the amortization period for certain purchased callable debt securities held at a premium by shortening the amortization period for the premium to the earliest call date. The new standard became effective for us on January 1, 2019. This standard did not have a significant impact on our consolidated financial statements and related disclosures.

In March 2018, the FASB issued a new standard to incorporate the U.S. Securities and Exchange Commission, or SEC, Staff Accounting Bulletin No. 118, or SAB 118, which addresses the accounting implications of the Tax Cuts and Jobs Act, or TCJA, enacted on December 22, 2017. SAB 118 allows a company to record provisional amounts during a measurement period not to extend beyond one year of the enactment date and was effective upon issuance. We finalized our assessment of the TCJA during the fourth quarter of 2018, described more fully below at Note 12.

In June 2018, the FASB issued amendments to simplify the accounting for share-based payment awards to nonemployees by aligning the measurement and classification guidance, with certain exceptions, to that for share-based payment awards to employees. The amendments expand the scope of the accounting standard for share-based payment awards to include share-based payment awards granted to non-employees in exchange for goods or services used or consumed in an entity's own operations and supersedes the guidance related to equity-based payments to non-employees. We elected to early adopt these amendments on July 1, 2018. The adoption of these amendments did not have a significant impact on our consolidated financial statements and related disclosures.

In August 2018, the FASB issued amendments that eliminate, add and modify certain disclosure requirements on fair value measurements. The amendments become effective for our fiscal year, including interim periods, beginning January 1, 2020. Early adoption of the amendments, in full or only the provisions that eliminate or modify the disclosure requirements for fair value measurements is permitted. We are currently evaluating the timing of our adoption and the expected impact that these amendments could have on our disclosures.

In August 2018, the SEC issued a final rule amending certain disclosure requirements that were redundant, duplicative, overlapping, outdated or superseded. In addition, the amendments expanded the disclosure requirements on the analysis of stockholders' equity for interim financial statements. Under the amendments, an analysis of changes in each caption of stockholders' equity presented in the consolidated balance sheet must be provided in a note or separate statement. This analysis should present a reconciliation of the beginning balance to the ending balance of each caption in stockholders' equity for each period for which a consolidated statement of comprehensive loss is required to be filed. This final rule became effective on November 5, 2018. However, the SEC issued guidance that they will not object if a company initially presents the changes in stockholders' equity in its first quarterly report for the quarter that begins after the effective date of the final rule. Our adoption of the final rule resulted in the removal of certain duplicative and/or outdated disclosures in this annual report on Form 10-K.

In November 2018, the FASB issued guidance to clarify the interaction between the accounting guidance for collaborative arrangements and revenue from contracts with customers. The amendments become effective for our fiscal year, including interim periods, beginning January 1, 2020. Early adoption, including adoption in any interim period, is permitted. This guidance is required to be applied retrospectively as of the date of our adoption of the new revenue standard on January 1, 2018. We are currently evaluating the timing of our adoption and the expected impact this guidance could have on our consolidated financial statements and related disclosures.

### Subsequent Events

We did not have any material recognized subsequent events. However, we did have the following nonrecognized subsequent event, which is more fully described in Note 10.

In January 2019, we sold an aggregate of 5,000,000 shares of our common stock through an underwritten public offering at a price to the public of \$77.50 per share.

### 3. PRODUCT REVENUES, NET

During the year ended December 31, 2018, we recorded product revenues, net of \$12.5 million, which consisted of commercial sales of ONPATTRO in the U.S. and several countries in Europe.

The following table summarizes balances and activity in each product revenue allowance and reserve category during the year ended December 31, 2018, in thousands, related to sales of ONPATTRO subsequent to its approval by the FDA and EC in August 2018:

	Chargebacks	Rebates	Trade Discounts and Allowances	Returns Reserve	Other Incentives	Total
Beginning balance	\$ —	\$ —	\$ —	\$ —	\$ —	\$ —
Provision related to current						
period sales	1,553	2,528	292	106	551	5,030
Credit or payments made						
during the period	(640 )	—	(74 )	—	(336 )	(1,050)
Total	\$ 913	\$ 2,528	\$ 218	\$ 106	\$ 215	\$ 3,980

### 4. SIGNIFICANT AGREEMENTS

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

Description	Year Ended		
	December 31, 2018	2017	2016
Sanofi Genzyme	\$46,000	\$54,625	\$32,015
Vir Biotechnology	12,778	1,464	—
MDCO	2,789	30,217	11,220
Other	806	3,606	3,924
Total net revenues from collaborators	\$62,373	\$89,912	\$47,159

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

Description	Year Ended		
	December 31,		
	2018	2017	2016
Sanofi Genzyme	\$91,738	\$54,625	\$32,015
Vir Biotechnology	12,778	1,464	—
MDCO	7,184	30,217	11,220
Other	806	3,606	3,924
Total net revenues from collaborators	\$112,506	\$89,912	\$47,159

The following table presents the balance of our contract liabilities related to our collaboration agreements at December 31, 2018 and January 1, 2018, in thousands:

	At December 31, 2018	At January 1, 2018
Contract liabilities:		
Deferred revenues	\$ 3,954	\$16,570

During the year ended December 31, 2018, we recognized the following revenues as a result of the change in the contract liability balances related to our collaboration agreements, in thousands:

Revenue recognized in the period from:	Year Ended
	December 31, 2018
Amounts included in contract liability at the beginning of the period	\$ 16,570

The following table provides the research and development expenses incurred by type that are directly attributable to our collaboration agreements by collaboration partner for the periods indicated, in thousands:

	Year Ended December 31,				2017				2016			
	2018		Sanofi		Sanofi		MDCO		Sanofi		Ionis	
	Genzyme	Vir	MDCO	Ionis	Genzyme	Vir	MDCO	Ionis	Genzyme	Vir	MDCO	Ionis
Research and development												
Clinical trial and manufacturing	\$36,600	\$7,272	\$1,664	\$—	\$174,901	\$1,134	\$5,421	\$—	\$150,179	\$—	\$1,211	\$—
External services	5,340	8,251	2	2,150	4,475	926	—	3,250	7,366	—	—	—
Other	1,279	548	203	1,097	5,327	—	106	—	3,035	—	64	525
Total research and development expenses	\$43,219	\$16,071	\$1,869	\$3,247	\$184,703	\$2,060	\$5,527	\$3,250	\$160,580	\$—	\$1,275	\$525

The research and development expenses incurred for each agreement listed in the table above consist of costs incurred for external development and manufacturing services for which we are reimbursed, licensing payments made to the counterparty to such agreement and costs directly attributable to Sanofi Genzyme transition services. In addition, these expenses include a reasonable estimate of compensation and related costs as billed to our counterparties. As part of our revenue recognition policy adopted January 1, 2018, the costs in the above table are considered an input in our determination of transaction price when they relate to consideration received for the delivery of goods or services. For the years ended December 31, 2018, 2017 and 2016, we did not incur material selling, general and administrative expenses related to our significant agreements.

#### Product Alliances

##### Sanofi Genzyme Collaboration

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, referred to as the 2014 Sanofi Genzyme collaboration. The 2014 Sanofi Genzyme collaboration superseded and replaced the previous collaboration between us and Sanofi Genzyme entered into in October 2012 to develop and commercialize RNAi therapeutics targeting TTR for the treatment of hereditary ATTR amyloidosis, including patisiran and revusiran, in Japan and the Asia-Pacific region.

On January 6, 2018, we and Sanofi Genzyme entered into an amendment to our 2014 Sanofi Genzyme collaboration. In connection and simultaneously with entering into the amendment to the 2014 Sanofi Genzyme collaboration, we and Sanofi Genzyme also entered into the Exclusive TTR License and the AT3 License Terms. As a result, we have the exclusive right to pursue the further global development and commercialization of all TTR products, including ONPATTRO, vutrisiran and any back-up products, and Sanofi Genzyme has the exclusive right to pursue the further global development and commercialization of fitusiran and any back-up products.

The January 2018 transaction was subject to customary closing conditions and clearances, including clearance under the Hart-Scott-Rodino Antitrust Improvements Act, and closed during the first quarter of 2018.

#### 2012 Sanofi Genzyme Agreement

Under the 2012 Sanofi Genzyme agreement, Sanofi Genzyme paid us an upfront cash payment of \$22.5 million. We were also entitled to receive certain milestone payments under the 2012 Sanofi Genzyme agreement. In the fourth quarter of 2013, we earned \$11.0 million in patisiran development milestones under the 2012 Sanofi Genzyme agreement.

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

2014 Sanofi Genzyme Collaboration, as amended in January 2018

In January 2014, we entered into the 2014 Sanofi Genzyme collaboration. As noted above, the 2014 Sanofi Genzyme collaboration superseded and replaced the 2012 Sanofi Genzyme agreement and was amended in January 2018, at which time we also entered into the Exclusive TTR License and the AT3 License Terms.

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 Proof-of-Principle Study Completion (as defined in the Sanofi Genzyme master agreement), or Human POP, by the end of 2019, subject to extension to the end of 2021 in various circumstances. We will retain product rights in the U.S., 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 worldwide rights for one product. Sanofi Genzyme's rights under the 2014 Sanofi Genzyme collaboration, described in detail below, are structured as an opt-in that is triggered upon achievement of Human POP. We maintain development control for all programs prior to Sanofi Genzyme's opt-in and maintain development and commercialization control after Sanofi Genzyme's opt-in for all programs in the Alnylam Territory. We will retain global rights to any RNAi therapeutic Genetic Medicine program that does not reach Human POP by the end of 2019, subject to certain limited exceptions. We retain full rights to all current and future RNAi therapeutic programs outside of the field of Genetic Medicines, including the right to form new collaborations.

Under the 2014 Sanofi Genzyme collaboration, Sanofi Genzyme's specific license rights and the programs which Sanofi Genzyme opted into prior to the 2018 amendment include the following:

**Regional license terms and programs** — Upon opt-in, we will retain product rights in the Alnylam Territory, while Sanofi Genzyme will obtain exclusive rights to develop and commercialize the product in the Sanofi Genzyme Territory. Sanofi Genzyme can elect this license for any of our current and future Genetic Medicine programs that complete Human POP by the end of 2019, subject to limited extension. Development costs for products once Sanofi Genzyme exercises an option will be shared between Sanofi Genzyme and us, with Sanofi Genzyme responsible for twenty percent of the global development costs. Sanofi Genzyme will be required to make payments totaling up to \$75.0 million per regional product, consisting of up to \$55.0 million in development milestones and \$20.0 million in commercial milestones. Sanofi Genzyme will also be required to pay tiered double-digit royalties up to twenty percent for each regional product based on annual net sales, if any, of such regional product by Sanofi Genzyme, its affiliates and sublicensees. Upon the effective date of the 2014 Sanofi Genzyme collaboration, Sanofi Genzyme expanded the scope of its regional license and collaboration for patisiran, which was originally established under the 2012 Sanofi Genzyme agreement. In September 2015, Sanofi Genzyme elected to opt into our fitusiran clinical development program for the treatment of hemophilia and other rare bleeding disorders under the regional license terms. Cost-sharing for the fitusiran program began in January 2016 under the regional license terms. Sanofi Genzyme also had the right to elect to co-develop and co-commercialize fitusiran in the Alnylam Territory pursuant to the co-development/co-commercialize license terms described below. In November 2016, Sanofi Genzyme exercised that right and elected to co-develop and co-commercialize fitusiran in the Alnylam Territory. In addition, during 2016, Sanofi Genzyme elected not to opt into the development and commercialization of givosiran or cemisiran in the Sanofi Genzyme Territory.

Sanofi Genzyme's rights with respect to patisiran and fitusiran were modified in connection with the 2018 amendment, the Exclusive TTR License and the AT3 License Terms, as described below. Sanofi Genzyme continues to have the right to opt into our future rare genetic disease programs for development and commercialization in the Sanofi Genzyme Territory under the regional license terms.



Co-development/co-commercialize license terms and programs — Upon opt-in, we retained product rights in the Alnylam Territory, while Sanofi Genzyme obtained exclusive rights to develop and commercialize the product in the Sanofi Genzyme Territory, and to co-commercialize the product in the Alnylam Territory. Upon the effective date of the 2014 Sanofi Genzyme collaboration, Sanofi Genzyme expanded its regional rights for revusiran, which were originally granted under the 2012 Sanofi Genzyme agreement, to include a co-development/co-commercialize license and collaboration. In October 2016, we decided to discontinue development of revusiran. In our TTR program, we are also developing vutrisiran. Sanofi Genzyme had a right to elect a co-development/co-commercialize license for vutrisiran. As noted above, in November 2016, Sanofi Genzyme exercised its right to elect a co-development/co-commercialize license for fitusiran. Development costs for co-development/co-commercialize products, once Sanofi Genzyme exercised an option, were shared between Sanofi Genzyme and us, with Sanofi Genzyme responsible for fifty percent of the global development costs. In connection with the exercise of its co-development/co-commercialize rights for fitusiran, Sanofi Genzyme paid us approximately \$6.0 million in January 2017 for its incremental share of co-development costs incurred from January 2016 through September 2016. Sanofi Genzyme was required to make certain milestone payments for fitusiran, and, prior to the discontinuation of the revusiran program, was required to make certain milestone payments for

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revusiran. In December 2014, we earned a development milestone payment of \$25.0 million based upon the initiation of the first global Phase 3 clinical trial for revusiran. Sanofi Genzyme was also obligated to pay us a milestone of \$25.0 million upon the dosing of the first patient in our ATLAS Phase 3 program for fitusiran. In addition, Sanofi Genzyme was required to pay tiered double-digit royalties up to twenty percent for each co-development/co-commercialize product based on annual net sales, if any, in the Sanofi Genzyme Territory for such co-development/co-commercialize product by Sanofi Genzyme, its affiliates and sublicensees. The parties were to share profits equally and we expected to book product sales in the Alnylam Territory.

In connection with the 2018 amendment, the Exclusive TTR License and the AT3 License Terms, as described below, we and Sanofi Genzyme agreed to terminate the co-development and co-commercialization rights related to revusiran, vutrisiran and fitusiran under the 2014 Sanofi Genzyme collaboration. No future rights will be granted to Sanofi Genzyme for co-development and co-commercialization under the 2014 Sanofi Genzyme collaboration, as amended by the 2018 amendment.

Global license terms and programs — Sanofi Genzyme continues to have one right to a global license through 2019, subject to limited extension, for a future Genetic Medicine program that was not one of our defined Genetic Medicine programs as of the effective date of the 2014 Sanofi Genzyme collaboration. Upon opt-in, Sanofi Genzyme will obtain a worldwide license to develop and commercialize the product. Sanofi Genzyme shall be responsible for one hundred percent of global development costs for a global license product. Sanofi Genzyme will be required to make payments totaling up to \$200.0 million for such global product, including up to \$100.0 million in development milestones and \$100.0 million in commercial milestones. Sanofi Genzyme will also be required to pay tiered double-digit royalties up to twenty percent for such global product based on annual net sales, if any, of each global product by Sanofi Genzyme, its affiliates and sublicensees. During the first quarter of 2018, Sanofi Genzyme elected not to exercise its global option for our lumasiran program.

Exclusive TTR License and AT3 License Terms

As noted above, the 2018 amendment, together with the Exclusive TTR License and the AT3 License Terms, revise the terms and conditions of the 2014 Sanofi Genzyme collaboration to (i) provide us the exclusive right to pursue the further global development and commercialization of all TTR products, including ONPATTRO, vutrisiran and any back-up products, (ii) provide Sanofi Genzyme the exclusive right to pursue the further global development and commercialization of fitusiran and any back-up products and (iii) terminate the previous co-development and co-commercialization rights related to revusiran, vutrisiran and fitusiran under the 2014 Sanofi Genzyme collaboration. Going forward, we are funding all development and commercialization costs for ONPATTRO and vutrisiran. We also funded development and commercialization costs for fitusiran through the transition period, up to a cap of \$50.0 million, after which Sanofi Genzyme became responsible for funding all development and commercialization costs for fitusiran. We completed the transition period relating to the transition of the fitusiran program to Sanofi Genzyme in 2018. Each party was responsible for its costs associated with the transfer of the respective program to the other party.

Under the 2018 amendment and the Exclusive TTR License, Sanofi Genzyme will be eligible to receive (i) royalties up to twenty-five percent, increasing over time, based on annual net sales of ONPATTRO in territories excluding the U.S., Canada and Western Europe, provided royalties on annual net sales of ONPATTRO in Japan will be twenty-five percent beginning as of the effective date of the Exclusive TTR License, (ii) tiered royalties of fifteen to thirty percent based on global annual net sales of vutrisiran (consistent with the royalties due to us from Sanofi Genzyme on fitusiran), and (iii) tiered royalties of up to fifteen percent based on global annual net sales of any back-up products, in each case by us, our affiliates and our sublicensees. Except as described below, there will be no additional milestones due to either party with respect to ONPATTRO, vutrisiran or fitusiran.

In consideration for the rights granted to Sanofi Genzyme under the 2018 amendment and the AT3 License Terms, Sanofi Genzyme was required to make one milestone payment of \$50.0 million following the dosing of the first

patient in the ATLAS Phase 3 program for fitusiran. This milestone was achieved in the first quarter of 2018. In addition, we will be eligible to receive tiered royalties of fifteen to thirty percent based on global annual net sales of fitusiran and up to fifteen percent based on global annual net sales of any back-up products, in each case by Sanofi Genzyme, its affiliates and its sublicensees. We intend to continue to work with Sanofi Genzyme to ensure continuity for the supply of fitusiran for ongoing clinical studies, and, at Sanofi Genzyme's request, commercial sales. Sanofi Genzyme also has the right to manufacture fitusiran.

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 Sanofi Genzyme under the 2014 Sanofi Genzyme collaboration, as amended, or any royalty payments under the AT3 License Terms.

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The 2014 Sanofi Genzyme collaboration, as amended, will continue to be governed by an alliance joint steering committee that is comprised of an equal number of representatives from each party. Additional committees manage various aspects of each regional and global program and oversee certain matters that may arise under the Exclusive TTR License and the AT3 License Terms.

The original master agreement (including the license terms appended thereto), as well as the Exclusive TTR License and the AT3 License Terms, contain certain termination provisions, including for material breach by the other party. In addition, we have the right to terminate Exclusive TTR License without cause with respect to any or all licensed products at any time upon six months' prior written notice and Sanofi Genzyme has the right to terminate the AT3 License Terms without cause with respect to any particular licensed product at any time upon six months' prior written notice.

Unless terminated earlier pursuant to its terms, the master agreement will terminate upon the last to expire of any of the option periods under the master agreement or the license terms appended thereto. The term of the Exclusive TTR License expires on a licensed product-by-licensed product and country-by-country basis upon expiration of the last royalty term to expire under the agreement, where a royalty term is defined as the latest to occur of (a) expiration of the last valid claim of patent rights covering a licensed product; (b) the expiration of Regulatory Exclusivity for a licensed product, as defined in the Exclusive TTR License; or (c) the twelfth anniversary of the first commercial sale of the licensed product in such country. The term of the AT3 License Terms expires on a licensed product-by-licensed product and country-by-country basis upon expiration of the last royalty term to expire under the agreement, where a royalty term is defined as the latest to occur of (x) the expiration of the last valid claim of patent rights covering a licensed product; (y) the expiration of Regulatory Exclusivity for a licensed product, as defined in the AT3 License Terms; or (z) the twelfth anniversary of the first commercial sale of the licensed product in such country.

As noted above, the Sanofi Genzyme collaboration originally entered into in 2012 was materially modified during its term when the agreement was amended in 2014, prior to our adoption of the new revenue standard on January 1, 2018. In accordance with the new revenue standard, we evaluated the Sanofi Genzyme collaboration with the aggregate effect of all modifications when identifying performance obligations, determining the transaction price and allocating the transaction price. We determined that certain promises included in these agreements are within the scope of the new revenue standard since Sanofi Genzyme is a customer with respect to the license of the rights to its territories. We also determined, however, that certain aspects of these agreements are within the scope of the collaboration accounting guidance with respect to co-commercialization activities as these activities are joint risk-sharing and are not reflective of a vendor-customer relationship. We apply the new revenue standard to all promises associated with the transfer of goods and services to a customer.

We concluded that Sanofi Genzyme meets the definition of a customer as we were delivering intellectual property and know-how rights as well as research and development activities for the TTR programs and fitusiran programs in support of territories in which we are not jointly sharing the risks and rewards. We concluded that the accounting for the original 2014 Sanofi Genzyme collaboration, and the collaboration, as amended, should be assessed as separate contracts for (i) the patisiran and revusiran (TTR) programs, upon the initiation of the 2014 Sanofi Genzyme collaboration, and (ii) the subsequent opt-in by Sanofi Genzyme for the fitusiran program. In addition, we determined that the Sanofi Genzyme collaboration met the requirements to be accounted for as a contract, including that it is probable that we will collect the consideration to which we are entitled in exchange for the goods or services that will be delivered to Sanofi Genzyme. We identified contract promises or deliverables for licenses to our intellectual property and know-how rights, associated development activities, joint steering committee participation and information exchange. We determined that, pursuant to the new revenue standard (and consistent with our accounting prior to the adoption of the new revenue standard), the performance obligations were not separately identifiable and were not distinct (and did not have standalone value) due to the specialized nature of the services to be provided by us and the dependent relationship between the performance obligations. Given this fact pattern, we concluded each of the

TTR and fitusiran contracts have a single identified or combined performance obligation.

When applying the previous revenue standard, we determined that the co-commercialization activities prior to the 2018 amendment were within the scope of the collaboration accounting standard since both parties would actively participate in the co-commercialization and be subject to significant risks and rewards. As a result of this determination, we recorded any payments or cash receipts for these joint risk-sharing activities as an adjustment to the related operations expense captions. The amounts recorded as a reduction of our selling, general and administrative activities were not material.

The transaction price as of January 1, 2018 of \$127.6 million for the 2014 Sanofi Genzyme collaboration related to the license to the TTR programs included the \$22.5 million upfront payment and \$11.0 million of development milestone payments earned under the now superseded 2012 Sanofi Genzyme agreement, a \$25.0 million development milestone payment for revusiran achieved in 2014, the estimated patisiran and revusiran cost-share reimbursements, net of payments to Sanofi Genzyme, of \$63.6 million and \$57.0 million, respectively, and the \$51.5 million equity discount related to the stock purchase agreement, described below. Since the fair value of the stock at the time of closing was more than the consideration received by us by \$51.5 million, we reduced the transaction price of the license and collaboration contract, treating the equity discount in a manner consistent with a payment to the

customer. The transaction price related to our license to the fitusiran program as of January 1, 2018, accounted for as a separate agreement, included estimated fitusiran development cost-share reimbursements of \$147.3 million, net of payments to Sanofi Genzyme. There are no refund provisions in the agreement and, therefore, none of the consideration received to date has been excluded from the transaction price calculation. None of the unearned milestones as of January 1, 2018 were included in the transaction price, as all unearned milestone amounts were not considered likely of achievement. We considered several factors, including that achievement of the milestones is outside our control and contingent upon success in clinical trials and regulatory decisions and the licensee's efforts. Any consideration related to sales-based royalties (including milestones) will be recognized when the related sales occur as they were determined to relate predominantly to the license granted to Sanofi Genzyme and as a result have also been excluded from the transaction price.

We allocated the transaction price to the combined performance obligation. We have determined that this combined performance obligation is satisfied over time based on our performance that is creating or enhancing an asset that Sanofi Genzyme controls. In this instance, Sanofi Genzyme received control over the asset, or the licensed intellectual property, and know-how, at the time the contract was executed since the licensed intellectual property and know-how meet the definition of functional intellectual property per the new revenue standard, which defines functional intellectual property as intellectual property that derives a substantial portion of its utility from its standalone functionality rather than the entity's ongoing activities (thus, once the asset is fully developed, our ongoing involvement is not required for the licensee to derive value). The other promises included in the performance obligation, however, are enhancing the controlled asset, and thus the combined performance obligation is being satisfied over time.

The new revenue standard requires a single method of measuring performance for each performance obligation satisfied over time. Since we do not have a reliable method of estimating progress based upon its outputs, it was determined that the most reliable method of estimating progress would be using a cost-to-cost input method. We have determined that our completion of certain clinical and regulatory development tasks is relevant and directly related to our progress in completing the combined performance obligation. As such, we measured our progress upon adoption and will continue to measure our progress during each reporting period based upon the amount of development costs incurred divided by the total amount of development costs expected to be incurred over the course of the agreement. We exclude costs that are not related to our completion of this performance obligation, such as the completion of tasks (and incurring of costs) associated with the marketing and commercialization of the drug. We estimated our internal costs during the last three years, excluding non-reimbursable costs that were not deemed to directly relate to the delivery of the development services to Sanofi Genzyme. Historically, we have been unable to reliably measure our performance based upon our lack of historical experience in completing the development of a drug candidate and have, as a result, defaulted to straight-line attribution for many of our licensing agreements. At the time of adoption of the new revenue standard, however, we have completed a substantial portion of our development obligations and determined we have sufficient information to estimate the remaining development costs for the fitusiran program and sufficient experience to reasonably estimate our development costs.

We determined that the 2018 amendment, together with the Exclusive TTR License and the AT3 License Terms, referred to as the 2018 restructured agreement, are included in the scope of the modification provisions of the new revenue standard. We had identified that the agreement for the TTR programs under the 2014 Sanofi Genzyme collaboration should be accounted for separately from any subsequent option exercises, including with respect to fitusiran. Therefore, we concluded it is appropriate to account for the 2018 restructured agreement as two separate modifications to the 2014 Sanofi Genzyme collaboration: one related to the TTR programs and one related to the fitusiran program. Our conclusions related to scoping under the prior revenue standard are consistent with the new revenue standard.

As noted above, the 2018 amendment, together with the Exclusive TTR License, provide us with the exclusive right to pursue the further global development and commercialization of all TTR products, including ONPATTRO. We are responsible for all development and commercialization costs for ONPATTRO and vutrisiran. As of the 2018 restructured agreement, we are no longer required to complete the delivery of any of the performance obligations under the agreement related to the TTR programs. As a result, the transaction price prior to the 2018 amendment has been reduced as we are no longer entitled to cost-share reimbursements or any of the previously constrained consideration, such as milestones and royalties. Since the 2018 amendment affected the transaction price but did not add any incremental and distinct performance obligations, we concluded this amendment should be accounted for as a change to the existing agreement and recorded the revenue on a cumulative catch-up basis. At the time of the 2018 amendment, we had \$2.9 million in revenue deferred as a contract liability on our consolidated balance sheet related to this contract for TTR programs, all of which we recognized in the first quarter of 2018 under a cost-to-cost input model as we no longer expected to incur costs associated with the delivery of goods or services. If we had not adopted the new revenue standard, at the time of the 2018 restructured agreement, we would have had \$25.8 million of deferred revenues on our consolidated balance sheet that would have been recognized in full upon the date of the 2018 restructured agreement as we would have similarly concluded there were no ongoing deliverables under the 2018 restructured agreement related to the TTR programs. We expect to record future royalties payable to Sanofi Genzyme with respect to any sales of ONPATTRO within cost of goods sold on our consolidated statements of comprehensive loss as Sanofi Genzyme is no longer considered our customer after the 2018 restructured agreement for sales of all TTR products, including ONPATTRO, and as such, these royalty payments are outside of the scope of the new revenue standard, including with respect to principal versus agent guidance.

The 2018 amendment, together with the AT3 License Terms, as noted above, provide Sanofi Genzyme the exclusive right to pursue the further global development and commercialization of fitusiran and any back-up products and terminates the previous co-development and co-commercialization rights related to fitusiran under the 2014 Sanofi Genzyme collaboration. The 2018 restructured agreement provides a broader license that permits global development, manufacturing and commercialization, and we were required to facilitate the transfer of all ongoing activities, contracts, intellectual property, know-how and other materials and information related to fitusiran to Sanofi Genzyme.

In connection with the 2018 restructured agreement for fitusiran, we funded development and commercialization costs for fitusiran through the transition period, which was completed in 2018, up to a limit of \$50.0 million. The only milestone under the 2018 restructured agreement, which was achieved in the first quarter of 2018, was considered variable consideration for the license and transition services related to the fitusiran program. We agreed to reimburse Sanofi Genzyme for certain transition activities that are reflected as a reduction in the transaction price. As a result, the transaction price has been reduced as we are no longer entitled to cost-share reimbursements or any of the previously constrained consideration, such as milestones and royalties.

We concluded that the modification that resulted from the 2018 restructured agreement related to fitusiran would be treated as a termination and replacement of the 2014 Sanofi Genzyme collaboration and accounted for prospectively as the remaining license and transition services are considered distinct from that under the agreement prior to this modification. However, the incremental consideration under the 2018 restructured agreement does not directly reflect the standalone selling price of the incremental performance obligation. Therefore, we concluded the 2018 restructured agreement for fitusiran should be accounted for on a prospective basis. At the time of the 2018 amendment, we had \$0.6 million in revenue deferred as a contract liability on our consolidated balance sheet related to the 2014 Sanofi Genzyme collaboration for the fitusiran program. The transaction price of the 2018 restructured agreement for fitusiran is \$37.6 million, primarily related to the \$50.0 million milestone that was achieved in the first quarter of 2018, offset by consideration paid to Sanofi Genzyme for its transition activities that were accounted for as a reduction of the transaction price. Consistent with our accounting prior to this 2018 modification, we are applying the sales-based royalty under the new revenue standard to exclude from the transaction price the royalties earned on Sanofi Genzyme's sales of fitusiran as we have determined in the context of all the performance obligations, including those delivered prior to the 2018 modification, that the value of the broader license will continue to represent a substantial portion of the value provided to Sanofi Genzyme; and therefore the license to the intellectual property is the predominant item to which the royalty relates.

We have determined that Sanofi Genzyme's right to purchase additional clinical and commercial material from us reflects optional purchases that are distinct from other performance obligations. Revenues associated with these purchases will be recognized in accordance with the right to invoice practical expedient and as Sanofi Genzyme obtains control of any purchased material.

We recognized the transaction price of the 2018 restructured agreement related to fitusiran under a separate cost-to-cost input model as we performed transition services over the transition period, which was completed in 2018. We measured our performance based on a percentage of our costs expected to be incurred in connection with the transition. During the transition, we incurred a total cost of \$38.0 million. During the year ended December 31, 2018, under a cost-to-cost input model, we recognized revenues of \$37.6 million related to the 2018 restructured agreement for fitusiran. If we had not adopted the new revenue standard, at the time of the 2018 restructured agreement, we would have had \$23.4 million of deferred revenues on our consolidated balance sheet, that would have represented an incremental \$22.8 million to the transaction price. Similar to under the new revenue standard, we consider the 2018 restructured agreement related to fitusiran to include a combined performance obligation. Under the prior revenue standard and our historical practice to account for contract modifications, we would apply a separate model to the consideration. Historically, we have measured our performance under our models based on the passage of time due to



our inability to estimate performance under another method. However, as a result of the 2018 restructured agreement related to fitusiran, we have the ability to measure our performance under the prior revenue standard based on costs expected to be incurred, and therefore measure performance under the prior standard consistent with that of the new revenue standard. Under the prior revenue standard, we would have recorded revenues of \$60.3 million in the year ended December 31, 2018 related to fitusiran.

We determined that the opt-in rights that Sanofi Genzyme continues to have for future Genetic Medicine programs represent separate and additional optional purchases that Sanofi Genzyme may receive from us in future periods.

#### Accounting for Equity Purchases in Connection with our 2014 Sanofi Genzyme Collaboration

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. Under the investor agreement, until the earlier of the fifth anniversary of the expiration or earlier termination of the 2014 Sanofi Genzyme collaboration and the date on which Sanofi Genzyme and its affiliates cease to beneficially own at least 5 percent of our outstanding common stock, Sanofi Genzyme and its affiliates are bound by certain “standstill” provisions. The standstill provisions include agreements not to acquire more than 30 percent of our outstanding

common stock, call stockholder meetings, nominate directors other than those approved by our board of directors, subject to certain limited exceptions, or propose or support a proposal to acquire us. Further, Sanofi Genzyme has agreed to vote, and cause its affiliates to vote, all shares of our voting securities they are entitled to vote, up to a maximum of 20 percent of our outstanding common stock, in a manner either as recommended by our board of directors or proportionally with the votes cast by our other stockholders, except with respect to certain change of control transactions or our liquidation or dissolution. Until Sanofi Genzyme owns less than 7.5 percent of our outstanding common stock, subject to Sanofi Genzyme's limited right to maintain its ownership percentage as described below, if we issue common stock or securities convertible into or exercisable for common stock to a third party that holds at least 30 percent of our outstanding common stock or, in connection with a collaboration or license transaction, to a third party that will initially hold at least the percentage of our outstanding common stock represented by the shares purchased by Sanofi Genzyme at the closing of the equity transaction, we will offer Sanofi Genzyme an opportunity to amend the standstill and voting provisions in the investor agreement to be consistent with the terms provided to such third party.

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

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

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

We recorded the issuance of 8,766,338 shares of our common stock under the stock purchase agreement using the price of our common stock on the date the shares were issued to Sanofi Genzyme. Based on the common stock price of \$85.72, the fair value of the shares issued was \$751.5 million, which was \$51.5 million in excess of the proceeds received from Sanofi Genzyme for the issuance of our common stock. This \$51.5 million has been reflected as a reduction of the transaction price for the TTR programs. In addition, due to intraperiod tax allocation rules, upon closing of the equity transaction we recorded a benefit from income taxes of \$15.2 million due to the Sanofi Genzyme equity purchase being recorded in additional paid-in capital, net of tax.

In accordance with the investor agreement, as a result of our issuance of shares in connection with our acquisition of Sirna Therapeutics, Inc. in March 2014, Sanofi Genzyme exercised its right to purchase an additional 344,448 shares of our common stock for \$23.0 million. In addition, in connection with our public offerings, Sanofi Genzyme exercised its right to purchase directly from us, in concurrent private placements, 744,566 shares of common stock in January 2015 at the public offering price resulting in \$70.7 million in proceeds to us and 297,501 shares of common stock in May 2017 at the public offering price resulting in \$21.4 million in proceeds to us. The sales of common stock to Sanofi Genzyme were not registered as part of these public offerings, though they were consummated simultaneously with the public offering.

Sanofi Genzyme also has the right at the beginning of each year to purchase a number of shares of our common stock based on the number of shares we issued during the previous year for compensation-related purposes. Sanofi Genzyme exercised this right to purchase directly from us 196,251 shares of our common stock in January 2015 for \$18.3 million and 205,030 shares of our common stock in February 2016 for \$14.3 million. The sales of these shares to Sanofi Genzyme were consummated as private placements.

As of December 31, 2018, Sanofi Genzyme held approximately ten percent of our outstanding common stock.

We applied the guidance in the equity accounting standard for the stock purchase arrangement since the sale of our equity is not part of our ordinary activities and, therefore, does not qualify as a contract with a customer that is within the scope of the new revenue standard.

#### The Medicines Company Alliance

In February 2013, we and MDCO entered into a license and collaboration agreement pursuant to which we granted to MDCO an exclusive, worldwide license to develop, manufacture and commercialize RNAi therapeutics targeting proprotein convertase subtilisin/kexin type 9, or PCSK9, for the treatment of hypercholesterolemia and other human diseases, including inclisiran. MDCO paid us an upfront cash payment of \$25.0 million. Upon achievement of certain events, we will be entitled to receive milestone payments, up to an aggregate of \$180.0 million, including up to \$30.0 million in specified development milestones, \$50.0 million in specified regulatory milestones and \$100.0 million in specified commercialization milestones. In addition, we will be entitled to royalties ranging from the low- to high-teens based on annual worldwide net sales, if any, of licensed products by MDCO, its affiliates and sublicensees, subject to reduction under specified circumstances. To date, we have earned two development milestones totaling \$30.0 million under the MDCO agreement. We could potentially earn the next development milestone payment of \$25.0 million based upon regulatory approval of an NDA for inclisiran in the U.S. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any additional milestone payments or any royalty payments from MDCO.

Under the MDCO agreement, we had responsibility for the development of inclisiran until Phase 1 Completion, as defined in the MDCO agreement, at our cost, up to an agreed upon initial development cost cap. In late 2015, MDCO assumed responsibility for all development and commercialization of inclisiran, at its sole cost. The collaboration between us and MDCO is governed by a joint steering committee comprised of an equal number of representatives from each party.

We were solely responsible for obtaining supply of finished product reasonably required for the conduct of our obligations under the initial development plan through Phase 1 Completion, and for supplying MDCO with finished product reasonably required for the first Phase 2 clinical trial of inclisiran conducted by MDCO, at our expense, subject to certain caps. In April 2016, we and MDCO entered into a supply and technical transfer agreement to provide for our supply of inclisiran to MDCO, in accordance with the terms of the MDCO agreement. MDCO now has the sole right and responsibility to manufacture and supply inclisiran for development and commercialization under the MDCO development plan, subject to the terms of the MDCO agreement and the supply and technical transfer agreement.

Unless terminated earlier in accordance with the terms of the agreement, the MDCO agreement expires on a licensed product-by-licensed product and country-by-country basis upon expiration of the last royalty term for any licensed product in any country, where a royalty term is defined as the latest to occur of (1) the expiration of the last valid claim of patent rights covering a licensed product, (2) the expiration of the Regulatory Exclusivity, as defined in the MDCO agreement, and (3) the twelfth anniversary of the first commercial sale of the licensed product in such country. We estimate that our fundamental RNAi patents covering licensed products under the MDCO agreement will expire both in and outside of the U.S. generally between 2016 and 2028. We also estimate that our inclisiran product-specific patents covering licensed products under the MDCO agreement in the U.S. and elsewhere will expire at the end of 2033. These patent rights are subject to potential patent term extensions and/or supplemental protection certificates extending such terms in countries where such extensions may become available. In addition, more patent filings relating to the collaboration may be made in the future.

Either party may terminate the MDCO agreement in the event the other party fails to cure a material breach or upon patent-related challenges by the other party. In addition, MDCO has the right to terminate the agreement without

cause at any time upon four months' prior written notice.

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

In accordance with the new revenue standard, we evaluated the MDCO agreement and concluded that MDCO meets the definition of a customer and that the MDCO agreement is a contract. We determined the transaction price, identified the performance obligations and allocated the transaction price to each performance obligation. We also determined that substantially all of our performance obligations are within the scope of the new revenue standard as they relate to the delivery of goods and services to a customer for that customer's use in monetizing an asset. Specifically, we concluded that MDCO meets the definition of a customer as we are delivering intellectual property and know-how rights as well as research and development activities. In addition, we determined that the MDCO agreement met the requirements to be accounted for as a contract, including that it is probable that we will collect the

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consideration to which we are entitled in exchange for the goods or services that will be delivered to MDCO. We identified contract promises or deliverables for licenses to our intellectual property development and manufacturing know-how rights, associated development activities, joint steering committee participation and information exchange. In connection with the supply and technical transfer agreement, we assessed the new revenue standard to conclude if this modification should be accounted for as a separate contract or as a modification to the existing contract. We determined that the modification should not be treated as a separate agreement as the related performance obligations are not distinct as the value produced by these promises are highly dependent on the other promises in the contract. We determined that, pursuant to the new revenue standard (and consistent with our accounting prior to the adoption of the new revenue standard), the performance obligations were not separately identifiable and were not distinct (and did not have standalone value) due to the specialized nature of the services to be provided by us and the dependent relationship between the performance obligations. Given this fact pattern, we have concluded the MDCO agreement has a single identified or combined performance obligation.

The transaction price as of January 1, 2018 of \$72.9 million for the MDCO agreement included the \$25.0 million upfront payment, \$30.0 million of development milestones and \$17.9 million of cost reimbursement. There are no refund provisions in the MDCO agreement and, therefore, none of the consideration received to date has been excluded from the transaction price calculation. None of the unearned milestones as of January 1, 2018 were included in the transaction price, as all unearned milestone amounts were not considered likely of achievement. We considered several factors, including that achievement of the milestones is outside our control and contingent upon success in clinical trials and regulatory decisions and the licensee's efforts. Any consideration related to sales-based royalties (including milestones) will be recognized when the related sales occur as they were determined to relate predominantly to the license granted to MDCO and as a result have also been excluded from the transaction price.

Under the previous accounting standard, the initial upfront payment of \$25.0 million from MDCO was initially recorded as deferred revenue. During the fourth quarter of 2014, we recognized as revenue a portion of the \$10.0 million milestone payment earned in December 2014 equal to the percentage of the performance period completed when the milestone was earned. During the fourth quarter of 2017, we recognized as revenue a portion of the \$20.0 million milestone payment earned in November 2017 equal to the percentage of the performance period completed when the milestone was earned.

We allocated the transaction price to the combined performance obligation. We have determined that this combined performance obligation is satisfied over time based on our performance that is creating or enhancing an asset that MDCO controls. In this instance, MDCO received control over the asset, or the licensed intellectual property, and know-how, at the time the contract was executed since the licensed intellectual property and know-how meet the definition of functional intellectual property per the new revenue standard, which defines functional intellectual property in that it derives a substantial portion of its utility from its standalone functionality rather than the entity's ongoing activities (thus, once the asset is fully developed, our ongoing involvement is not required for the licensee to derive value). The other promises included in the performance obligation, however, are enhancing the controlled asset, and thus the combined performance obligation is being satisfied over time.

The new revenue standard requires a single method of measuring performance for each performance obligation satisfied over time. Since we do not have a reliable method of estimating progress based upon its outputs, it was determined that the most reliable method of estimating progress would be using a cost-to-cost input method. We have determined that our completion of certain clinical and regulatory development tasks is relevant and directly related to our progress in completing the combined performance obligation. As such, we measured our progress upon adoption and will continue to measure our progress during each reporting period based upon the amount of development costs incurred divided by the total amount of development costs expected to be incurred over the course of the agreement. We exclude costs that are not related to our completion of this performance obligation, such as the completion of tasks (and incurring of costs) associated with the marketing and commercialization of the drug. We estimated our internal

costs during the last three years, excluding non-reimbursable costs that were not deemed to directly relate to the delivery of the development services to MDCO. Historically, we have been unable to reliably measure our performance based upon our lack of historical experience in completing the development of a drug candidate and have, as a result, defaulted to straight-line attribution for many of our licensing agreements. At the time of adoption of the new revenue standard, however, we have completed a substantial portion of our development obligations and determined we have sufficient information to estimate the remaining development costs for the inclisiran program and sufficient experience to reasonably estimate our development costs.

We recognized the transaction price as we satisfied our performance obligations over time. Beginning with the inception of the MDCO agreement and through the year end December 31, 2017, we incurred \$17.8 million of the \$17.9 million of total costs expected. If we had not adopted the new revenue standard, we would have had \$5.7 million of deferred revenues on our consolidated balance sheet as of January 1, 2018. We completed the performance obligations identified in the MDCO agreement, including the supply and technical transfer agreement, during 2018, although we may receive additional orders for supply. We consider such orders as promised goods to be distinct from the other performance obligations since MDCO now has the ability to begin manufacturing on its own through its own vendors. Such option orders will be treated as separate agreements and any associated revenue will be recognized upon transfer of control.

#### Vir Biotechnology, Inc. Alliance

In October 2017, we formed an exclusive licensing agreement with Vir for the development and commercialization of RNAi therapeutics for infectious diseases, including chronic hepatitis B virus infection. We received an upfront payment, comprised of cash and shares of Vir common stock, which currently is not material to our consolidated financial statements.

#### Other Strategic License Agreements

##### Ionis Collaboration and License Agreement

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.

Pursuant to the 2015 Ionis agreement, Ionis granted to us an exclusive, low single-digit royalty-bearing license to its chemistry, motif, mechanism and target-specific intellectual property for oligonucleotide therapeutics against four targets. In exchange, we granted to Ionis an exclusive, low single-digit royalty-bearing license to our chemistry, motif, mechanism and target-specific intellectual property for oligonucleotide therapeutics against four targets.

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

Under the original 2004 agreement, Ionis licensed to us its patent estate related to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi products in exchange for a previously disclosed technology access fee, participation in fees for our partnering programs and future milestone and royalty payments from us for programs that incorporate Ionis' intellectual property. We have the right to use Ionis' intellectual property in our development programs or in collaborations and Ionis agreed not to grant licenses under these patents to any other organization for the discovery, development and commercialization of double-stranded RNA products designed to work through an RNAi mechanism, except in the context of a collaboration in which Ionis plays an active role.

In turn, under the original 2004 agreement, 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. We granted these licenses for RNAi therapeutics in exchange for option fees, and future milestone and royalty payments from Ionis for RNAi programs that incorporate certain of our intellectual property.

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



As set forth in the 2015 Ionis agreement, under the original 2004 agreement, we paid Ionis an upfront license fee of \$5.0 million and we agreed to pay Ionis milestone payments, totaling up to approximately \$3.4 million, upon the occurrence of specified development and regulatory events, and low single-digit royalties on sales, if any, for each product that we or a collaborator develop using Ionis intellectual property. In addition, we agreed to pay to Ionis a percentage of specified fees from strategic collaborations we may enter into that include access to Ionis' intellectual property.

Ionis has the right to elect up to ten non-exclusive target licenses under the agreement and has the right to purchase one additional non-exclusive target per year during the term of the collaboration. Ionis agreed to pay us, per therapeutic target, a license fee of \$0.5 million, milestone payments for double-stranded RNAi products totaling approximately \$3.4 million, payable upon the occurrence of specified development and regulatory events, and low single-digit royalties on sales, if any, for each double-stranded RNAi or single-stranded RNAi product developed by Ionis or a collaborator that utilizes our intellectual property. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any additional milestone payments or any royalty payments from Ionis.

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

## 5. INVENTORY

The following table presents our inventory of ONPATTRO at December 31, 2018 and 2017, in thousands:

	At December 31,	
	2018	2017
Raw materials	\$8,709	\$ —
Work in process	15,262	—
Finished goods	97	—
Total inventory	\$24,068	\$ —

At December 31, 2018, all of our inventory was related to ONPATTRO, which was approved by the FDA and the EC in August 2018. In the third quarter of 2018, we began to capitalize inventory costs for ONPATTRO as a result of the approval of ONPATTRO by the FDA and commercial sales forecasts for ONPATTRO. Prior to the third quarter of 2018, we recorded the costs associated with manufacturing ONPATTRO as research and development expenses on our consolidated statements of comprehensive loss. At December 31, 2018, we determined a reserve related to ONPATTRO inventory is not required based on our evaluation of factors including commercial sales forecasts for ONPATTRO and the shelf life of ONPATTRO inventory.

## 6. FAIR VALUE MEASUREMENTS

The following tables present information about our assets that are measured at fair value on a recurring basis at December 31, 2018 and 2017, and indicate the fair value hierarchy of the valuation techniques we utilized to determine such fair value, in thousands:

Description	At	Quoted	Significant	Significant
		Prices in	Observable	Unobservable

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	December 31, 2018	Active Markets (Level 1)	Inputs (Level 2)	Inputs (Level 3)
<b>Cash equivalents:</b>				
U.S. treasury securities	\$221,281	\$—	\$ 221,281	\$ —
Money market funds	102,445	102,445	—	—
<b>Marketable debt securities:</b>				
Certificates of deposit	8,951	—	8,951	—
Commercial paper	57,197	—	57,197	—
Corporate notes	232,410	—	232,410	—
U.S. government-sponsored enterprise securities	39,018	—	39,018	—
U.S. treasury securities	325,227	—	325,227	—
Marketable equity securities	1,206	1,206	—	—
Restricted cash (money market funds)	1,477	1,477	—	—
<b>Total</b>	<b>\$989,212</b>	<b>\$105,128</b>	<b>\$ 884,084</b>	<b>\$ —</b>

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Description	At December 31, 2017	Quoted		
		Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents:				
Commercial paper	\$82,262	\$—	\$82,262	\$—
Corporate notes	18,116	—	18,116	—
U.S. government-sponsored enterprise securities	231,122	—	231,122	—
U.S. treasury securities	62,855	—	62,855	—
Money market funds	122,986	122,986	—	—
Marketable debt securities:				—
Certificates of deposit	30,200	—	30,200	—
Commercial paper	56,951	—	56,951	—
Corporate notes	373,252	—	373,252	—
U.S. government-sponsored enterprise securities	398,298	—	398,298	—
U.S. treasury securities	200,475	—	200,475	—
Restricted cash (money market funds)	1,471	1,471	—	—
Total	\$1,577,988	\$124,457	\$1,453,531	\$—

For the years ended December 31, 2018 and 2017, there were no transfers between Level 1 and Level 2 financial assets. The carrying amounts reflected in our consolidated balance sheets for cash, accounts receivable, net, other current assets, accounts payable and accrued expenses approximate fair value due to their short-term maturities. The fair value of our long-term debt at December 31, 2018, computed pursuant to a discounted cash flow technique using a market interest rate, was \$30.1 million and is considered a Level 3 fair value measurement. The effective interest rate reflects the current market rate.

#### 7. MARKETABLE DEBT SECURITIES

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

The following tables summarize our marketable debt securities at December 31, 2018 and 2017, in thousands:

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	At December 31, 2018			
	Gross		Gross	
	Amortized	Unrealized	Unrealized	Fair
	Cost	Gains	Losses	Value
Certificates of deposit	\$8,951	\$ —	\$ —	\$8,951
Commercial paper	57,197	—	—	57,197
Corporate notes	232,695	—	(285 )	232,410
U.S. government-sponsored enterprise securities	39,031	—	(13 )	39,018
U.S. treasury securities	325,350	1	(124 )	325,227
Total	\$663,224	\$ 1	\$ (422 )	\$662,803

	At December 31, 2017			
	Gross		Gross	
	Amortized	Unrealized	Unrealized	Fair Value
	Cost	Gains	Losses	Fair Value
Certificates of deposit	\$30,200	\$ —	\$ —	\$30,200
Commercial paper	56,951	—	—	56,951
Corporate notes	373,736	11	(495 )	373,252
U.S. government-sponsored enterprise securities	399,281	—	(983 )	398,298
U.S. treasury securities	200,649	1	(175 )	200,475
Total	\$1,060,817	\$ 12	\$ (1,653 )	\$1,059,176

We classify our debt security investments based on their contractual maturity dates. The following table summarizes our available-for-sale debt securities by contractual maturity, at December 31, 2018, in thousands:

	At December 31, 2018 Amortized Fair	
	Cost	Value
Less than one year	\$663,224	\$662,803
Greater than one year but less than five years	—	—
Total	\$663,224	\$662,803

#### 8. PROPERTY, PLANT AND EQUIPMENT, NET

Property, plant and equipment, net consist of the following at December 31, 2018 and 2017, in thousands:

	At December 31,	
	2018	2017
Laboratory equipment	\$43,427	\$40,462
Computer equipment and software	13,495	9,608
Furniture and fixtures	7,238	5,844
Leasehold improvements	65,928	50,612
Land	9,080	9,080
Construction in progress	260,975	133,645
	400,143	249,251
Less: accumulated depreciation	(79,485 )	(67,351 )
	\$320,658	\$181,900

During the years ended December 31, 2018, 2017 and 2016, we recorded \$12.8 million, \$11.9 million and \$9.6 million, respectively, of depreciation expense related to our property, plant and equipment.

#### Manufacturing Facility

In April 2016, we purchased 12 acres of undeveloped land in Norton, Massachusetts. We are constructing a manufacturing facility at this site for drug substance for clinical and commercial use. At December 31, 2018 and 2017, property, plant and equipment, net, on our consolidated balance sheets reflects \$227.7 million and \$140.5 million, respectively, of land and associated costs related to the construction of our drug substance manufacturing facility.

## 9.COMMITMENTS AND CONTINGENCIES

## Technology License and Other Commitments

We have licensed from third parties the rights to use certain technologies and information in our research processes as well as in ONPATTRO and any other products that we may develop. In accordance with the related license or technology agreements, we are required to make certain fixed payments to the counterparty over various agreement terms. Many of these agreement terms are consistent with the remaining lives of the underlying intellectual property that we have licensed. At December 31, 2018, we expect to make the following fixed and cancelable payments under existing license agreements, in thousands:

Year Ending December 31,	
2019	\$1,453
2020	795
2021	745
2022	545
2023	525
Thereafter	525
Total	\$4,588

We in-license technology from a number of sources, including Ionis, Merck Sharp & Dohme Corp, or Merck, and Arbutus Biopharma Corporation (formerly Tekmira Pharmaceuticals Corporation), or Arbutus. In addition, we have collaboration agreements

relating to the research, development and commercialization of certain of our product candidates. Pursuant to these agreements, we will be required to make additional payments, including in some cases milestone payments if and when we achieve specified development, regulatory and commercialization events, as well as royalty payments on commercial sales of ONPATTRO and potentially other products, if approved. Amounts related to contingent milestone payments are not considered contractual obligations as they are contingent upon the successful achievement of such milestones. Based on our current development plans as of December 31, 2018, potential future milestone payments to third parties could equal up to \$53.7 million, including \$9.9 million in development milestones, \$40.2 million in regulatory milestones and \$3.6 million in commercial milestones. These milestones generally become due and payable upon achievement. Because the achievement of these milestones was not considered probable as of December 31, 2018, such contingencies have not been recorded in our consolidated financial statements.

#### Facility Leases

##### 300 Third Street

We lease office and laboratory space located at 300 Third Street, Cambridge, Massachusetts which to date has served as our corporate headquarters under a non-cancelable real property lease agreement by and between us and ARE-MA Region No. 28, LLC, or ARE-MA, dated as of September 26, 2003, as amended by five amendments, referred to collectively as the 300 Third Street Lease. Pursuant to the 300 Third Street Lease, we lease a total of approximately 129,000 square feet of office and laboratory space. The term of the 300 Third Street Lease was set to expire on September 30, 2021.

On August 14, 2018, we and ARE-MA entered into a Sixth Amendment to Lease, or the Sixth Amendment, pursuant to which the term of the 300 Third Street Lease was extended for an additional twelve years and four months, through January 31, 2034. Under the Sixth Amendment, we have the option to extend the 300 Third Street Lease, as amended, for two additional five-year terms.

Beginning in October 2021, annual rent under the 300 Third Street Lease, as amended by the Sixth Amendment, exclusive of operating expenses and real property taxes, will be \$10.5 million for the first twelve months, with annual increases of 2.5 percent thereafter. Under the terms of the Sixth Amendment, ARE-MA will provide a tenant improvement allowance up to \$8.4 million, which may be used to fund appropriate improvements to the premises.

##### 665 Concord Avenue

On February 10, 2012, we entered into a non-cancelable real property lease agreement, or the BMR-665 Concord Avenue Lease, with BMR-Fresh Pond Research Park LLC for our manufacturing facility for patisiran formulated bulk drug product. In August 2016, we amended the BMR-665 Concord Avenue Lease to extend the term. Under the BMR-665 Concord Avenue Lease, we lease approximately 15,000 square feet of office and laboratory space located at 665 Concord Avenue, Cambridge, Massachusetts. The term of the BMR-665 Concord Avenue Lease expires on August 31, 2022. Under the amended BMR-665 Concord Avenue Lease, we have the option to extend the term for one additional five-year period.

##### 675 West Kendall Street

In April 2015, we entered into a non-cancelable real property lease, or the BMR-675 West Kendall Lease, with BMR-675 West Kendall Street, LLC, or BMR, for laboratory and office space located at 675 West Kendall Street, Cambridge, Massachusetts. We intend to move our corporate headquarters and research facility to this location in 2019.



Under the terms of the BMR-675 West Kendall Lease, we lease approximately 295,000 square feet of laboratory and office space. The term of the BMR-675 West Kendall Lease commenced on May 1, 2018 and monthly rent payments became due commencing on February 1, 2019 upon substantial completion of the building improvements, and continue for 15 years, with options to renew for two terms of five years each, subject to the terms of the BMR-675 West Kendall Lease.

Annual rent under the BMR-675 West Kendall Lease, exclusive of operating expenses and real property taxes, is \$19.8 million for the first year, with annual increases of 3 percent thereafter. Under the terms of the BMR-675 West Kendall Lease, BMR will contribute a total of \$56.1 million toward the cost of base building and tenant improvements. As of December 31, 2018, in connection with base building and tenant improvements to date, we received \$25.4 million and have \$12.5 million due to us from BMR that is included in prepaid expenses and other current assets on our consolidated balance sheet.

In addition, in connection with the May 1, 2018 commencement of the BMR-675 West Kendall Lease, we were required to provide a \$14.8 million security deposit that is recorded as restricted investments on our consolidated balance sheet as of December 31, 2018.

## 101 Main Street

In May 2015, we entered into a non-cancelable real property lease agreement with RREEF America REIT II CORP. PPP, or RREEF, for office space located on several floors at 101 Main Street, Cambridge, Massachusetts. This lease supplements the initial lease entered into in March 2015 between us and RREEF for office space on a separate floor at the 101 Main Street location.

Under the terms of the 101 Main Street leases, we lease approximately 72,000 square feet of office space at the 101 Main Street location. The term of the initial 101 Main Street lease, that commenced in March 2015, was set to expire on March 31, 2019. On September 27, 2018, we and RREEF entered into a Second Amendment to Lease, pursuant to which the term of the initial 101 Main Street lease was extended for an additional five years, through March 31, 2024, with an option to renew for one five-year term. The term of the additional 101 Main Street lease commenced in January 2016, and continues for five and a half years, with an option to renew for one five-year term.

Initial annual rent for the initial lease and the additional lease, exclusive of operating expenses and real property taxes, was \$1.7 million and \$3.5 million, respectively, with annual increases of \$1/square foot under each lease thereafter. Rent payments commenced in May 2015 under the initial lease and rent payments commenced in May 2016 under the additional lease. Beginning in April 2019, annual rent under the initial lease, as amended by the Second Amendment, will be \$2.1 million for the first twelve months, with annual increases of 2.0 percent thereafter.

We have \$1.5 million in restricted cash that is recorded in long-term other assets as of December 31, 2018 and 2017 in connection with an irrevocable standby letter of credit with RREEF.

Our facility leases described above generally contain customary provisions allowing the landlords to terminate the leases if we fail to remedy a breach of any of our obligations under any such lease within specified time periods, or upon our bankruptcy or insolvency.

Total rent expense, including operating expenses, under our real property leases was \$40.6 million, \$18.7 million and \$15.9 million for the years ended December 31, 2018, 2017 and 2016, respectively.

In addition to the lease agreements described above, we also lease additional office space in several locations in and outside of the U.S. to support our operations and growth.

Future minimum payments under our non-cancelable facility leases, including rent payments for the BMR-675 West Kendall Lease which commenced in February 2019, are approximately as follows, in thousands:

Year Ending December 31,	
2019	\$ 32,228
2020	34,826
2021	34,410
2022	34,826
2023	35,270
Thereafter	390,455
<b>Total</b>	<b>\$ 562,015</b>

## Credit Agreements

On April 29, 2016, we entered into (i) a Credit Agreement, or the BOA Credit Agreement, with Alnylam U.S., Inc., our wholly-owned subsidiary, as the borrower, us, as a guarantor, and Bank of America N.A., or BOA, as the lender and (ii) a Credit Agreement, or the Wells Credit Agreement, together with the BOA Credit Agreement, the Credit Agreements, by and among Alnylam U.S., Inc., as the borrower, us, as a guarantor, and Wells Fargo Bank, National Association, or Wells, as the lender. The Credit Agreements were entered into in connection with the planned build out of our new drug substance manufacturing facility.

The BOA Credit Agreement provided for a \$120.0 million term loan facility and was scheduled to mature on April 29, 2021. In December 2017, we repaid in full the \$120.0 million outstanding principal amount under the BOA Credit Agreement and the BOA Credit Agreement terminated in accordance with its terms upon repayment of the outstanding indebtedness. The Wells Credit Agreement provides for a \$30.0 million term loan facility and matures on April 29, 2021. The proceeds of the borrowing under the BOA Credit Agreement were, and under the Wells Credit Agreement are, to be used for working capital and general corporate purposes. Interest on borrowings under the BOA Credit Agreement was, and under the Wells Credit Agreement is calculated based on LIBOR plus 0.45 percent, except in the event of default. The borrower may prepay loans under the Wells Credit Agreement at any time, without premium or penalty, subject to certain notice requirements and LIBOR breakage costs.

The obligations of the borrower and us under the BOA Credit Agreement were, and under the Wells Credit Agreement 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 such Credit Agreement at such time. At December 31, 2018 and 2017, we had recorded \$30.0 million of cash collateral in connection with the Wells Credit Agreement as restricted investments on our consolidated balance sheets. The Wells Credit Agreement contains limited representations and warranties and limited affirmative and negative covenants, including quarterly reporting obligations, as well as certain customary events of default.

### Litigation

From time to time, we are a party to legal proceedings in the course of our business, including the matters described below. The claims and legal proceedings in which we could be involved include challenges to the scope, validity or enforceability of patents relating to our product candidates, and challenges by us to the scope, validity or enforceability of the patents held by others. These include claims by third parties that we infringe their patents. The outcome of any such legal proceedings, regardless of the merits, is inherently uncertain. In addition, litigation and related matters are costly and may divert the attention of our management and other resources that would otherwise be engaged in other activities. If we were unable to prevail in any such legal proceedings, our business, results of operations, liquidity and financial condition could be adversely affected. Our accounting policy for accrual of legal costs is to recognize such expenses as incurred.

### Silence Litigation

In October 2017, Silence Therapeutics plc served its previously announced claim in the High Court of England and Wales, issued in the name of Silence Therapeutics GmbH, and together with Silence Therapeutics plc, referred to as Silence, against Alnylam UK Ltd., Alnylam Pharmaceuticals, Inc., and The Medicines Company UK Limited, seeking a declaration that Silence was entitled to a Supplementary Protection Certificate for Silence's European Patent No. 2 258 847, when each of patisiran, fitusiran, givosiran and inclisiran obtained a marketing authorization in Europe. In June 2018, Silence withdrew this claim against both us and The Medicines Company UK Limited. Silence also withdrew its previously filed claim alleging infringement of its European Patent No. 1 857 547, referred to as the '547 patent, by fitusiran.

Silence also served patent infringement proceedings against us in Portugal alleging that patisiran infringes the '547 patent as granted. Silence was seeking a permanent injunction against the commercialization of patisiran in Portugal.

On October 10, 2018, Silence filed for Preliminary Relief with the District Court of The Hague, The Netherlands, related to its European Patent No. 3 222 724, referred to as the '724 patent, alleging that ONPATTRO infringes one or more claims of the '724 patent, seeking a cross-border preliminary injunction in those European countries where the patent has been validated

On December 9, 2018, we and our wholly owned subsidiary, Alnylam UK Ltd. and Silence entered into a settlement and license agreement resolving all ongoing claims, administrative proceedings, and regulatory proceedings worldwide between the companies regarding, among other issues, patent infringement, patent invalidity and breach of contract, referred to collectively as the Proceedings. The terms of the settlement and license agreement include mutual releases and provide for the dismissal, withdrawal or discontinuation with prejudice of all claims and counterclaims in the Proceedings between the parties. Each party will bear its own attorney fees and costs incurred in the Proceedings. The settlement and license agreement does not include any admission of liability or wrongdoing by any party.

Under terms of the settlement and license agreement, beginning on January 1, 2019 through 2023, Silence will be entitled to receive a low, tiered royalty ranging from 0.33 percent to 1.0 percent on annual net sales of ONPATTRO in the European Union, or EU, only.

The settlement and license agreement includes the grant from Silence to us of a non-exclusive, global, irrevocable license, with the right to sublicense to affiliates and additional licensees (including our current and future collaborators and distributors), to all relevant patents for all current and future products of ours, whether commercialized by us or a collaborator or licensee (including without limitation ONPATTRO, vutrisiran, givosiran, lumasiran, inclisiran, fitusiran, cemdisiran, ALN-HBV02, ALN-AAT02, and all other investigational therapeutics in our current and future pipeline). Such license is fully paid up with no milestones or royalties, except for the limited royalty on ONPATTRO net sales in the EU only, as described above.

### Securities Litigation

On September 26, 2018, Caryl Hull Leavitt individually and on behalf of all others similarly situated, filed a class action complaint for violation of federal securities laws against us, our Chief Executive Officer and our Chief Financial Officer in the United States District Court for the Southern District of New York. The complaint purports to bring a federal securities class action on behalf of a class of persons who acquired our securities between February 15, 2018 and September 12, 2018 and seeks to recover damages caused by defendants' alleged violations of the federal securities laws and to pursue remedies under Sections 10(b) and 20(a) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and Rule 10b-5 promulgated thereunder. The complaint alleges, among other things, that the defendants made materially false and misleading statements related to the efficacy and safety of our product, ONPATTRO. The plaintiff seeks, among other things, the designation of this action as a class action, an award of unspecified compensatory damages, interest, costs and expenses, including counsel fees and expert fees, and other relief as the court deems appropriate.

By stipulation of the parties and Order of the Court dated November 20, 2018, the action was transferred to the United States District Court for the District of Massachusetts. Motions for the appointment of lead plaintiff and lead counsel were required to be filed by November 26, 2018. There are three such motions currently pending. We anticipate the filing of an amended complaint following the Court's appointment of lead plaintiff and lead counsel.

We believe that the allegations contained in the complaint are without merit and intend to defend the case vigorously. We cannot predict at this point the length of time that this action will be ongoing or the liability, if any, which may arise therefrom.

### Dicerna Litigation

On June 10, 2015, we filed a trade secret misappropriation lawsuit against Dicerna in the Superior Court of Middlesex County, Massachusetts seeking to stop misappropriation by Dicerna of our confidential, proprietary and trade secret information related to the RNAi assets we purchased from Merck, including certain N-acetylgalactosamine, or GalNAc, conjugate technology. In addition to permanent injunctive relief, we were also seeking monetary damages from Dicerna. In August 2017, Dicerna successfully added counterclaims against us in the trade secret lawsuit alleging that our lawsuit represented abuse of process and claiming tortious interference with its business. In September 2017, we filed a motion to dismiss Dicerna's counterclaims, which motion was denied. In addition, in August 2017, Dicerna filed a lawsuit against us in the United States District Court of Massachusetts alleging attempted monopolization by us under the Sherman Antitrust Act. In October 2017, we filed a motion to dismiss the antitrust lawsuit.

On April 18, 2018, we and Dicerna entered into a Settlement Agreement resolving all ongoing litigation between the companies. The terms of the Settlement Agreement include mutual releases and dismissal with prejudice of all claims and counterclaims in the following litigation between the parties: (i) Alnylam Pharmaceuticals, Inc. v. Dicerna Pharmaceuticals, Inc., No. 15-4126, pending in the Massachusetts Superior Court for Middlesex County; and (ii) Dicerna Pharmaceuticals, Inc. v. Alnylam Pharmaceuticals, Inc., No. 1:17-cv-11466, pending in the United States District Court for the District of Massachusetts.

Under the terms of the Settlement Agreement, Dicerna will pay us an aggregate of \$25.0 million, including an upfront cash payment of \$2.0 million and 983,208 shares of Dicerna common stock, valued at \$10.0 million, that were received in the second quarter of 2018, and an additional \$13.0 million due over the next four years, the timing of which was dependent upon revenue Dicerna received pursuant to future partnerships and collaborations related to GalNAc-conjugated RNAi research and development. As a result of Dicerna collaborations entered into subsequent to the Settlement Agreement, we were due the additional \$13.0 million as of December 31, 2018, of which \$2.5 million and \$10.5 million was received in December 2018 and January 2019, respectively. In addition, Dicerna is restricted in its development and other activities relating to oligonucleotide-based therapeutics directed toward a defined set of targets, for periods ranging from 18 months up to four years. The Settlement Agreement does not include any license to our GalNAc conjugate intellectual property or any licenses to any other intellectual property from either party. Nor does the Settlement Agreement include any admission of liability or wrongdoing by either company.

#### Indemnifications

In connection with our license agreements with Max Planck relating to the Tuschl I and Tuschl II patent applications, we are required to indemnify Max Planck Gesellschaft zur Foerderung der Wissenschaften e.V., or Max Planck, for certain damages arising in connection with the intellectual property rights licensed under the agreements. Under the Max Planck indemnification agreement, we are responsible for paying the costs of any litigation relating to the license agreements or the underlying intellectual property rights, including the costs associated with certain litigation regarding the Tuschl patents, which was settled during 2011, as well as certain costs associated with defending prior litigation with the University of Utah, or Utah, which was fully resolved in 2017. In connection with the settlement of the litigation regarding the Tuschl patents, we also agreed to indemnify the Whitehead Institute for Biomedical Research, or Whitehead, Massachusetts Institute of Technology and the University of Massachusetts for certain costs

associated with defending the Utah litigation. In connection with our research agreement with Acuitas Therapeutics Inc., or Acuitas (formerly AlCana Technologies, Inc.), we agreed to indemnify Acuitas for certain legal costs, subject to certain exceptions and limitations, associated with certain litigation with Arbutus, which has been settled. These indemnification costs were charged to selling, general and administrative expense. We are also a party to a number of agreements entered into in the ordinary course of business, which contain typical provisions that obligate us to indemnify the other parties to such agreements upon the occurrence of certain events. Such indemnification obligations are usually in effect from the date of execution of the applicable agreement for a period equal to the applicable statute of limitations.

Our maximum potential future liability under any such indemnification provisions is uncertain. However, to date, other than certain costs associated with certain previously settled litigation related to the Tuschl patents and the litigation with Arbutus referenced above, and certain defense costs related to the Utah litigation described above, we have not incurred material costs to defend lawsuits or settle claims related to these indemnification provisions. We have determined that the estimated aggregate fair value of our potential liabilities under all such indemnification provisions is minimal and had not recorded any liability related to such indemnification provisions at December 31, 2018 or 2017.

## 10. STOCKHOLDERS' EQUITY

### Preferred Stock

We have authorized up to 5,000,000 shares of preferred stock, \$0.01 par value per share, for issuance. The preferred stock will have such rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, as shall be determined by our board of directors upon its issuance. At December 31, 2018 and 2017, there were no shares of preferred stock outstanding.

### Public Offerings

In January 2019, we sold an aggregate of 5,000,000 shares of our common stock through an underwritten public offering at a price to the public of \$77.50 per share. As a result of the offering, we received aggregate net proceeds of \$381.9 million, after deducting underwriting discounts and commissions and other estimated offering expenses of \$5.6 million.

In November 2017, we sold an aggregate of 6,440,000 shares of our common stock through an underwritten public offering at a price to the public of \$125.00 per share. As a result of the offering, which included the full exercise of the underwriters' option to purchase additional shares, we received aggregate net proceeds of \$784.5 million, after deducting underwriting discounts and commissions and other offering expenses of \$20.5 million.

In May 2017, we sold an aggregate of 5,000,000 shares of our common stock through an underwritten public offering at a price to the public of \$71.87 per share. As a result of the offering, we received aggregate net proceeds of \$355.2 million, after deducting underwriting discounts and commissions and other offering expenses of \$4.2 million.



## 11. STOCK-BASED COMPENSATION

### Stock Plans

In June 2009, our stockholders approved our 2009 Stock Incentive Plan which was amended and restated in May 2015 with stockholder approval to increase the number of shares of common stock authorized for issuance from 5,900,000 to 11,700,000. In May 2017, our stockholders approved a second amendment and restatement of the 2009 Stock Incentive Plan, or the Second Amended and Restated 2009 Plan, which increased the number of shares of common stock authorized for issuance from 11,700,000 to 15,480,000. In May 2018, our stockholders approved our 2018 Stock Incentive Plan, or the 2018 Plan, which provides for the issuance of up to 3,500,000 shares in addition to the shares that remained available for grant under our Second Amended and Restated 2009 Plan as of May 10, 2018, the date of approval of the 2018 Plan by stockholders, and any shares underlying any awards granted under the Second Amended and Restated 2009 Plan that expire, or are terminated, surrendered or canceled without having been fully exercised or are forfeited in whole or in part after the date of our 2018 annual meeting. Consistent with the terms of the Second Amended and Restated 2009 Plan, the 2018 Plan provides for the granting of stock options, restricted stock and restricted stock units (together, restricted stock awards), stock appreciation rights and other stock-based awards, and has a fungible share pool. Any award that is not a full value award is counted against the authorized share limits specified as one share for each share of common stock subject to the award, and all full value awards, defined as restricted stock awards or other stock-based awards, are counted as one and a half shares for each one share of common stock subject to such full value award.

At December 31, 2018, an aggregate of 17,491,117 shares of common stock were reserved for issuance under our stock plans, including outstanding stock options to purchase 12,572,522 shares of common stock, 36,083 outstanding restricted stock units, 4,433,370 of common stock available for additional equity awards and 449,142 shares available for future grant under our Amended and Restated 2004 Employee Stock Purchase Plan, or the Amended and Restated ESPP. Each stock option shall expire within ten years of issuance. Time-based stock options granted by us to employees generally vest as to 25 percent of the shares on the first anniversary of the grant date and 6.25 percent of the shares at the end of each successive three-month period thereafter until fully vested. Performance-based stock options granted to employees in 2013 and 2014 vested, with respect to each year, as to one-third of the shares upon the achievement of each of three specific clinical development or regulatory events, as approved by our compensation committee. Performance-based stock options granted to employees in 2015 and 2016 vest, with respect to each year, as to one-fourth of the shares upon the later of the one-year anniversary of the grant date and the achievement of each of four specific clinical development, regulatory or commercial events, as approved by our compensation committee. Historically, stock option awards to employees for annual performance, including performance-based stock option awards beginning in 2013, were approved for grant by the compensation committee of our board of directors at year-end. However, with respect to 2017 annual awards as well as future annual awards, our compensation committee intends to approve the grant of any such awards in the first quarter of the following year. For example, on March 1, 2018, our compensation committee approved performance-based stock options with respect to 2017 annual awards that vest, as to one-third of the shares upon the later of the one-year anniversary of the grant date and the achievement of each of three specific clinical development, regulatory or commercial events, as approved by our compensation committee.

#### Change in Control Agreements

On November 7, 2017, we entered into a Change in Control, or CIC, Agreement with each member of our management board. If a member of our management board is terminated by us without Cause, as defined in the CIC Agreement, or if a management board member terminates his or her employment for Good Reason, as defined in the CIC Agreement, in either case, within 12 months following a CIC, such management board member will be entitled to receive certain benefits, including the immediate acceleration of all outstanding unvested stock options and other stock-based awards. In accordance with accounting guidance for stock-based compensation expense, we expect to record the modification date fair value for any equity grants that were not considered probable of vesting as of November 7, 2017 that ultimately vest. During the years ended December 31, 2018 and 2017, we recorded \$20.8 million and \$1.1 million, respectively, related to this modification.

#### Inducement Equity Grants

Effective as of each of May 8, 2017 and September 19, 2016, respectively, our compensation committee approved a grant to a newly hired executive of non-qualified stock options to purchase an aggregate of 150,000 shares of common stock. For each executive, time-vested options to purchase 125,000 shares of common stock will vest as to 25 percent of the shares on the first anniversary of the respective grant date and 6.25 percent of the shares at the end of each successive three-month period thereafter until fully vested. For each executive, performance-based stock options to purchase 25,000 shares of common stock were subject to vest upon the later of the one-year anniversary of the respective grant date and the launch of our first internally developed product, the achievement of which occurred in the third quarter of 2018. In addition, effective as of February 6, 2017, our compensation committee approved a grant to a newly hired vice president level employee, of non-qualified stock options to purchase an aggregate of 50,000 shares of common stock. This time-vested option grant will vest as to 25 percent of the shares on the first anniversary of the grant date and 6.25 percent of the shares at the end of each successive three-month period thereafter until fully vested. Each of the May 8, 2017, February 6, 2017 and September 19, 2016 option award was granted as an

inducement grant outside of our stockholder approved stock plans in accordance with Nasdaq Listing Rule 5635(c)(4). Each of these stock options has a ten-year term and an exercise price equal to the closing price of our common stock on the respective grant date.

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## Stock-Based Compensation

The following table summarizes stock-based compensation expense during the three years ended December 31, 2018, in thousands:

	2018	2017	2016
Stock-based compensation expense by type of award:			
Time-based stock options	\$83,403	\$61,802	\$62,800
Performance-based stock options	56,419	23,260	8,337
Time-based restricted stock units	538	541	497
Performance-based restricted stock units	13,144	—	—
ESPP share issuances	2,842	2,155	1,360
Other equity programs	1,345	1,946	1,846
Non-employee stock options	1,485	3,115	688
Less: Stock-based compensation expense capitalized to inventory	(1,424 )	—	—
	\$157,752	\$92,819	\$75,528

The following table summarizes our unrecognized stock-based compensation expense, net of estimated forfeitures, at December 31, 2018 by type of awards, and the weighted-average period over which that expense is expected to be recognized:

	At December 31, 2018 Unrecognized	
Type of award:	Expense,	Weighted-
	Net of	average
	Estimated	Recognition
	Forfeitures	Period
	(in	(in
	thousands)	years)
Time-based stock options	\$156,192	2.53
Performance-based stock options	57,586	*
Time-based restricted stock units	769	0.78
Performance-based restricted stock units	1,747	*
ESPP share issuances	984	0.33

\*

Performance-based stock options and performance-based restricted stock units are recorded as expense beginning when vesting events are determined to be probable.

#### Valuation Assumptions for Stock Options

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

	2018	2017	2016
Risk-free interest rate	2.7-2.9%	1.9-2.3%	0.9-2.2%
Expected dividend yield	—	—	—
Expected option life	5.7-7.2 years	5.7-7.2 years	3.5-7.5 years
Expected volatility	64-67%	61-67%	55-65%

## Stock Option Activity

The following table summarizes the activity of our stock option plans and the inducement grants described above, excluding performance-based stock options:

	Number of Options (in thousands)	Weighted- average Exercise Price	Weighted- average Remaining Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding, December 31, 2017	9,101	\$ 60.18		
Granted	2,273	110.11		
Exercised	(1,181 )	46.92		
Cancelled	(364 )	82.89		
Outstanding, December 31, 2018	9,829	\$ 72.48	6.68	\$ 149,518
Exercisable at December 31, 2018	5,734	\$ 58.90	5.31	\$ 127,051
Vested or expected to vest at December 31, 2018	9,327	\$ 71.36	6.56	\$ 147,144

The weighted-average fair value of stock options granted was \$66.49, \$44.76 and \$31.66 per share for the years ended December 31, 2018, 2017 and 2016, respectively. The intrinsic value of stock options exercised was \$87.1 million, \$111.3 million and \$22.0 million for the years ended December 31, 2018, 2017 and 2016, respectively. We satisfy stock option exercises with newly issued shares of our common stock.

## Performance-Based Stock Options

With respect to the performance-based portion of the annual stock option awards, a portion of the shares subject to the performance-based stock option will vest upon the later of the one-year anniversary of the date of grant and the achievement of specific clinical development, regulatory and/or commercial events, as approved by our compensation committee. During each of the years ended December 31, 2017 and 2016, we also granted an option to purchase 25,000 shares of common stock to a newly hired executive that were subject to vest upon the later of the one-year anniversary of the grant date and the achievement of a commercial event.

The following table summarizes the activity of our performance-based stock options granted under our equity plans and the performance-based portion of the inducement grants described above:

Number of Options (in thousands)	Weighted- average Exercise	Weighted- average Remaining	Aggregate Intrinsic Value
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		Price	Contractual Term (in years)	(in thousands)
Outstanding, December 31, 2017	2,138	\$ 69.14		
Granted	912	119.13		
Exercised	(149 )	67.04		
Cancelled	(157 )	88.64		
Outstanding, December 31, 2018	2,744	\$ 84.75	7.24	\$ 23,694
Exercisable at December 31, 2018	1,420	\$ 74.29	6.21	\$ 13,134

During the years ended December 31, 2018, 2017 and 2016, there were 763,982, 614,796 and 159,122 performance-based stock options that vested, respectively. The intrinsic value of performance-based stock options exercised was \$8.0 million, \$1.8 million and \$35,000 for the years ended December 31, 2018, 2017 and 2016, respectively. We satisfy performance-based stock option exercises with newly issued shares of our common stock. During the years ended December 31, 2018, 2017 and 2016, for each performance-based stock option that was determined to be probable of vesting, we began to record expense during the year. In addition, as of December 31, 2018, we had determined that certain stock option awards vesting upon the achievement of commercial sales targets were probable of achievement and we began to record stock-based compensation expense during the second half of 2018 following the approval and launch of ONPATTRO. During 2018, we recorded \$16.1 million of the estimated \$30.3 million of the expense related to these stock option awards.

### Performance-Based Restricted Stock Units

In January 2016, we granted 172,718 shares of performance-based restricted stock units to certain employees, excluding our chief executive officer and president. These performance-based restricted stock units were valued at \$16.1 million on the grant date. The vesting of these performance-based restricted stock units was predicated on the launch of our first internally developed product, which was achieved in August 2018. As of the grant date and until we received regulatory approval from the FDA for ONPATTRO on August 10, 2018, for accounting purposes we had determined that the performance criteria for these performance-based restricted stock units was not probable of being achieved. As a result, we recorded the total stock-based compensation expense of \$11.8 million for the 124,833 performance-based restricted stock units that vested upon the launch of ONPATTRO during August 2018. The total fair value of these performance-based restricted stock units that vested (measured on the date of vesting) was \$11.4 million.

### Employee Stock Purchase Plan

In 2004, we adopted the 2004 Employee Stock Purchase Plan with 315,789 shares authorized for issuance. In June 2010, our stockholders approved an amendment to the 2004 Employee Stock Purchase Plan, which increased the shares authorized for issuance from 315,789 shares to 715,789 shares. In May 2017, our stockholders approved the Amended and Restated ESPP, which further increased the shares authorized for issuance from 715,789 shares to 1,215,789 shares. Under the Amended and Restated ESPP, each offering period is six months, at the end of which employees may purchase shares of common stock through payroll deductions made over the term of the offering. The per-share purchase price at the end of each offering period is equal to the lesser of 85 percent of the closing price of our common stock at the beginning or end of the offering period. We issued 78,085, 103,666 and 53,499 shares during the years ended December 31, 2018, 2017 and 2016, respectively, and at December 31, 2018, 449,142 shares were available for issuance under the Amended and Restated ESPP.

The weighted-average fair value of stock purchase rights granted as part of the Amended and Restated ESPP was \$35.67, \$17.10 and \$24.90 per share for the years ended December 31, 2018, 2017 and 2016, respectively. The fair value was estimated using the Black-Scholes option-pricing model. During the year ended December 31, 2018, we used a weighted-average stock-price volatility of 63 percent, expected option life assumption of six months and a risk-free interest rate of 2 percent. During the year ended December 31, 2017, we used a weighted-average stock-price volatility of 91 percent, expected option life assumption of six months and a risk-free interest rate of 0.7 percent. During the year ended December 31, 2016, we used a weighted-average stock-price volatility of approximately 55 percent, expected option life assumption of six months and a risk-free interest rate of approximately 0.1 percent.

## 12. INCOME TAXES

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

	2018	2017	2016
Domestic	\$(573,245)	\$(378,293)	\$(350,704)
Foreign	(187,429)	(112,581)	(59,404)
Loss before income taxes	\$(760,674)	\$(490,874)	\$(410,108)



The provision for income taxes for each of the years ended December 31, 2018, 2017 and 2016 consisted of the following:

	2018	2017	2016
<b>Current provision:</b>			
Domestic	\$—	\$ —	\$ —
Foreign	(1,611)	—	—
Total current provision	(1,611)	—	—
<b>Deferred benefit:</b>			
Federal	788	—	—
Foreign	—	—	—
Total deferred benefit	788	—	—
Total provision for income taxes	\$(823 )	\$ —	\$ —

Deferred income taxes reflect the tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting and income tax purposes. We establish a valuation allowance when uncertainty exists as to whether all or a portion of the net deferred tax assets will be realized. Components of the net deferred tax (liability) asset at December 31, 2018 and 2017 are as follows, in thousands:

	2018	2017
Deferred tax assets:		
Net operating loss carryforwards	\$506,574	\$405,784
Research and development and ODC credits	220,776	192,094
AMT credits	788	788
Capitalized research and development and start-up costs	12,139	13,163
Deferred revenue	—	13,576
Deferred compensation	57,268	42,990
Property, plant and equipment, net	—	2,471
Intangible assets	50,121	9,018
Other	20,660	9,137
Total deferred tax assets	868,326	689,021
Deferred tax liabilities:		
Property, plant and equipment, net	(6,550 )	—
Unrealized gain on marketable securities	(903 )	(765 )
Deferred tax asset valuation allowance	(860,085)	(688,256)
Net deferred tax asset	\$788	\$—

Our effective income tax rate differs from the statutory federal income tax rate as follows for the years ended December 31, 2018, 2017 and 2016:

	2018	2017	2016
At U.S. federal statutory rate	21.0 %	35.0 %	35.0 %
State taxes, net of federal effect	2.1	3.8	3.7
Stock-based compensation	0.8	3.3	(1.4 )
Tax credits	4.2	9.9	11.8
Orphan drug credit	—	(3.4 )	(3.5 )
Other permanent items	(0.3 )	(1.0 )	(0.4 )
Foreign rate differential	(5.3 )	(8.1 )	(5.1 )
Tax reform change	—	(46.5)	—
Revaluation of deferred credits due to rate change	(3.5 )	—	—
Other	—	(0.9 )	—
Valuation allowance	(19.0)	7.9	(40.1)
Effective income tax rate	— %	— %	— %

We have evaluated the positive and negative evidence bearing upon the realizability of our deferred tax assets. We have concluded, in accordance with the applicable accounting standards, that it is more likely than not that we may not realize the benefit of all of our deferred tax assets, with the exception of the deferred asset related to alternative minimum tax credits as these have become refundable over the following four years. Accordingly, we have recorded a valuation allowance against the deferred tax assets that management believes will not be realized. We re-evaluate the positive and negative evidence on a quarterly basis. The valuation allowance increased by \$171.8 million, \$112.9 million and \$177.9 million for the years ended December 31, 2018, 2017 and 2016, respectively, due primarily to additional operating losses.

On December 22, 2017, the President of the United States signed into law the TCJA tax reform legislation. The TCJA makes significant changes in U.S. tax law including a reduction in the corporate tax rates, changes to net operating loss carryforwards and carrybacks, and a repeal of the corporate alternative minimum tax. The TCJA reduced the U.S. corporate tax rate from the current rate of 35 percent down to 21 percent starting on January 1, 2018. As a result of the TCJA, we were required to revalue deferred tax assets and liabilities at 21 percent. This revaluation resulted in a provision of \$227.9 million to income tax expense in continuing operations and a corresponding reduction in the valuation allowance for the year ended December 31, 2017. As a result, there was no impact to our consolidated statements of comprehensive loss as a result of the reduction in tax rates. The other provisions of the TCJA did not

have a material impact on our consolidated financial statements. Our final determination of the TCJA impact and the remeasurement of our deferred assets and liabilities was completed prior to the deadline of one year from the enactment of the TCJA. For the year ended December 31, 2018, there were no material changes to our analysis originally performed as of December 31, 2017.

During the year ended December 31, 2018, we recorded a net provision for income taxes of \$0.8 million related to \$1.6 million due to foreign income taxes recorded during the year ended December 31, 2018 partially offset by a \$0.8 million benefit for refundable credits related to the TCJA. There was no provision for income taxes recorded during the years ended December 31, 2017 or 2016.

At December 31, 2018, we had federal and state net operating loss carryforwards of \$1.9 billion and \$1.6 billion, respectively, to reduce future taxable income that will expire at various dates through 2038. At December 31, 2018, approximately \$0.5 billion of our federal net operating loss carryforward can be carried forward indefinitely. At December 31, 2018, we had federal and state research and development, including Orphan Drug, and state investment tax credit carryforwards of \$208.0 million and \$16.2 million, respectively, available to reduce future tax liabilities that expire at various dates through 2038. At December 31, 2018, we had alternative minimum tax credits of \$0.8 million that will either be available to reduce future regular tax liabilities or be fully refundable in 2021. We have a valuation allowance against the net operating loss and credit deferred tax assets as it is unlikely that we will realize these assets. Ownership changes, as defined in the Internal Revenue Code, including those resulting from the issuance of common stock in connection with our public offerings, may limit the amount of net operating loss and tax credit carryforwards that can be utilized to offset future taxable income or tax liability. The amount of the limitation is determined in accordance with Section 382 of the Internal Revenue Code. We have performed an analysis of ownership changes through December 31, 2018. Based on this analysis, we do not believe that any of our tax attributes will expire unutilized due to Section 382 limitations.

At December 31, 2018, 2017 and 2016, we had no unrecognized tax benefits and have recorded no interest and penalties since inception, accordingly.

The tax years 2015 through 2018 remain open to examination by major taxing jurisdictions to which we are subject, which are primarily in the U.S., as carryforward attributes generated in years past may still be adjusted upon examination by the Internal Revenue Service or state tax authorities if they have or will be used in a future period.

### 13. ACCRUED EXPENSES

Accrued expenses consist of the following at December 31, 2018 and 2017, in thousands:

	At December 31,	
	2018	2017
Compensation and related	\$37,301	\$33,826
Clinical trial and manufacturing	36,500	20,004
Consulting and professional services	10,450	7,276
Product revenue allowances	2,696	—
Pre-clinical	2,138	239
Other	23,634	10,858
	\$112,719	\$72,203

## 14. QUARTERLY FINANCIAL DATA (UNAUDITED)

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

	Three Months Ended			
	March 31,	June 30,	September 30,	December 31,
	2018	2018	2018	2018
	(In thousands, except per share data)			
Revenues	\$21,899	\$29,907	\$2,069	\$21,033
Operating costs and expenses	169,304	222,261	256,627	241,389
Net loss	\$(141,214)	\$(163,560)	\$(245,282)	\$(211,441)
Net loss per common share — basic and diluted	\$(1.41 )	\$(1.63 )	\$(2.43 )	\$(2.09 )
Weighted-average common shares — basic and diluted	99,979	100,519	100,783	101,066

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	Three Months Ended			
	March 31,	June 30,	September 30,	December 31,
	2017	2017	2017	2017
	(In thousands, except per share data)			
Revenues	\$18,960	\$15,932	\$17,096	\$37,924
Operating costs and expenses	125,471	136,406	142,896	185,227
Net loss	\$(107,290)	\$(118,420)	\$(122,937)	\$(142,227)
Net loss per common share — basic and diluted	\$(1.25 )	\$(1.34 )	\$(1.34 )	\$(1.48 )
Weighted-average common shares — basic and diluted	86,027	88,098	91,828	96,139

On January 1, 2018, we adopted the new revenue standard by applying the modified retrospective method to all contracts that were not completed as of January 1, 2018. Please read Note 2 for further discussion of our adoption of the new revenue standard.

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

None.

**ITEM 9A. CONTROLS AND PROCEDURES**

Our management, with the participation of our Chief Executive Officer (principal executive officer) and senior vice president, Chief Financial Officer (principal financial officer), evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2018. The term “disclosure controls and procedures,” as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC’s rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company’s management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2018, our Chief Executive Officer and Senior Vice President, Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

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

No change in our internal control over financial reporting occurred during the fiscal quarter ended December 31, 2018 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

**ITEM 9B. OTHER INFORMATION**

None.

PART III

**ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE**

Incorporated by reference from the information in our Proxy Statement for our 2019 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this annual report on Form 10-K relates.

**ITEM 11. EXECUTIVE COMPENSATION**

Incorporated by reference from the information in our Proxy Statement for our 2019 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this annual report on Form 10-K relates.

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

Incorporated by reference from the information in our Proxy Statement for our 2019 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this annual report on Form 10-K relates.

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

Incorporated by reference from the information in our Proxy Statement for our 2019 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this annual report on Form 10-K relates.

**ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES**

Incorporated by reference from the information in our Proxy Statement for our 2019 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this annual report on Form 10-K relates.



PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

(a) (1) Financial Statements

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

<u>Management’s Annual Report on Internal Control Over Financial Reporting</u>	Page 98
<u>Report of Independent Registered Public Accounting Firm</u>	99
<u>Consolidated Balance Sheets at December 31, 2018 and 2017</u>	101
<u>Consolidated Statements of Comprehensive Loss for the Years Ended December 31, 2018, 2017 and 2016</u>	102
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(a) (2) List of Schedules

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

(a) (3) List of Exhibits

Exhibit No.	Exhibit
2.1†*	<u>Stock Purchase Agreement dated as of January 10, 2014 by and among the Registrant, Sirna Therapeutics, Inc., Merck Sharp &amp; Dohme Corp., and solely for the purposes of certain specified provisions, Merck &amp; Co., Inc. (filed as Exhibit 2.1 to the Registrant’s Quarterly</u>

- Report on Form 10-Q  
filed on May 9, 2014  
(File No. 001-36407)  
for the quarterly period  
ended March 31, 2014  
and incorporated  
herein by reference)
- 3.1 Restated Certificate of  
Incorporation of the  
Registrant (filed as  
Exhibit 3.1 to the  
Registrant's Annual  
Report on Form 10-K  
filed on February 12,  
2016 (File  
No. 001-36407) for the  
year ended  
December 31, 2015  
and incorporated  
herein by reference)
- 3.2 Amended and Restated  
Bylaws of the  
Registrant, as amended  
(filed as Exhibit 3.1 to  
the Registrant's  
Quarterly Report on  
Form 10-Q filed on  
May 4, 2018 (File  
No. 001-36407) for the  
quarterly period ended  
March 31, 2018 and  
incorporated herein by  
reference)
- 4.1 Specimen certificate  
evidencing shares of  
common stock (filed as  
Exhibit 4.1 to the  
Registrant's  
Registration Statement  
on Form S-1 (File  
No. 333-113162) and  
incorporated herein by  
reference)
- 10.1\*\* 2002 Employee,  
Director and  
Consultant Stock Plan,  
as amended, together

- with forms of Incentive Stock Option Agreement, Non-qualified Stock Option Agreement and Restricted Stock Agreement (filed as Exhibit 10.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
- 10.2\*\* 2003 Employee, Director and Consultant Stock Plan, as amended, together with forms of Incentive Stock Option Agreement, Non-qualified Stock Option Agreement and Restricted Stock Agreement (filed as Exhibit 10.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
- 10.3\*\* Amended and Restated 2004 Stock Incentive Plan (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on August 8, 2014 (File No. 001-36407) for the quarterly period ended June 30, 2014 and incorporated herein by reference)
- 10.4\*\* Forms of Incentive Stock Option Agreement and

Nonstatutory Stock  
Option Agreement  
under 2004 Stock  
Incentive Plan, as  
amended (filed as  
Exhibit 10.2 to the  
Registrant's Quarterly  
Report on Form 10-Q  
filed on August 8,  
2014 (File  
No. 001-36407) for the  
quarterly period ended  
June 30, 2014 and  
incorporated herein by  
reference)

10.5\*\* Second Amended and  
Restated 2009 Stock  
Incentive Plan (filed as  
Exhibit 10.1 to the  
Registrant's Quarterly  
Report on Form 10-Q  
filed on August 9,  
2017 (File  
No. 001-36407) for the  
quarterly period ended  
June 30, 2017 and  
incorporated herein by  
reference)

Exhibit No.	Exhibit
10.6**	<u>Forms of Incentive Stock Option Agreement, Nonstatutory Stock Option Agreements, Restricted Stock Agreement and Restricted Stock Unit Award Agreement under Second Amended and Restated 2009 Stock Incentive Plan (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on August 9, 2017 (File No. 001-36407) for the quarterly period ended June 30, 2017 and incorporated herein by reference)</u>
10.7**	<u>Form of Nonstatutory Stock Option Agreement for Non-Plan Inducement Grant (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on November 3, 2016 (File No. 001-36407) for the quarterly period ended September 30, 2016 and incorporated herein by reference)</u>
10.8**	<u>Amended and Restated 2004 Employee Stock Purchase Plan (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed on August 9, 2017 (File</u>

- No. 001-36407) for the quarterly period ended June 30, 2017 and incorporated herein by reference)
- 10.9\*\* 2018 Stock Incentive Plan (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on August 2, 2018 (File No. 001-36407) for the quarterly period ended June 30, 2018 and incorporated herein by reference)
- 10.10\*\* Forms of Incentive Stock Option Agreement, Nonstatutory Stock Option Agreements, Restricted Stock Agreement and Restricted Stock Unit Award Agreement under 2018 Stock Incentive Plan (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on August 2, 2018 (File No. 001-36407) for the quarterly period ended June 30, 2018 and incorporated herein by reference)
- 10.11\*\* Letter Agreement between the Registrant and John M. Maraganore, Ph.D. dated October 30, 2002 (filed as Exhibit 10.7 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162)

and incorporated  
herein by reference)

10.12\*\* Letter Agreement  
between the Registrant  
and Barry E. Greene  
dated September 29,  
2003 (filed as Exhibit  
10.10 to the  
Registrant's  
Registration Statement  
on Form S-1 (File No.  
333-113162) and  
incorporated herein by  
reference)

10.13\*\* Letter Agreement  
between the Registrant  
and Yvonne L.  
Greenstreet, MBChB  
dated August 12, 2016  
(filed as Exhibit 10.14  
to the Registrant's  
Annual Report on  
Form 10-K filed on  
February 15, 2017  
(File No. 001-36407)  
for the year ended  
December 31, 2016  
and incorporated  
herein by reference)

10.14\*\* Letter Agreement  
between the Registrant  
and Manmeet S. Soni  
dated April 20, 2017  
(filed as Exhibit 10.4  
to the Registrant's  
Quarterly Report on  
Form 10-Q filed on  
August 9, 2017 (File  
No. 001-36407) for the  
quarterly period ended  
June 30, 2017 and  
incorporated herein by  
reference)

10.15\*\* Consulting Agreement  
dated as of March 1,  
2006 by and between  
the Registrant and

- Phillip A. Sharp, Ph.D., as amended (filed as Exhibit 10.16 to the Registrant's Annual Report on Form 10-K filed on February 19, 2013 (File No. 000-50743) for the year ended December 31, 2012 and incorporated herein by reference)
- 10.16\*\* Consulting Agreement dated as of April 20, 2012 by and between the Registrant and Dennis A. Ausiello, M.D. (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on April 23, 2012 (File No. 000-50743) and incorporated herein by reference)
- 10.17\*\* Forms of Director and Officer Indemnification Agreements (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on August 4, 2016 (File No. 001-36407) for the quarterly period ended June 30, 2016 and incorporated herein by reference)
- 10.18\*\* Form of Change in Control Agreement (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on November 7, 2017 (File No. 001-36407) for the quarterly period



ended September 30, 2017 and incorporated herein by reference)

10.19 Lease, dated as of September 26, 2003 by and between the Registrant and Three Hundred Third Street LLC (filed as Exhibit 10.15 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)

10.20 First Amendment to Lease, dated March 16, 2006, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on March 17, 2006 (File No. 000-50743) and incorporated herein by reference)

10.21 Second Amendment to Lease, dated June 26, 2009, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q filed on August 7, 2009 (File No. 000-50743) for the quarterly period ended June 30, 2009 and incorporated herein by reference)



Exhibit No.	Exhibit
10.22	<u>Third Amendment to Lease, dated May 11, 2010, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on August 5, 2010 (File No. 000-50743) for the quarterly period ended June 30, 2010 and incorporated herein by reference)</u>
10.23	<u>Fourth Amendment to Lease, dated November 4, 2011, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.19 to the Registrant's Annual Report on Form 10-K filed on February 13, 2012 (File No. 000-50743) for the year ended December 31, 2011 and incorporated herein by reference)</u>
10.24	<u>Fifth Amendment to Lease, dated March 27, 2014, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.5 to the Registrant's Amendment No. 1 to its Quarterly Report on Form 10-Q/A filed on January 9, 2015)</u>

- (File No. 001-36407)  
for the quarterly  
period ended March  
31, 2014 and  
incorporated herein  
by reference)
- 10.25 Sixth Amendment to  
Lease, dated August  
14, 2018, by and  
between the  
Registrant and  
ARE-MA Region No.  
28, LLC. (filed as  
Exhibit 10.1 to the  
Registrant's Quarterly  
Report on Form 10-Q  
filed on November 7,  
2018 (File No.  
001-36407) for the  
quarterly period  
ended September 30,  
2018 and  
incorporated herein  
by reference)
- 10.26† Lease entered into as  
of February 10, 2012  
by and between  
BMR-Fresh Pond  
Research Park LLC  
and the Registrant  
(filed as Exhibit 10.2  
to the Registrant's  
Quarterly Report on  
Form 10-Q filed on  
May 3, 2012 (File  
No. 000-50743) for  
the quarterly period  
ended March 31,  
2012 and  
incorporated herein  
by reference)
- 10.27 First Amendment to  
Lease entered into as  
of August 2, 2016 by  
and between  
BMR-Fresh Pond  
Research Park LLC  
and the Registrant

(filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on November 3, 2016 (File No. 001-36407) for the quarterly period ended September 30, 2016 and incorporated herein by reference)

10.28 Lease dated as of March 18, 2015 between RREEF America REIT II CORP. PPP and the Registrant, as amended by First Amendment to Lease dated as of April 16, 2015 (filed as Exhibit 10.5 to the Registrant's Quarterly Report on Form 10-Q filed on August 7, 2015 (File No. 001-36407) for the quarterly period ended June 30, 2015 and incorporated herein by reference)

10.29 Second Amendment to Lease, dated September 27, 2018, by and between Registrant and RREEF America REIT II CORP. PPP. (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on November 7, 2018 (File No. 001-36407) for the quarterly period ended September 30, 2018 and incorporated herein by reference)

- 10.30 Lease dated as of May 5, 2015 between RREEF America REIT II CORP. PPP and the Registrant (filed as Exhibit 10.6 to the Registrant's Quarterly Report on Form 10-Q filed on August 7, 2015 (File No. 001-36407) for the quarterly period ended June 30, 2015 and incorporated herein by reference)
- 10.31 Lease entered into as of April 3, 2015 by and between BMR-675 West Kendall Street LLC and the Registrant (filed as Exhibit 10.7 to the Registrant's Quarterly Report on Form 10-Q filed on August 7, 2015 (File No. 001-36407) for the quarterly period ended June 30, 2015 and incorporated herein by reference)
- 10.32 Purchase and Sale Agreement entered into as of February 10, 2016 by and between 20 Commerce LLC and the Registrant (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed on May 4, 2016 (File No. 001-36407) for the quarterly period ended March 31, 2016 and incorporated herein by reference)

10.33† Co-exclusive License Agreement between Garching Innovation GmbH (now known as Max Planck Innovation GmbH) and Alnylam U.S., Inc. dated December 20, 2002, as amended by Amendment dated July 8, 2003 together with Indemnification Agreement by and between Garching Innovation GmbH (now known as Max Planck Innovation GmbH) and Alnylam Pharmaceuticals, Inc. effective April 1, 2004 (filed as Exhibit 10.19 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)

10.34† Co-exclusive License Agreement between Garching Innovation GmbH (now known as Max Planck Innovation GmbH) and Alnylam Europe, AG dated July 30, 2003 (filed as Exhibit 10.20 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)

10.35†

Agreement between  
the Registrant,  
Garching Innovation  
GmbH (now known  
as Max Planck  
Innovation GmbH),  
Alnylam U.S., Inc.  
and Alnylam Europe  
AG dated June 14,  
2005 (filed as  
Exhibit 10.8 to the  
Registrant's Quarterly  
Report on Form 10-Q  
filed on August 11,  
2005  
(File No. 000-50743)  
for the quarterly  
period ended June 30,  
2005 and  
incorporated herein  
by reference)



- Exhibit No. Exhibit
- 10.36 Confidential Settlement Agreement and Mutual Release entered into as of March 14, 2011 by and between Max-Planck-Gesellschaft zur Förderung der Wissenschaften e. V., Max-Planck-Innovation GmbH and the Registrant, on the one hand, and Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, and the University of Massachusetts, on the other hand (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on October 2, 2015 (File No. 001-36407) and incorporated herein by reference)
- 10.37 Exclusive License Agreement for Tuschl II United States Patents and Patent Applications dated as of March 14, 2011, by and between the Registrant and University of Massachusetts (filed as Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed on October 2, 2015 (File No. 001-36407) and incorporated herein by reference)
- 10.38 Amendment to Co-Exclusive License Agreement dated as of March 14, 2011, by and between the Registrant, on the one hand, and

Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology and Max-Planck-Innovation GmbH (filed as Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q filed on May 5, 2011 (File No. 000-50743) for the quarterly period ended March 31, 2011 and incorporated herein by reference)

10.39† License and Collaboration Agreement entered into as of May 27, 2008 by and among Takeda Pharmaceutical Company Limited and the Registrant (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on August 8, 2008 (File No. 000-50743) for the quarterly period ended June 30, 2008 and incorporated herein by reference)

10.40† Amended and Restated License and Collaboration Agreement, entered into as of January 1, 2009, by and among the Registrant, Ionis Pharmaceuticals, Inc. (formerly Isis Pharmaceuticals, Inc.) and Regulus Therapeutics Inc. (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed on May 8, 2009 (File No. 000-50743) for the quarterly period ended March 31, 2009 and

incorporated herein by reference)

- 10.41† Founding Investor Rights Agreement entered into as of January 1, 2009, by and among Regulus Therapeutics Inc., Ionis Pharmaceuticals, Inc. (formerly Isis Pharmaceuticals, Inc.) and the Registrant (filed as Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q filed on May 8, 2009 (File No. 000-50743) for the quarterly period ended March 31, 2009 and incorporated herein by reference)
- 10.42† Sublicense Agreement dated effective January 8, 2007 among the Registrant and INEX Pharmaceuticals Corporation (now Arbutus Biopharma Corporation, as successor in interest) (filed as Exhibit 10.38 to the Registrant's Annual Report on Form 10-K filed on February 18, 2011 (File No. 000-50743) for the year ended December 31, 2010 and incorporated herein by reference)
- 10.43† Sponsored Research Agreement dated as of July 27, 2009 by and among the Registrant, The University of British Columbia and Acuitas Therapeutics Inc. (formerly AlCana Technologies, Inc.) (filed as Exhibit 10.1 to the

Registrant's Current Report on Form 8-K filed on June 29, 2011 (File No. 000-50743) and incorporated herein by reference)

10.44† Supplemental Agreement effective July 27, 2009 by and among the Registrant, Arbutus Biopharma Corporation (formerly Tekmira Pharmaceuticals Corporation), Protiva Biotherapeutics Inc., The University of British Columbia and Acuitas Therapeutics Inc. (formerly AlCana Technologies, Inc.) (filed as Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed on June 29, 2011 (File No. 000-50743) and incorporated herein by reference)

10.45† Amendment No. 1, dated as of July 27, 2011, to the Sponsored Research Agreement dated as of July 27, 2009 by and among the Registrant, The University of British Columbia and Acuitas Therapeutics Inc. (formerly AlCana Technologies, Inc.) (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on November 3, 2011 (File No. 000-50743) for the quarterly period ended September 30, 2011 and incorporated herein by reference)

- 10.46† Cross-License Agreement dated as of November 12, 2012 by and among the Registrant, Arbutus Biopharma Corporation (formerly Tekmira Pharmaceuticals Corporation) and Protiva Biotherapeutics Inc. (filed as Exhibit 10.50 to the Registrant's Annual Report on Form 10-K filed on February 19, 2013 (File No. 000-50743) for the year ended December 31, 2012 and incorporated herein by reference)
- 10.47† Settlement Agreement and General Release entered into as of November 12, 2012 by and among Arbutus Biopharma Corporation (formerly Tekmira Pharmaceuticals Corporation), Protiva Biotherapeutics Inc., the Registrant and Acuitas Therapeutics Inc. (formerly AlCana Technologies, Inc.) (filed as Exhibit 10.51 to the Registrant's Annual Report on Form 10-K filed on February 19, 2013 (File No. 000-50743) for the year ended December 31, 2012 and incorporated herein by reference)
- 10.48† License and Collaboration Agreement dated as of February 3, 2013 by and among The Medicines Company and the Registrant (filed as Exhibit 10.2 to the Registrant's Amendment

No. 1 to its Quarterly  
Report on Form 10-Q/A  
filed on July 26, 2013  
(File No. 000-50743) for  
the quarterly period  
ended March 31, 2013  
and incorporated herein  
by reference)

- | Exhibit No. | Exhibit   |
|-------------|---|
| 10.49       | <u>Stock Purchase Agreement dated as of January 11, 2014 by and between the Registrant and Sanofi Genzyme (formerly Genzyme Corporation) (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on May 9, 2014 (File No. 001-36407) for the quarterly period ended March 31, 2014 and incorporated herein by reference)</u> |
| 10.50†      | <u>Investor Agreement dated as of February 27, 2014 by and between the Registrant and Sanofi Genzyme (formerly Genzyme Corporation) (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed on May 9, 2014 (File No. 001-36407) for the quarterly period ended March 31, 2014 and incorporated herein by reference)</u>      |
| 10.51†      | <u>Master Collaboration Agreement dated as of January 11, 2014 by and between the Registrant and Sanofi Genzyme (formerly Genzyme Corporation), including the Regional, Global and Co-Co License Terms Appended thereto (filed as Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q filed on May 9, 2014 (File No. 001-36407) for</u>  |

the quarterly period ended March 31, 2014 and incorporated herein by reference)

10.52† Amendment No. 1 effective as of July 1, 2015 to Master Collaboration Agreement dated as of January 11, 2014, including certain Regional, Global and Co-Co License Terms attached thereto, by and between the Registrant and Sanofi Genzyme (formerly Genzyme Corporation) (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on November 9, 2015 (File No. 001-36407) for the quarterly period ended September 30, 2015 and incorporated herein by reference)

10.53† Amendment No. 2 entered into as of January 6, 2018 to the Master Collaboration Agreement dated as of January 11, 2014, as amended by Amendment No. 1, including certain Regional, Global and Co-Co License Terms attached thereto, by and between the Registrant and Genzyme Corporation (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on May 4, 2018 (File No. 001-36407) for the quarterly period ended March 31, 2018 and incorporated herein



by reference)

10.54† Exclusive License Agreement entered into as of January 6, 2018 by and between the Registrant and Genzyme Corporation (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on May 4, 2018 (File No. 001-36407) for the quarterly period ended March 31, 2018 and incorporated herein by reference)

10.55† ALN-AT3 Global License Terms entered into as of January 6, 2018 by and between the Registrant and Genzyme Corporation (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed on May 4, 2018 (File No. 001-36407) for the quarterly period ended March 31, 2018 and incorporated herein by reference)

10.56† Second Amended and Restated Strategic Collaboration and License Agreement dated January 8, 2015 between Ionis Pharmaceuticals, Inc. (formerly Isis Pharmaceuticals, Inc.) and the Registrant (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on May 8, 2015 (File No. 001-36407) for the quarterly period ended March 31, 2015 and incorporated herein

by reference)

- 10.57† Amendment No. 1 dated as of July 13, 2015 to Second Amended and Restated Strategic Collaboration and License Agreement dated as of January 8, 2015 by and among the Registrant and Ionis Pharmaceuticals, Inc. (formerly Isis Pharmaceuticals, Inc.) (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on November 9, 2015 (File No. 001-36407) for the quarterly period ended September 30, 2015 and incorporated herein by reference)
- 10.58† Amended and Restated Development and Manufacturing Services Agreement effective as of July 6, 2015 by and between the Registrant and Agilent Technologies, Inc. (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed on November 9, 2015 (File No. 001-36407) for the quarterly period ended September 30, 2015 and incorporated herein by reference)
- 10.59† Manufacturing Services Agreement effective as of March 28, 2018 by and between the Registrant and Agilent Technologies, Inc. (filed as Exhibit 10.4 to the

- Registrant's Quarterly Report on Form 10-Q filed on May 4, 2018 (File No. 001-36407) for the quarterly period ended March 31, 2018 and incorporated herein by reference)
- 10.60 Credit Agreement dated as of April 29, 2016 among Alnylam U.S., Inc., the Registrant and Bank of America N.A. (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on August 4, 2016 (File No. 001-36407) for the quarterly period ended June 30, 2016 and incorporated herein by reference)
- 10.61 Credit Agreement dated as of April 29, 2016 among Alnylam U.S., Inc., the Registrant and Wells Fargo Bank, National Association (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed on August 4, 2016 (File No. 001-36407) for the quarterly period ended June 30, 2016 and incorporated herein by reference)
- 21.1# Subsidiaries of the Registrant
- 23.1# Consent of PricewaterhouseCoopers LLP, an Independent Registered Public Accounting Firm

Exhibit No.	Exhibit
31.1#	<u>Certification pursuant to Section 302 of the Sarbanes-Oxley Act of 2002, Rule 13(a)-14(a)/15d-14(a), by Principal Executive Officer</u>
31.2#	<u>Certification pursuant to Section 302 of the Sarbanes-Oxley Act of 2002, Rule 13(a)-14(a)/15d-14(a), by Principal Financial Officer</u>
32.1#	<u>Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, by Principal Executive Officer</u>
32.2#	<u>Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, by Principal Financial Officer</u>

101#           The following materials from Registrant's Annual Report on Form 10-K for the year ended December 31, 2018, formatted in XBRL (Extensible Business Reporting Language):  
(i) the Consolidated Balance Sheets,  
(ii) the Consolidated Statements of Comprehensive Loss, (iii) the Consolidated Statements of Stockholders' Equity, (iv) the Consolidated Statements of Cash Flows and  
(v) Notes to Consolidated Financial Statements

\*               Schedules, exhibits and similar supporting attachments or agreements to the Stock Purchase Agreement are omitted pursuant to Item 601(b)(2) of Regulation S-K. The Registrant agrees

to furnish a supplemental copy of any omitted schedule or similar attachment to the Securities and Exchange Commission upon request.

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

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

# Filed herewith.

ITEM 16.FORM 10-K SUMMARY

Not applicable.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this Report to be signed on its behalf by the undersigned, thereunto duly authorized, on February 14, 2019.

ALNYLAM  
PHARMACEUTICALS, INC.

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

Pursuant to the requirements of the Securities Exchange Act of 1934, the Report has been signed below by the following persons on behalf of the Registrant and in the capacities indicated as of February 14, 2019.

Name	Title
/s/ John M. Maraganore, Ph.D. John M. Maraganore, Ph.D.	Director and Chief Executive Officer (Principal Executive Officer)
/s/ Manmeet S. Soni Manmeet S. Soni	Senior Vice President, Chief Financial Officer (Principal Financial and Accounting Officer)
/s/ Dennis A. Ausiello, M.D. Dennis A. Ausiello, M.D.	Director
/s/ Michael W. Bonney Michael W. Bonney	Director
/s/ Marsha H. Fanucci Marsha H. Fanucci	Director
/s/ Margaret A. Hamburg, M.D. Margaret A. Hamburg, M.D.	Director
/s/ Steven M. Paul, M.D. Steven M. Paul, M.D.	Director
/s/ David E. I. Pyott David E. I. Pyott	Director
/s/ Colleen F. Reitan Colleen F. Reitan	Director
/s/ Paul R. Schimmel, Ph.D.	Director

Paul R. Schimmel, Ph.D.

/s/ Amy W. Schulman                      Director  
Amy W. Schulman

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